Waiting for the second coming

Contraceptive research is seriously in need of revitalization.

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Pregnant pause: the discontinuation rate for contraception is almost 50% after one year.

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Even developed countries have a staggeringly high incidence of unplanned pregnancies. In the United States about half are unintended at the time of conception, and many involve couples practising some form of contraception. This reflects the inconsistent use of effective methods and a discontinuation rate approaching 50% after one year. Contraceptives are simply not meeting the needs of society. Despite epidemiological and demographic data that make a compelling case for immediate and substantial investment in contraceptive research and development, the academic community and industry seem unmoved by these needs.

Successive reports issued over more than a decade by the Institute of Medicine (IOM) show that a second contraceptive revolution, or at least a revitalization of contraception research, is sorely needed[1–3]. In developed countries, the high discontinuation rate shows that consumers want safer, more effective and more user-friendly contraceptives. In contrast, the developing world lacks universal access to effective, inexpensive and appropriate contraception — let alone methods that also protect against sexually transmitted diseases. The widely used oral contraceptives have adverse cardiovascular side effects in a small number of users, and there is debate about a possible small cancer risk. And apart from vasectomy and condoms, there are virtually no male methods.

Yet the number of patents relating to contraception is modest compared with the number issued for drugs to treat high blood pressure (Fig. 1). Only 2.3% of the new molecular entities approved by the US Food and Drug Administration (FDA) during the past six years have been for contraceptive products, and all of these were steroids, and so only incremental advances (Fig. 2). There are more than 1.5 billion women of reproductive age, more than one billion of whom are married and presumably in need of some family-planning method, whereas an estimated 600 million people have high blood pressure. Given the universal need, fertility regulation should rank among the most important quality-of-life concerns. So what gives?

This is a problem of the compartmentalization of reproductive sciences and clinical development, and a failure to direct resources, both monetary and legislative, into programmes that will turn reproductive biology into products. Unfortunately, most reproductive biologists have little knowledge of drug development and do not appreciate what makes an attractive drug target, even at the very early stages of the process. And academia contains very few translational scientists who can advise on product development and early-stage clinical trials. Here we examine some of the factors impeding progress in contraceptive development, and offer some suggestions to address them.

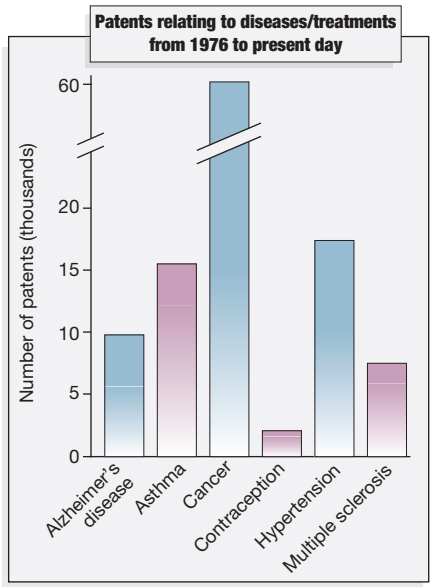

Figure 1 **Number of US patents issued for contraceptives and other treatments.**

SOURCE: US PATENT & TRADEMARK OFFICE

Lost in translation

Two obvious places to seek targets for contraceptive development are the genes and proteins selectively expressed in the female and male reproductive organs. Reproduction is all about interactions between cells, changes in membrane structure and membrane fusion, which are critical to processes such as the preparation of sperm for fertilization and fertilization itself. Carbohydrate moieties and lipids are crucial to these processes, and the reproductive tract, particularly of the male, contains unique forms of them. We hope that forays into 'glycomics' and 'lipidomics', new technologies for large-scale analysis of carbohydrates and lipids, will reveal promising new leads.

Although this is a good starting place, there is a bottleneck between basic science and product development. Academic investigators tend not to be attracted to applied research, as they are uncertain how funding agencies will receive it. Few of them have access to the costly infrastructure, such as high-throughput screening facilities and chemical libraries, needed to move on to the next step.

To feed the pipeline of potential contraceptives, academic investigators will need to better understand how the system works, how to access the tools needed to move their discoveries along, and how to 'de-risk' a concept, target or lead compound to make it tantalizing enough for industry to bite. This may require new data to overcome concerns

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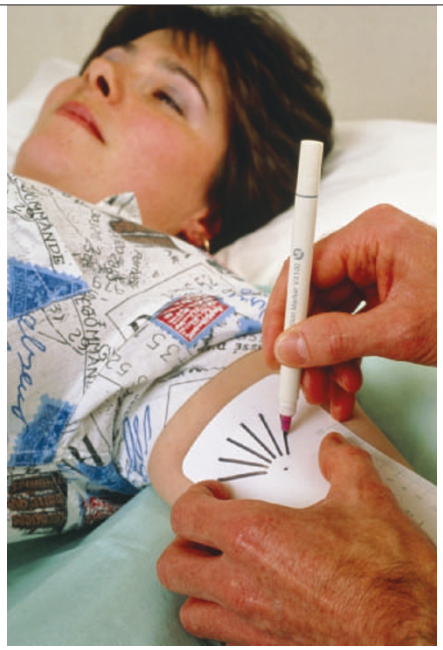

Five years of fighting litigation over the safety of the hormonal implant Norplant, although successful, was a heavy financial burden for its manufacturer Wyeth.

about efficacy, delivery method, cost of production and market penetration.

