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several issues remain to be resolved. For example, given the short amino acid sequence, it has not yet been possible to detect the gene encoding this product in either human or mammalian tumor cells, primarily because of the potential degeneracy in the coding sequence. The sequence is similar, although not identical, to a streptococcal antigen implicated in the pathogenesis of acute poststreptococcal glomerulonephritis, and although the tumor appeared to be free of microbiological contamination, it is not yet certain whether this material is of mammalian origin. Given the large component of glycosaminoglycans and associated sulfated content, it is also unclear whether this molecule is acting on skeletal muscle directly through a specific receptor, through indirect competition or through modifications induced by lectin binding, which may trigger a subsequent cascade of events that may promote muscle catabolism. However, the ability to promote muscle proteolysis *in vitro* is unique among the proposed mediators of cachexia.

In any event, the potency and specificity of this molecule are remarkable. The degree of weight loss following injection of this purified molecule is 5–10 percent of the body weight of the mouse within a 48-hour interval, and a large component of this weight loss appears to be associated with changes in adipose tissue. Although the level of plasma glucose was significantly decreased, no alteration in plasma triglycerides were observed after intravenous injection, in contrast to effects seen with cytokines[7,11,12,14].

Thus, it would appear that this molecule, whatever its source and its mechanism of action, is both potent and distinct from previously described cachexia-inducing factors. The ability to detect a similar immunoreactive material in the urine of cancer patients suggests that this mediator of cancer cachexia may have implications that extend beyond the murine model that has provided the basis for its isolation. Although many questions remain to be answered, the elucidation of specific factors that can induce profound cachexia in murine models and human cancer provides important leads that may help to unravel the complex metabolic and biochemical changes that result in one of the devastating consequences of human cancer. The availability of a neutralizing monoclonal antibody from the mouse provides encouragement that it may be possible to develop antagonists to this reagent. If so, a variety of preclinical and clinical models will facilitate the development of therapies at the same time that more is learned about the specificity and mechanism of this novel potential mediator of cancer cachexia.


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# The myth of a male pill

**Should the male pill be a contraceptive priority? (pages 470–472)**

MALCOLM POTTS

Undoubtedly, there is a need for new contraceptives. Rapid population growth a generation ago has fueled the momentum of today's global population crisis, and although growth rate has now peaked, the absolute annual increase in human numbers continues to rise alarmingly. Currently, there are one million more births than deaths every 100 hours. A Population Summit by the World's Scientific Academies concluded that if population growth and human activity "remain unchanged, science and technology may not be able to prevent irreversible degradation of the natural environment and continued poverty for much of the world"[1]. It is estimated that more than 100 million couples would like to limit the size of their families but are unable to obtain, or do not use, a contraceptive method. In light of this, it seems reasonable to suggest that the more choices available, the more contraception will be used. In this issue of *Nature Medicine*, Breton *et al.*[2] take the first steps toward what could be a novel approach to male contraception. They present data concerning the biochemical mechanism underlying acidification of the vas deferens and epididymis and provide a framework upon which to develop a new method for controlling male fertility.

Breton and colleagues show that acidification of the vas deferens and epididymis is largely maintained by the activity of a plasma membrane proton ATPase pump located on the luminal surface of specialized epithelial cells that line the vas deferens (see figure). As sperm travel from the testis through the epididymis (the long, convoluted duct in which sperm continue to develop) and then on through the vas deferens (the duct leading to the urethra), the continued acid environment ensures that the sperm mature efficiently and do not become prematurely motile. The authors propose that this acidification mechanism may prove to be a potential target for regulating male fertility. In theory, a new male method of contraception might perhaps be a great boon, but is private industry or the public sector prepared to make the investment to bring the male pill to the marketplace?

