Industry Wary of Tech Transfer Bills

Technology transfer legislation is not likely to start moving through Congress until fall, but provisions in the House and Senate bills already are creating a stir. The proposals' aim is to enhance productivity of the nation's 380 federally owned research laboratories and to increase industry's access to technologies spawned by these facilities.

At first glance, it does not appear that there is much to debate. The legislation has attracted the support of Senate Majority Leader Robert Dole (R–Kans) and House Minority Leader Robert Michel (R–Ill.), who are sponsoring S. 65 and H.R. 695, respectively. And a similar bill, H.R. 1572, is being sponsored by five members of the House subcommittee on science, research and technology. But industry lobbyists are scrutinizing provisions in the House and Senate bills dealing with royalty assignments.

The sponsors of the three bills want to give federal labs greater authority to enter into joint agreements with private parties and to provide a better reward system for federal inventors. Under the legislative proposals, the laboratories would get 100 percent of all royalties paid by manufacturers for inventions. The revenues could be used to finance new research programs as well as pay inventors' royalty fees and cover related administrative costs.

The proposed amendments to the Stevenson-Wydler Technology Innovation Act of 1980 are targeted at federally operated laboratories like the National Bureau of Standards. It would permit them to transfer technology to industry and to enter into technology development pacts. Except for a handful of Department of Energy facilities, federal labs have lacked adequate legal authority to reassign patent rights. Passage of these provisions would cap a 3-year effort by the Reagan administration to improve industry's access to federal laboratory inventions and facilities.

The most controversial issue is a proposal to reward government inventors with "at least 15 percent" of the royalties on any invention licensed for commercial uses. Industry views it as a potential threat—because it could trigger legislation to require specific compensation for private inventors. "It would set an unfortunate precedent . . . " and have an "anti-innovative impact," contends Richard C. Witte, chief counsel for Procter & Gamble Co., and chairman of the National Association of Manufacturers' task force on intellectual property.

"I don't think that NASA, DOD, or DOE employees should be moonlighting on the job," says Russell C. Drew, the Institute of Electrical and Electronics Engineers' (IEEE) vice president for professional affairs. "We don't want the laboratories mission subverted," says Drew, who fears the laboratories might change their orientation to short-term research that has greater commercial value. "We don't need any more competition from federal laboratories, says Drew, a former NASA scientist. His company, Viking Instruments Corp., manufactures a portable spectrometer under an exclusive license from the National Aeronautics and Space Administration (NASA).

The Reagan Administration has yet to take a position on the legislative proposals so far. In part, this is because agencies such as the NASA and the Department of Defense are at odds with the compensation formula, which the Department of Commerce supports. NASA, which has its own reward system, says the the legislation is not balanced. It fails to consider the need to compensate scientists and inventors with discoveries that don't have products or ideas with commercial applications, they argue.

Furthermore, the legislation leaves it to each of the national laboratories to make its own deals. This decentralized approach can be unwise and in some cases unworkable for some agencies, DOE officials say. The laboratories, they note, frequently need legal and technical guidance from headquarters. In addition, DOE officials say there is a need to be able to reward other people who have contributed to the development of an invention but are not the legal inventors.

Management needs the flexibility to make awards that are commensurate with the value of an invention and to compensate other people, says Representative Edward Zschau (R–Calif.). A sponsor of H.R. 695, he says the legislation must be revised to address these problems.

In the wake of testimony presented 21 and 22 May before the House subcommittee on science, research and technology and the absence of a formal administration position, congressional aides are saying the legislation must be overhauled. Commerce Department officials concede that some modification of existing language to provide administrative flexibility will be required.

To help foster this technology transfer, H.R. 1572 contains a provision that establishes a Federal Laboratory Consortium for Technology Transfer within the National Science Foundation. This organization already exists at NSF but is slated to be shut down in fiscal year 1986, which begins 1 October. In line with the Administration's plan, NSF is officially opposed to reestablishing the consortium within the agency. And there are indications that Congress may does not want the group centered at NSF.