Academic scientists might also need a reality check. RNA interference may be a great contraceptive for worms, but its near-term potential in human contraception is questionable. Ideas for post-fertilization contraceptive methods are nixed by some from the beginning because of a potential backlash from pro-life advocates. Consideration of the social perspective to answer the all-important question, 'If we build it, will they use it?', is rarely contemplated by the bench and translation investigators in academe.

Out in the cold

Another obstacle is the paucity of researchers focused on contraception. There is no shortage of reproductive biologists. The Society for the Study of Reproduction, for example, has about 2,300 members, yet only a few identify contraception as their primary interest. The society's annual meeting this year did not have a single session dedicated to contraception. Basic reproductive biology is not synonymous with contraception research; there is a difference between an investigator who studies the process of ovulation and one trying to discover how to inhibit ovulation.

Contraception research needs to attract talented scientists and physician-investigators who can offer advice on product development and clinical trials. It is not clear whether the National Institutes of Health's Loan Repayment Program (LRP), which aims to attract such workers into contraception and infertility research by paying for debts accumulated during undergraduate and graduate medical education, has addressed these needs, at least for contraception. For example, of 56 individuals originally receiving LRP support, only five were doctoral-level investigators whose research was directly relevant to contraception. Few existing graduate and postgraduate programmes focus on contraception, and those that do tend to emphasize epidemiological studies and late-stage clinical trials.

It is rare for reproductive biologists to focus on the nitty-gritty work of getting a new target or compound off the ground. This problem can only be resolved by federal funding agencies and foundations establishing infrastructure and training programmes to cultivate such individuals.

Healthcare industries are essential for developing contraceptive products, but there is no guarantee of interested parties. A number of questions must be addressed. For example, how well does a contraceptive fit with the current business and customer base? What advantages does it offer over existing methods? How difficult will it be to carry out the necessary research, what is the likelihood of approval, and what are the liability risks? What are the competing products and the likely returns on the investment? Without a strong business rationale and a champion to propel a development plan forward, contraception may be a non-starter in many companies.

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Industry research has a finite budget, and most companies have a stable of competing therapeutic needs and business cases. Investment decisions must be weighed carefully, given that only 22% of phase I candidates are ever approved, and there is only a 57% chance of drugs surviving phase III clinical trials and winning FDA approval. The gamble on contraception R&D will be most attractive to companies already involved in some related field, where they can just expand their core competencies.

Showing that a new contraceptive is as safe or safer than current products could take many years — possibly longer than the patent life. Developing better products requires scientific validation, and the affordability of this is an ever-present issue. It may be worth targeting development at a particular segment of the population, such as men at risk of sexually transmitted diseases, women at different times after childbirth, poor compliers or diabetics. But such segmentation of the user base may magnify the previously mentioned challenges, and limit the financial returns.

The approval process for women's contraceptives is relatively straightforward; there is much less experience for men's products. Existing approaches, such as the steroid hormones oestrogen and progestin, are well served by current preclinical and clinical guidelines, but it is not clear that these will suffice for novel methods, or whether compliance with these principles will satisfy the tort system.

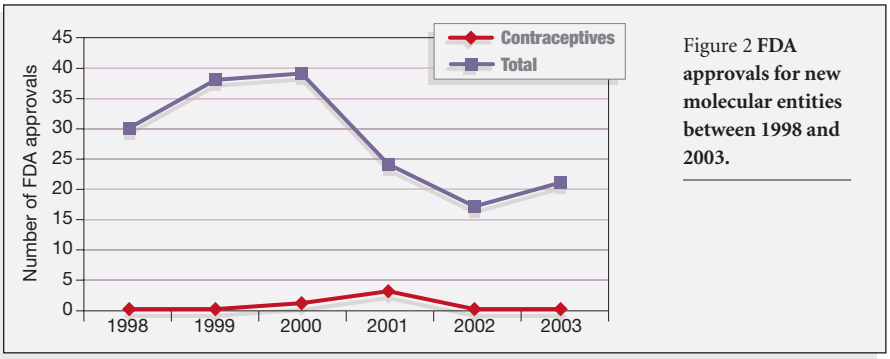
Some insurance companies' refusal to provide liability coverage for contraceptives further hampers new product development. Contraceptive methods are used primarily by healthy populations, potentially for long periods of time. This would seem to encourage drug development, but it is counterbalanced by the risk of making healthy people ill. Given the large number of potential users, even a small proportion of adverse effects would have dire consequences, not only for the manufacturer, but also for public perception of the safety and value of specific methods or contraception in general. Unfortunately, without national or international databases there is little hope that reliable epidemiological data could inform regulatory and legal solutions.

