

A career of many contributions: Daniel R. Mishell, Jr, MD, describes 4 decades of developments in contraception

Daniel R. Mishell, Jr, MD, has perhaps done more than anyone to educate obstetricians and gynecologists, family practitioners, and other physicians in the United States about the benefits and safety of contraceptives. Recently, Dr Mishell spoke with Robert W. Rebar, MD, about the profound changes that have shaped the field during his 40-year career.

RWR: How did you become interested in contraceptive research?

DRM: When I finished my residency at Harbor General Hospital-UCLA in 1963, Luigi Mastroianni, the chairman of the department there, offered me a faculty position. Instead of having me join him in researching infertility, however, he encouraged me to do research in contraception. He pointed out that no one was doing it and that it was a very important field.

RWR: That was a time of real change in contraceptive usage in the United States.

DRM: That's absolutely right. Before 1960, the methods of contraception were barrier techniques, withdrawal, or natural family planning, called the rhythm method then. Every gynecologist knew how to fit diaphragms. Condoms were not as easily available in drugstores as they are today; they were hidden, and it was considered embarrassing to ask for them. These techniques frequently were not used in the heat of passion, so we had many unwanted pregnancies in those years.

The first oral contraceptives (OCs) were approved in 1959 and became very popular. So did intrauterine devices (IUDs), which were coming on the market about then. At the time the US Food and Drug Administration (FDA) had no authority to regulate medical devices; so various companies made IUDs of different shapes and sizes and designs, with and without tail strings, and just marketed them.

RWR: What were your first projects in the area?

DRM: Beginning in 1963, I did several studies of Depo-Provera, which Upjohn was developing as a contraceptive method.¹ At about

the same time, I was fortunate to do a study, funded by the Population Council in New York, on the risk of infection with IUDs,² which was a great concern at the time. We put a loop IUD in women scheduled for vaginal hysterectomies and then obtained endometrial cultures after the hysterectomy. The results showed that insertion of the IUD transported organisms normally present in the vagina and ectocervix to the endometrial cavity, but the host defenses killed the bacteria in a very short time. The IUD did not allow continued transport of bacteria from the lower to the upper genital tract.

RWR: What are your thoughts about the IUD at this point?

DRM: It's an extremely effective, long-lasting, rapidly reversible method of contraception, with no or minimal systemic effects. It is vastly underutilized in the United States, mainly due to misperceptions. We had the Dalkon Shield, which did cause infection; that was an IUD, so it has painted the whole field with a black brush. We've seen similar boom-and-bust phenomena. A method of contraception is approved, gets great press, and everyone thinks it's wonderful. Then a few side effects occur and are widely publicized. The risks are very remote, but everyone stops using the method.

RWR: What do you see as your greatest personal contributions to the field of contraception?

DRM: Showing that the IUD does not facilitate pelvic inflammatory disease was important. In 1966, I also did the first clinical study of a contraceptive vaginal ring.^{3,4} We showed that it was effective in preventing ovulation, although a vaginal ring didn't



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come on the market until 2001—a good 35 years later!

RWR: What do you think has been the greatest contribution to the field during your lifetime?

DRM: Development of the OCs, by far. This was one of the main factors in the emancipation of women, because it allowed women to plan their families more easily and pursue careers. I was disappointed that Dr Gregory Pincus didn't win the Nobel Prize for his role in developing these agents. Modifications have really improved OCs, and we've learned about their noncontraceptive health benefits, including reduction in rates of endometrial and ovarian cancer. I wasn't the first to demonstrate noncontraceptive benefits, but I was the first to collate them from a variety of sources and to list them in a journal article.⁵

RWR: What unmet needs are there in the field of contraception?

DRM: There's a great need to develop additional methods of contraception that are effective, safe, rapidly reversible, acceptable to women, and—most important—accessible. Half of the 6.3 million pregnancies that occur each year in the United States are unintended. Half of those women are using contraception incorrectly; the other half, not using contraception at all. Although we have a large number of contraceptive methods, the percentage of women who use no method has increased since 1994.

RWR: Why do you think that percentage is increasing?

DRM: I think cost is a major reason. These agents are costly, although the cost of an unwanted pregnancy is much higher. Also, pharmaceutical companies have stopped marketing some contraceptives that the FDA has approved. For example, monthly injections of estrogen and progestin, widely used in Latin America and desired by Latina women here in the United States, are not marketed.

RWR: It seems you are a great advocate for developing as many different types of contraception as possible.

DRM: That's right. Given our ethnic and cultural diversity and the reports women hear from various sources about the dangers (which are overemphasized in the media), we need to develop new methods of contraception that have fewer side effects.

RWR: When are we going to see a male contraceptive?

DRM: I've been asked that question for 40

years, and my answer is the same: not in the next 10 years. Effective male contraceptives have made it to phase 2 trials, but there are problems with administration and especially with the fact that inhibiting spermiogenesis also inhibits testosterone production.

RWR: What advances in contraception should we look for in the next decade?

DRM: I think we're going to have methods that are longer-acting—for example, a vaginal ring that can be effective for 1 year instead of 1 cycle—and new steroids with fewer adverse effects. We're going to have birth control pills with the natural hormone estradiol.

RWR: What's going to be the first contraceptive drug that doesn't involve steroids?

DRM: It may be a progesterone receptor antagonist. Clinical trials have not begun, but some experimental data suggest efficacy.

RWR: The challenge is that people want contraceptive drugs to have absolutely no side effects or complications because they're otherwise healthy.

DRM: That's true. I'd like to see more uniform methodology for calculating side effects and more head-to-head comparisons before new agents are approved. Of course, the need to demonstrate safety is an important factor in the time and cost of developing contraceptives. It takes decades from initial studies of a contraceptive until it's marketed. I remember working on Norplant back at the Population Council in the 1970s, and it wasn't approved until 1991.

RWR: If you could effect one change in the field of contraception today, what would it be?

DRM: If I could wave my magic wand, I'd make contraceptives available without cost to women. I don't know what it would cost, but it would be less than the cost of the 3 million unintended pregnancies that we have in the United States each year. ■

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