Senate legislation (S. 65) and the bill offered by the minority in the House (H.R. 695) call for empowering the Department of Commerce to monitor and promote technology transfer betweeen the national laboratories and the private sector. However, behind-the-scenes bad blood between some Commerce Department officials and their counterparts in affected federal agencies is fueling opposition to the concept. Just how this will be resolved remains unclear, although subcommittee chairman Doug Walgren (D–Pa.) favors giving Commerce the responsibility.

The speed with which the legislation moves through the House this fall may be affected by the cloud that has been cast over Commerce's role in this legislation. Representative John Dingell (D–Mich.), chairman of the House Energy and Commerce Committee requested the General Accounting Office to examine whether the department had gone too far in pushing legislation and had in fact lobbied.

Dingell raised this issue with Commerce Secretary Malcolm Baldrige in a 22 April letter, stating that "at the very least" it appeared as though there was "a Czar-like approach from Commerce officials toward other agencies and an intention to engage in lobbying activities not authorized by law." Commerce officials deny that their has been any wrongdoing. Nevertheless, Dingell has asked that Commerce's inspector general look into the matter and report on any violations of law.—**MARK CRAWFORD**

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extension of rehabilitation programs; and much more data-gathering. The report notes that federal efforts are now lamentably fragmented: most epidemiological and prevention research is done within the DOT; biomechanics is spread around the National Institutes of Health, and rehabilitation research is mostly conducted at the Veterans Administration. Surprisingly, the committee did not find any trauma research worth mentioning going on in the Department of Defense.

With regard to injury prevention, the report contends that "automatic protection" (such as collapsible steering wheels, or perhaps weaker liquor for drinkers) is the best strategy. Education is not seen as the answer: "neither safety-education campaigns nor driver-education programs have been shown by scientific evaluation to justify the faith and large budgets accorded them." Legal remedies are better, says the report, but laws "tend to be least effective among the very groups that are at highest risk of injury."

The committee decided the CDC was the best place for a Center for Injury Control because much of the work is too applied and too interdisciplinary for the National Institutes of Health. Besides, NIH doesn't want any more institutes. According to neurosurgeon Ayub K. Ommaya, a consultant to the DOT, the transportation subcommittee of the House Appropriations Committee, headed by William Lehman (D–Fla.), is now working on legislation to facilitate the panel's recommendations. Initial funding is to be by the DOT; no budget has yet been determined.—**Constance Holden**

California Gears Up to Bid for the SSC

California's congressional delegation is formally stepping into the fight to land the Superconducting Super Collider (SSC). On 23 May the state's representatives and senators announced the formation of the Superconducting Super Collider California Committee (SSCCC). The State of California already has appropriated $500,000 to the University of California to develop a site proposal for the project, outlays for which could total $6 billion if it is completed in the early 1990's. And aides to the California delegation say the state is preparing to match offers made by competing states.

Meanwhile, the state of Texas has established the Texas National Research Laboratory Commission to lead efforts to capture the high-energy particle accelerator. The state legislature has given the commission eminent domain authority to condemn land where necessary. Texas already has identified six potentially suitable sites, two of which have existing buildings that could be used to house laboratory facilities. Governor Mark White's Office of Economic Development indicates that the state will be able to donate the land. Contrary to previous reports, Texas has not committed, formally or informally, to construct the machine's tunnel. Nor has it agreed to erect any new buildings at this time.

Also vying for the SSC is the state of Illinois, which would like the project tied in to the Fermi National Accelerator Laboratory's existing 1-mile ring. To rally private sector support for locating the machine in Illinois, Governor James R. Thompson has established a private sector task force dubbed "SSC for Illinois, Inc." The state has appropriated $500,000 in 1984 and 1985 for related research and planning. That budget is being hiked to $2.5 million in 1986 to prepare a preliminary site proposal for submission in 1987. For 1987 the state is appropriating $5 million for acquiring rights-of-way for the SSC tunnel, which might have to be placed 300 to 400 feet underground because of uneven terrain and geologic problems, state officials say.

Even though these three states are moving aggressively to win the SSC, the project is not much more than a paper dream. High-ranking Department of Energy officials say the government's support for related research—about $20 million annually—does not mean the SSC will be built. Noting the chilly budgetary climate, one program head says: "Right now we are just trying to keep the idea alive."