The chequered past of contraceptive development has made the healthcare industry cautious. For example, plaintiff attorneys — perhaps inspired by the litigation surrounding silicone breast implants — targeted Wyeth over its contraceptive Norplant, a hormonal preparation encapsulated in a silicone elastomer. This was despite the FDA having no concerns over the drug's safety. During more than five years in court, the manufacturer won three jury verdicts, 20 pretrial judgments and dismissal of some 14,000 claims. A trial verdict against the manufacturer was overturned on appeal. Despite the favourable rulings, defending the product was a significant financial burden for Wyeth.

It should be no surprise, then, that the president of a large pharmaceutical research programme once told one of us that they would not touch contraception with a ten-foot pole.

A modest proposal

We have briefly touched on the opportunities and obstacles to contraception research, specifically those bottlenecks that limit collaboration between academia and industry. There are a number of under-explored



SOURCE: FDA

Figure 2 **FDA approvals for new molecular entities between 1998 and 2003.**

opportunities as well as measures to cross hurdles, but none alone will be sufficient.

First, there needs to be better interaction between academic investigators and the healthcare industry and regulatory agencies. These discussions should try to understand the impediments to product development. The notion of a round table of stakeholders, as proposed in the 2004 IOM report, resonates well with us[3]. Expanded partnerships between regulatory and academic bodies may foster forward-looking guidelines for novel methods.

Second, targeted public or private funding, perhaps from foundations concerned with global health, is needed to bridge the gap between discovery and product development. Those controlling funding must understand all aspects of contraceptive development. The US federal budget for extramural and intramural programmes related to translational contraception research needs to be increased, and the funds committed should be restricted to research targeted towards contraception, not tangential science. Cooperative funding mechanisms, in which NIH staff participate with extramural investigators, can make this possible, but NIH staff need the funds and technical expertise to invest in promising research. The Consortium for Industrial Collaboration in Contraceptive Research was an attempt to deal with some of these issues, and lessons from its successes and failures should be heeded.

The new NIH Roadmap offers opportunities to build the multidisciplinary research teams needed to pursue contraception research, if committed investigators can pool their strengths to address the translational hurdle. A recent request for applications from the United States Agency for International Development (USAID), which could provide $125 million over five years for research in contraceptive and reproductive technologies, is one encouraging sign of continuation of investment in contraception research at a time when a number of foundations previously active in this arena (Ford, Andrew W. Mellon, Rockefeller) have redirected their resources elsewhere.

Third, to stimulate industry interest in contraception, the nature and duration of trials and surveillance should be clarified. This would allow an estimate of the investment needed, which is especially problematic for methods targeting both sexually transmitted infections and contraception, as the efficacy of each activity must be evaluated.

Additional incentives for investment in contraception research are also needed. These could include tax benefits, expanded intellectual-property protection, and giving contraceptives the same status as vaccines — as public-health drugs. To address the thorny problem of liability insurance, we should consider: creating an independent review process to set compensation and oversee compensation programmes; having these principles of science and law set by experts rather than lay juries or plaintiff lawyers; establishing alternative compensation models for plaintiffs funded by industry, such as a compensation fund built on industry contributions and dispersed according to expert opinion, not jury award; and expanding liability protection for companies when the FDA has approved a contraceptive.

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Fourth, there is an urgent need to support training, career development and retention in contraception research. This can in part be addressed by training grants and mentored career development awards. Neglected areas such as male reproductive health deserve special attention. But despite the good news about the USAID request for applications, relatively few organizations could compete for this funding, limiting the number of sites for training and career development. This can be remedied by increasing the number of investigators in contraception research. Some of these individuals might become champions of contraceptive research in the healthcare industries.

Fifth, and finally, industry and foundations should seek opportunities for product development beyond the United States and Europe. For example, the biotechnology industry has flourished in Cuba, where it ranks third in economic terms behind sugar and tourism. Brazil has a long history of contributions to contraception research and a flourishing biotechnology sector. These successes, and those in other countries with smaller biomedical-research enterprises, reveal the promise of science in the developing world to contribute to contraception.

The development of methods that let humans promote and suppress fertility is one of the greatest scientific achievements of the past 50 years. But family-planning problems are far from solved, and the sense of mission and urgency that spurred the development of the first widely used contraceptives in the late 1950s and early 1960s is largely missing. Unfortunately, history tells us that the fervour may not emerge from academia or industry. Recommendations made in past IOM reports and those put forward here may languish without a missing ingredient. The first contraceptive revolution was sparked, and partly sponsored, by visionary lay people such as Margaret Sanger and Katherine Dexter McCormick. A concerned public with faith in science's ability to improve reproductive health is a powerful motivating force and an essential ally in the campaign to catalyse research in contraception. ■

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