The Politics of Contraception:

The View from Tokyo*

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On December 18, 1986, the Pharmaceutical Affairs Bureau of the Japanese Ministry of Health and Welfare (*Kosei-sho*) released a report by a "Research Group on the Medical Evaluation of Oral Contraceptives" ("Kobayashi Study Group"), recommending that the 25-year-old ban on oral contraceptives be relaxed. Relatively few persons in the West are aware of this anachronistic aspect of Japanese contraception, which is otherwise practiced extensively; even fewer know of the impending changes in that country, which have been defined appropriately[1] as one "that is ultramodern in so many other respects (but) has a family planning technology that was created in the 1930s." In a recent article[2] dealing with the prognosis for steroid contraception in the remainder of this century, I suggested that the use of steroid oral contraceptives, stagnant in recent years, would resume its growth in developed countries. Aside from listing four factors likely to operate in the U.S.A., I indicated that use of the Pill would also increase substantially in Spain, Italy and France, and especially in Japan -- the largest untapped market in the developed world for steroid oral contraceptives.

Yet in 1958, I was convinced that Japan would be one of the first countries in which steroid oral contraception would be introduced. There were no religious or moral scruples to its use. After the end of the war, the Japanese government encouraged effective birth control, a policy implemented primarily through readily available abortion provided by the *private medical sector*. Early that year, the late Dr. Edward T. Tyler (Los Angeles Planned Parenthood Center), Dr. Alejandro Zaffaroni (then Executive Vice President of Syntex) and I presented, under the auspices of the Japanese Pharmaceutical Society, a series of lectures on the chemistry, biochemistry and clinical results with norethindrone[3] as an orally effective progestational agent for menstrual regulation and for contraception. Indeed, not long thereafter, *Kosei-sho* authorized the use of such synthetic 19-norsteroids for the treatment of menstrual disorders -- i.e. within a couple of years of the 1957 approval of norethindrone and norethynodrel for the same indication. While FDA approval for oral contraceptive use followed fairly rapidly (1960 for norethynodrel; 1962 for norethindrone), ostensibly nothing happened in Japan. Why?

According to Kobayashi[4], a medical advisory committee to *Kosei-sho* did indeed continue to meet during the early 1960s and was on the verge of recommending approval of

norethindrone and norethynodrel for oral contraception. However, the Thalidomide episode and several other related drug toxicity issues arose, causing *Kosei-sho* to become extraordinarily cautious. Safety, rather than efficacy, has been the watchword ever since for the Japanese drug regulatory authorities. No wonder that Japan boasts of more "useless" but otherwise harmless drugs than any other modern country. Two other reasons[1] -- ironically associated with the unsurpassed efficacy of oral contraceptives -- kept the Pill from the Japanese market, although officially the delay was solely attributed to a concern for side effects.

One was the opposition of a segment of the Japanese medical profession that specializes in abortion and fears the loss of substantial income if the Pill were used widely in Japan. How substantial this income must be can be judged from the fact that most Japanese physicians charge for abortions outside the national health insurance system, and do so at rates that are nearly comparable to American ones[1]. Even more significant is the incidence of abortion: whereas official *Kosei-sho* statistics[5] cite an abortion rate (5.1/1000 in 1980) lower than that (5.7-6.8) estimated for the U.S.A., it is generally agreed[1,5] that both Japanese women and physicians grossly under-report the actual abortion incidence, which is almost certainly the highest in the world. Using Coleman's[1] minimal 1975 cost estimate ($110) and Muramatu's[6] medium estimate of actual 1975 abortions, one arrives at a figure of ca. $250 million for physicians' income from abortions in that year! One can only guess what it might be now.

The second reason is less devious: the fear that government approval of the Pill will also make it more readily available to the unmarried young and increase premarital sex. Such a concern is quite consistent with the Japanese social setting: its youth supposedly exhibits[1] one of the industrialized world's lowest rates of premarital sexual activity.

Given these reasons, why has the Japanese government suddenly decided to join the rest of the world in terms of modern contraception? Japan is famous for operating by consensus, be it in business or politics. In the 1980s, several factors arose which led to such a consensus among various medical groups. It was this pressure by the medical sector[7] that caused the government in March of 1986 to establish an advisory group chaired by Dr. T. Kobayashi, formerly Professor of Gynecology at the University of Tokyo, who at one time had carried out postdoctoral research under Gregory Pincus at the Worcester Foundation for

Experimental Biology. In addition to Kobayashi, the advisory group consisted of seven obstetricians and gynecologists as well as one person each from the fields of biochemistry, pharmacology, toxicology and internal medicine. (None of the members were female, prompting the following press comment[8]: "...all 12 members of the pill research group of the Health and Welfare Ministry were men. We do not know why the team was dominated by males, but this strikes us as strange.")