State officials are realizing that the SSC may be a long time in coming to fruition. Texas officials are instructing communities that are potential sites to plan for the SSC but not to count on it. Says one Illinois official about the prospect of the project being funded in the next few years: "We know it's pretty bleak."—**Mark Crawford**

NRC Considers Dropping University Reactor Rule

The staff of the Nuclear Regulatory Commission is expected to recommend on 19 June that the agency revise—and perhaps back away from—rules requiring university research reactors to convert to low-enriched uranium fuel. It is uncertain, however, whether the commission will support taking this tack, which would run counter to the NRC's proposed rule-making of a year ago.

Since 1982 the NRC has called for limiting the use of highly enriched uranium in research and test reactors to the maximum extent possible. And in June of 1984 the agency proposed that 31 university and industrial reactors be required to convert to low-enriched fuel. The broadly written rule provided for exempting unique facilities and took a flexible approach toward scheduling conversions.

The purpose of the fuel change was not only to stop bomb-grade material stored at U.S. universities from falling into the hands of terrorists, but to encourage foreign countries to make fuel conversions at their research reactors. Without fuel switches at American facilities, proponents argue, U.S. efforts to halt the spread of nuclear weapons overseas will fail.

But some U.S. reactor operators have opposed the fuel conversion because not all costs would be covered by the government. In some cases, NRC officials say, commercial operations at industrial facilities might be affected. In addition to expense that could be incurred, agency officials say some universities are concerned this action will set off a push to ban reactors from some campuses.

Since the rule-making was first proposed the number of universities with reactors using highly enriched fuel has dropped to about 21 and to five for industry. In total they possess about 300 kilograms of highly enriched fuel, only about 90 kilograms of which are unirradiated or slightly irradiated, NRC officials estimate.

—**Mark Crawford**

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I thank Professor Gregory Breit for suggestions and F. Riewe and L. D. Miller for assistance. Figure 1 is adapted from reference (*28*) and Fig. 5 from reference (*30*) with kind permission of the *Reviews of Modern Physics* and *The Physical Review*. Figures 2, 3, and 6 and portions of this work are taken from an article by the author in *OAR Res. Rev.* 8, No. 4 (1969) with the kind permission of the Office of Aerospace Research Review. Supported by the United States Air Force Office of Scientific Research grant AF-AFOSR-68-1397.

Birth Control after 1984

Carl Djerassi

"It is unmistakingly clear that unless something is done about the population explosion, we will be faced with an unprecedented catastrophe of overcrowding, famines, pestilence and war. . . . If we are to significantly help in the worldwide fight to curb the population explosion, there must be developed a simple and safe method that can be made available to populations on a massive scale."

These are the words of the U.S. Senate's most vocal critic (*1*) of oral contraceptives, and it behooves us to consider what some of the future contraceptive methods might be and especially what it might take, in terms of time and money, to convert them into reality. There are many publications on this subject, but none seems to have concerned itself with the logistic problems associated with the development of a new contraceptive agent. In that connection, it is instructive to note that, in Platt's list (*2*) of world crisis problems, only total nuclear or chemical-biological warfare receives higher ratings than the problems arising from the world's burgeoning population, and [illegible] of the four top priority problems, [illegible] control requires [illegible] legislation.

The surprisingly rapid acceptance during the last decade of intrauterine devices (IUD's) and of steroid oral contraceptives in many developing and developed countries is principally due to the fact that their use separates, for the first time, contraception from copulation, and it is clear that effective birth control methods of the future must exhibit this same property. A long list of new approaches to contraception could be developed from a recent World Health Organization report (*3*), but for the purposes of this article—the outlining of logistic problems, the determination of time and cost figures, and, finally, recommendations for implementation—I have selected only three topics.

1) A new female contraceptive (*4*), consisting of a "once-a-month" pill with abortifacient or luteolytic (menses-inducing) properties. I have selected such a method because it is scientifically feasible, it should lend itself to use in both developed and developing countries, and it addresses itself to the critically important subject of abortion. I also make some mention of prostaglandins in that connection.

2) A male contraceptive pill.

3) A draconian agent, such as an additive to drinking water. I included this approach, not to justify the Orwellian overtones of this article's title, but rather to place into realistic perspective the problems of developing such an agent, which is associated with increasing frequency as the final solution if voluntary methods should fail.