The history of the second half of the

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Breton, Smith, Lui & Brown

The plasma membrane $H^+$-ATPase (yellow staining) is concentrated at the apical pole of proton secreting cells in the rat epididymis. (Section is counterstained in red.)

twentieth century has been one of an ever widening gap between the insights of reproductive physiologists and their practical application to fertility regulation. In the West, regulatory requirements make the cost of introducing a new contraceptive method as high as $70 million and the duration of clinical trials leaves little of the 20-year patent life of the drug in which to recover this large investment. Fears of unreasonable product liability lawsuits are especially severe in the United States, and these fears are spreading to Europe and the developing world. Many major pharmaceutical companies have pulled out of contraceptive development. Roussell Uclaf, for example, which developed the effective abortifacient mefipristone (RU 486), recently closed their endocrine research laboratories. Compounding these problems, strident and ill-informed consumer advocates often oppose new contraceptive choices. Women's groups have blocked the use of injectable contraceptives in India, even though they are approved in the West and are popular among rural women in many parts of the world. The subdermal contraceptive implant, Norplant, was developed by the Population Council in New York, a charitable institution. Initially progress was slowed by insufficient capital and lack of industrial experience. Nevertheless, careful, consumer-oriented trials showed the implant had few failures and was well accepted. Even so, Norplant has suffered vitriolic attacks by self-appointed guardians of the public health, and use of this worthwhile method has plummeted. Perhaps the development of a new male contraceptive would be better received. However, although a method controlling male fertility might be politically correct is it physiologically or socially sound?

Oral contraceptives for women imitate the suppression of ovulation accompanying pregnancy and lactation, but no comparable natural interruption of fertility occurs in the male, around which a systemic method might be built. Contraceptive pill use in women significantly reduces their risk of endometrial[3] and ovarian cancer[4], and clinical trials are currently under way that might result in a pill also capable of reducing breast cancer[3]. There are, however, no biological grounds for assuming a male pill would offer men a similar advantage. Finally, even though women make a much greater investment in pregnancy than men, compliance with oral contraceptives among women is remarkably uneven. Compliance is likely to be even worse among men — therefore, should women trust men to use their pill correctly?

In a world of inadequate investment and swirling controversy, tough decisions must be made. A male pill is likely to have a number of limitations, and with dwindling resources for contraceptive development in both private industry and the public sector, perhaps more simple approaches to contraceptive development should be pursued. Voluntary sterilization is the single most widely used form of contraception, and an estimated 200 million couples will seek it in the developing world in the next decade. Although vasectomy can be offered in a primary health care center, female sterilization requires greater skill and more expensive facilities. It is difficult to maintain acceptable standards and find the money to pay for female sterilization in poor countries where surgeons do not even have an adequate supply of rubber gloves. However, quinacrine sterilization (QS), which uses the trans-cervical placement of quinacrine pellets to obstruct the Fallopian tubes, has been available for 20 years[7]. This is a simple technique and although it has been embraced by some — 30,000 cases have been performed in Vietnam[8] – to date not a single Ph.D. thesis has been devoted to the study of QS.

Millions of women suspect their partner may be exposing them to risk of HIV infection, but they cannot compel them to use a condom. Therefore, another imperative that should head any priority list is the development of an agent, for use by women, that provides both contraception and protection against HIV infection (and which preferably can be used surreptitiously). Several promising chemical entities already exist, and even the widely used spermicide, nonoxynol-9, may work in appropriate doses[9]. The need for a dual-action contraceptive has been discussed for at least ten years, but the UK's Medical Research Council and the US National Institutes of Health have only just started encouraging research in this potentially life-saving field.

In the current environment, the diversion of funds and skills into developing a male pill, or other methods with a long lead time and uncertain future, may be counterproductive. If the chasm between the laboratory and the realities of the field is to be bridged, then those interested in family planning must do a better job defining what is needed, while those working in basic research should understand the huge costs of developing and introducing a new contraceptive method. All parties would do well to remember that in many developing countries governments spend only a few dollars a year per capita on all aspects of health care and, sadly, contraception is a luxury they often cannot afford. Although the work presented by Breton *et al.* is to be applauded for its vision and novelty, its application to contraceptive development in the real world is likely to prove an uphill struggle.

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