According to the official report, supplemented by additional information[4,7], four main reasons convinced the committee and ultimately *Kosei-sho*:

(1) The relatively recent introduction in the West of low-dosage oral contraceptive formulations, notably biphasic and triphasic dosage regimens, which reduce substantially the overall estrogenic and progestational load administered to the woman. Therefore, fewer deleterious side effects are to be expected.

(2) The results, during the past eight years, of major studies in England and the U.S.A. reporting the occurrence of several important beneficial non-contraceptive effects associated with the use of the Pill.

(3) Consideration of the *real* incidence of abortion in Japan. Reduction of that incidence through wider use of oral contraceptives is now considered a significant benefit, which was not taken earlier into consideration.

(4) Current use by approximately 800,000 Japanese women[4] of the *Kosei-sho*-approved high-dosage progestin-estrogen combination. Ostensibly, such a regimen is only to be applied therapeutically for the treatment of gynecological disorders, but as many as 80% of these users actually employ them solely for contraceptive purposes. This means that well over 600,000 Japanese women may be consuming a high=dosage Pill, without having recourse to the lower dosages with their marked and well-documented advantages for long-term administration. Even more importantly, since the long-term use for contraception is not permitted, none of the presently available steroid preparations can contain any package inserts or other descriptive information warning a woman about the consequences of long-term consumption of high-dosage Pills.

According to various sources[4,9], condoms represent the principal (ca. 80%) method of contraception in Japan -- the highest incidence in the world. The rhythm method and IUDs (primarily the ota metal ring developed in the 1930s) follow next, with oral contraceptives supposedly constituting less than 3% of all contraceptive practice. In contrast to the dramatic shift towards sterilization in much of the rest of the world, this method plays a relatively small role in Japan[1,4]. If it is indeed true that 80% of the 800,000 women on the high-dose combination Pill employ it for contraceptive purposes, but only represent 3% of all contraceptive users in Japan, then theoretically over 21 million women are potential candidates for the Pill, since they already practice some form of contraception. Even if only 30% eventually select some low-dose formulation of the Pill -- a figure that seems reasonable based on Pill use in other countries[10] -- over six million women represent a realistic target (compared to 8-10 million in the U.S.A. with more than twice its population). This would make Japan the market with the greatest new potential in the world for oral contraceptives; it will be interesting to see how many pharmaceutical companies plan to enter it.

After 11 meetings, the "Kobayashi Study Group" released a detailed set of guidelines concerning clinical and other studies that need to be completed before the Central Drug Council of *Kosei-sho* will consider issuing marketing approval. One interesting compromise, compared to other (non-contraceptive) drugs, is the recommendation that "data on studies performed in foreign countries can be utilized as far as possible." Nevertheless, clinical trials in Japanese women are required with particular emphasis on dosage determination and on tests dealing with absorption, distribution, metabolism and excretion. For known steroids, approved and used abroad, a minimum of 2,400 cycles with at least 100 women is required. Continuous administration must proceed for at least one year, but some portion of the experimental group must be carried through two years. In the case of new steroid entities, 10,000 cycles in at least 200 women must be presented.

It is clear, therefore, that oral contraceptive use will not be sanctioned officially in Japan before 1989 at the earliest. It is equally clear that, by the middle 1990s, contraception in Japan will be very different from what it is now. In the meantime, the rather dormant field of Japanese clinical steroid endocrinology will receive a major boost, even though 2400 cycles with 100

women will teach nothing that has not been published several hundred times abroad. However, there is one intriguing epidemiological feature that may be of more than local interest: the new Japanese guidelines also require long-term follow-up studies after marketing approval. Virtually all current reports on the beneficial non-contraceptive effects of steroid oral contraceptives are based on work with relatively high dosages; it remains to be seen whether these beneficial effects will be observed with low-dose or phasic regimens. Japan, with such a large pool of non-Pill users may offer a superlative opportunity for significant epidemiological studies on the long-term effects of low-dose formulations.

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FOOTNOTE

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