Specifically excluded from my list are sterilization, for discussion of which I lack the needed technical familiarity, and mechanical devices. My reason for excluding mechanical devices, such as IUD's, which, unlike condoms or diaphragms, fall within the definition of "contraception divorced from coitus" is as follows: their rapid introduction into public use during the 1960's is due largely to the fact that, until now, clinical research with IUD's has fallen outside the scope of government regulatory agencies such as the Food and Drug Administration (FDA). However, it is highly likely that public (*5*) as well as scientific (*6*) pressure on government regulatory bodies will require that such devices also be brought within the scope of their control and that clinical use of these devices be preceded by the same type of stringent testing that is demanded for contraceptive drugs. I emphasize these arguments only to point out that the cost and time estimates made by me later in this article in connection with new chemical contraceptive agents probably will also apply to new devices of the IUD type.

All the advances in fertility control considered by the World Health Organization group (*3*) are based in one way or another on chemical approaches. As I have pointed out elsewhere (*7*), this type of research on fertility control is exceedingly complicated, in both its preclinical and clinical phases; the required manpower and financial resources are available only in the technologically most advanced countries. I emphasized (*7*) the fact that the new birth control agents of the future, even though they may be used predominantly in the developing countries, will almost certainly be generated only in countries of North America or Europe. They will, therefore, be subject to the governmental regulatory codes of [illegible]

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Table 1. Food and Drug Administration requirements for animal toxicological studies for contraceptives, estrogens, and progestogens (9).

Clinical study	Requirements
IND phase I (limited to a few subjects for up to 10 days' administration)	90-day studies in rats, dogs, and monkeys.
IND phase II (approximately 50 subjects for three menstrual cycles)	1-year studies in rats, dogs, and monkeys.
IND phase III (clinical trial)	2-year studies in rats, dogs, and monkeys. Initiation of 7-year studies in dogs and 10-year studies in monkeys prior to start of phase III. Reproduction and teratological studies in two species.
NDA (New Drug Application)	No further requirements, but must include up-to-date progress reports on long-term studies in dogs and monkeys.

before constructing "critical path maps" (CPM) for some new contraceptive agents (Figs. 1 and 2), I will review briefly the conditions under which such new contraceptive agents would probably have to be developed. As the FDA has such a crucial de facto power in many foreign countries, it is realistic to construct most CPM charts on the basis of the American milieu, where most research on human fertility control is being conducted at present.

FDA Requirements and Animal Toxicity Studies

Irrespective of the sponsor (whether industrial, governmental, or academic), no new drug can lawfully be administered to humans in the United States without an IND (Investigative New Drug) exemption issued by the FDA. The application for such an exemption must outline the clinical protocols to be followed, and for all practical purposes there exists no appeal to FDA decisions during this experimental phase. Appropriately, animal toxicity data must first be presented, and, for drugs outside the field of contraceptives, the FDA's requirements (*8*) in this regard are reasonable; in particular, the choice of the experimental animal is left to the discretion of the investigator.

However, different FDA requirements (*9*) exist for contraceptives (whether steroids or nonsteroids), and these must be taken into consideration in any time and cost estimate for new fertility control agents. These requirements are listed in Table 1. It should be noted that, in contrast to the requirements for noncontraceptive drugs, where the animal species is not specified (*8*), contraceptives must be tested in rats, dogs, and monkeys (*9*).

Nobody can dispute the wisdom of the requirement for data on toxicity in animals before a drug is administered to humans, even in short-term clinical experiments involving only a few individuals. Nevertheless, stipulation of the animal species to be used is extremely unwise. After all, the sole reason for selecting any animal is to provide a model for extrapolation to the human. The unfortunate choice by the FDA of the dog as one of the required species for testing oral contraceptives has been discussed elsewhere (*7*); it has already resulted in the suspension of clinical experimentation with three contraceptive agents, the most recent (January 1970) being the chlormadinone acetate "mini-pill." Indeed even the simple requirement for data on toxicity in the "monkey" may be close to meaningless in the area of reproductive physiology unless careful attention is given to the choice of the monkey species.

In order to gain as much knowledge as possible from animal studies, a species should be selected which most resembles man in its metabolic handling of the drug in question. Table 2 summarizes data accumulated recently (*10*) on excretion pattern and plasma half-life, in man and in seven animal species, for a new experimental (nonsteroid) drug. These animal studies with radioactive material (note this requirement in Figs. 1 and 2) were conducted in order to select the best animal model for man, who excretes 94 percent of the drug in the urine, and in whom the plasma half-life is 14 hours. Inspection of Table 2 demonstrates that, *for this particular drug*, the minipig is at least as good an animal model as the rhesus monkey and, even more strikingly, that the differences between the rhesus and the capuchin monkey are almost greater than the differences for any other two animal species of the study.

Another example can be cited, from the extensive work of Seal and Doe (*11*), which demonstrates the extreme variability among various monkey species of the corticosteroid-binding globulin (CBG) in mammalian pregnancy. It is obvious that if Gertrude Stein had said "a monkey is a monkey is a monkey" she would have been dead wrong from a metabolic standpoint.

My reason for going into such detail about toxicity requirements and metabolic differences in various animal spe-

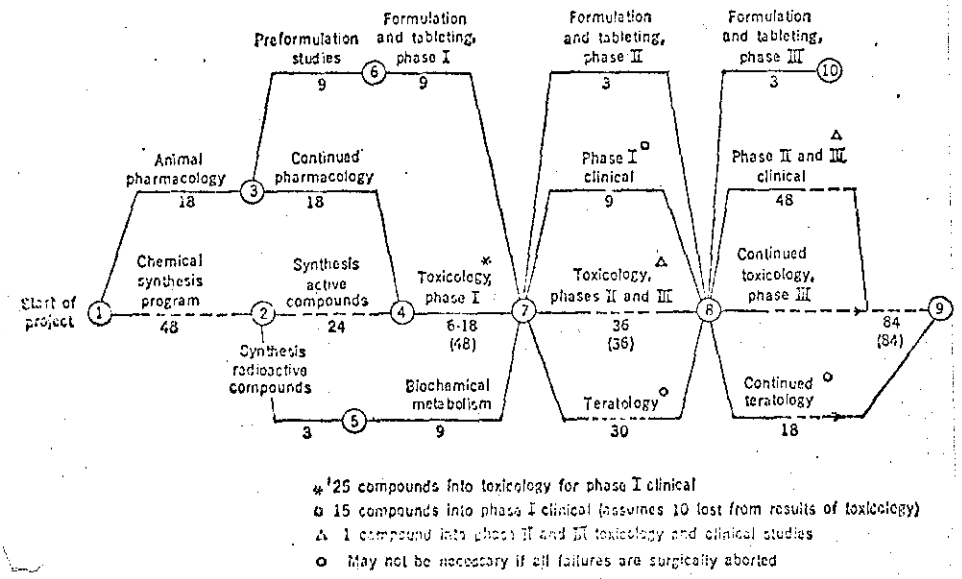


Fig. 1. Basic critical path map for a luteolytic or abortifacient agent. The circled numbers are step numbers; the numbers below the line are time periods, in months. Thus, for example, ①—(18)—③ means that the period from the beginning of step 1 to the beginning of step 3 is 18 months. Numbers in parentheses indicate time periods, in months, when the usual FDA toxicological-study requirements for contraceptives are a possible alternative.

...ies is to illustrate a crucial point on which most future fertility control research rests. Unless all research is to be performed directly on man—a suggestion which can hardly be entertained in case of completely new agents—much more work needs to be done in identifying useful animal models which have some predictive bearing on man's biological response to a given agent. Such work will require major efforts on the part of investigators, major financial inputs (notably into primate facilities), and, most importantly, some relaxing of the present FDA requirement (*9*) for rat, dog, and monkey. Although it is likely that the higher apes are the best models for human reproductive physiological behavior, insufficient biochemical work has been done to substantiate this claim, and the funding for such work or for the requisite primate facilities is not included in Tables 3 and 4. As implied in the preceding discussion, the smaller monkeys frequently bear little resemblance to humans in their metabolic response, but they are used almost exclusively because of ease of handling, availability, and lower cost. In addition to the price differential between monkeys and apes (for example, $75 for a rhesus monkey compared with $200 for a baboon, $1000 for a chimpanzee, and $2000 to $5000 for a gorilla), one must take into account the much higher handling and maintenance costs for apes as well as their limited availability. Indeed, unless extensive breeding facilities are established, such exploitation of the higher apes may lead to their extinction (*12*). It should be noted that all the cost estimates of Tables 3 and 4 are based on the use of rhesus monkeys and that major upward revisions would have to be made if apes were employed.

Table 2. Data on excretion patterns and plasma half-life for an experimental drug (*10*).

Species	Excretion		Plasma half-life (hours)
	Urine (%)	Feces (%)	
Man	94	1–2	14
Rat	90	2	4–6
Guinea pig	90	5	9
Dog	29	50	23–35
Rhesus monkey*	90	2	2–3
Capuchin monkey	45	54	20
Stump-tail monkey*	40	60	1
Mini-pig	86	1–2	4–7

* These two species belong to the same genus (*Macaca*).

Role of the Pharmaceutical Industry

Except for certain biologicals (special vaccines), essentially all modern prescription drugs were developed by pharmaceutical companies. I know of no case in which *all of the work* (chemistry, biology, toxicology, formulation, analytical studies, and clinical studies through phase III) leading to governmental approval of a drug (for example, by the FDA in the United States) was performed by a government laboratory, a medical school, or a nonprofit research institute. This does not mean that many of the basic discoveries leading to the development of a drug ultimately used by the public are not discovered in such nonindustrial laboratories, or that certain important steps (for example, much of the clinical work) are not performed outside of industry. Nevertheless, it is a simple fact that, in modern industrial nations, pharmaceutical firms play an indispensable role in the development of any drug. Socialist countries have, of course, developed counterparts to the pharmaceutical industry, but so far these counterparts have had very little impact on drug innovation.

The public and legislators are frequently unaware of this key function of the creative elements of the pharmaceutical industry. This function is not directly related to the marketing function of these firms (indeed, some pharmaceutical companies do no research but simply acquire their products from other companies). Rather it speaks for their *unique ability* to organize, stimulate, and finance multidisciplinary research covering the entire gamut of the scientific disciplines required (see, for instance, Fig. 1 and Table 3) in converting a laboratory discovery into a practical drug. In addition, the organizational efforts involved (*13*) in preparing a complete New Drug Application (NDA) in the United States are completely outside the capabilities of nonprofit institutions and are not undertaken by government agencies, although the latter could presumably mobilize the requisite manpower and funds for such purposes.

At present, all of the expenses associated with the development of a new prescription drug are borne by private industry and eventually recovered from sales. The ever-increasing cost of drug development is certainly responsible in part for the progressively decreasing number of new drugs introduced in the United States. For the time being the present system still seems to work, even though major improvements will have to be instituted before long. All of the oral contraceptive agents now being used were developed under such circumstances, but this situation is unlikely to hold for many contraceptive agents developed in the future.

Some of the special requirements that have been imposed in the case of drugs used for fertility control are understandable and justified; similar requirements would undoubtedly be imposed in the case of any other drug

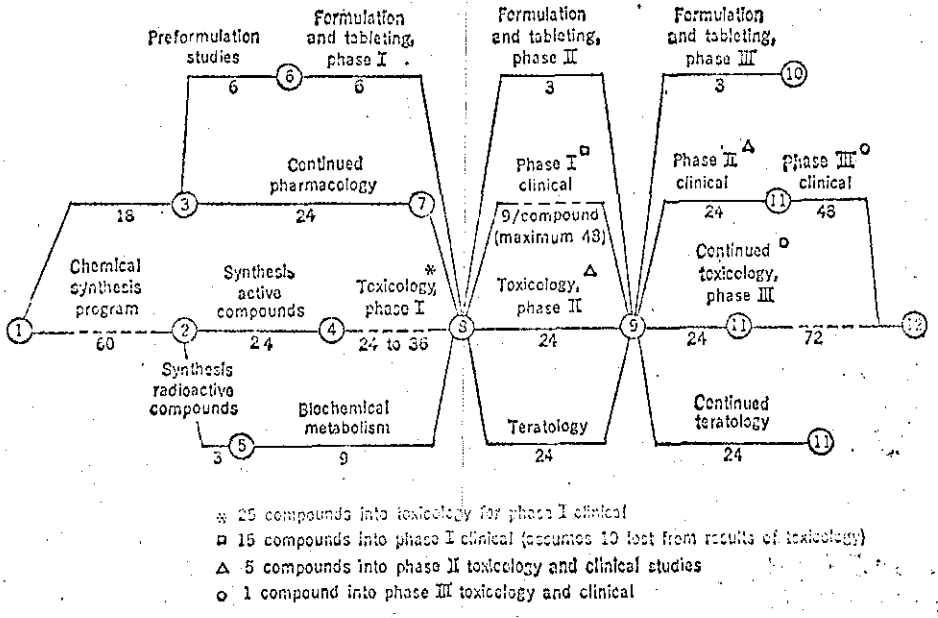


Fig. 2. Critical path map for development of a male antifertility agent (see legend to Fig. 1).

(for example, preventive medication in atherosclerosis) administered for long periods (usually years) to normal populations. These requirements are a response to our gradually increasing knowledge of human reproductive physiology in general, our accumulated experience with oral contraceptives in particular, and especially the surprisingly rapid acceptance by so many women of these new birth control agents.

Unfortunately, neither the public nor the government is facing realistically the following facts. The costs of developing such agents have escalated to such an extent that it is unlikely that the traditional course of drug development will lead rapidly, or even eventually, to the creation of fundamentally new contraceptive agents. If the present climate and requirements had prevailed in 1955, oral contraceptive steroids would still be a laboratory curiosity in 1970. Yet it is obvious that toxicity and testing requirements will become more stringent and time-consuming, not less

Table 3. Cost and time data for the development of a luteolytic or abortifacient agent.

Step Identity No.	Function	Duration of function (months)	Cost (including overhead) (thousands of dollars)
1	Start of project.		
1 to 2	Chemical synthesis of compounds in 0.5 to 1 g amounts for biological screening program (four chemists at $45,000 per chemist per year).	48	720
1 to 3	Development of biological models to test luteolytic or abortifacient compounds. Use of synthesized compounds in test systems in rodents and monkeys to determine mechanism of action.	18	200
2 to 4	Synthesis of larger amounts of active compounds selected in biological test systems to be used in preformulation, formulation, and phase I toxicological and clinical studies.	24	200
2 to 5	Synthesis of radioactive material of the most active compound in biological tests for use in biochemical metabolism.	3	10
3 to 4	Continued biological studies on mechanism of action of active compounds.	18	150
3 to 6	In vitro and in vivo studies of stability, solubility, and absorption of active compounds to assist formulation and tableting.	9	100*
4 to 7	Toxicological studies for phase I clinical studies. It is assumed that, since only short-term therapy is envisaged, FDA will not require toxicological studies such as are required for current oral contraceptives. It will be sufficient to study LD_{50} in 60 rats and 16 dogs per compound, using 25 compounds; 15 compounds are expected to be found satisfactory for phase I clinical studies.	6–18	125
	If usual phase I contraceptive toxicological studies are required (see Table 1), the following numbers of animals will be needed for 25 compounds: 12,000 rats, 2,400 rabbits, 800 dogs, and 5,400 primates for LD_{50}, 90-day toxicological, teratological, and abortifacient‡ studies.	(48)†	(14,000)†
5 to 7	Formulation and tableting for phase I clinical studies.	9	100*
5 to 7	Metabolic studies in rodent or primate and human with synthetic radioactive material already prepared. Both oral and intravenous administration may be studied.	9	25
7 to 8	Formulation and tableting for phase II clinical studies.	3	50*
7 to 8 to 9	Toxicological and teratological studies for phase II and phase III clinical studies. Although FDA may require very limited studies for clinical phase I because of short-term dosing, it has been assumed that toxicological studies required for later clinical work will be as stringent as in current oral contraceptive development, involving long-term teratological and repetitive-abortion studies of five compounds for 1 year, in 160 rats, 32 dogs, and 32 primates (phase II), and, for the best of the five compounds, 2-year studies in 240 rats, 7-year studies in 64 dogs, and 10-year studies in 80 primates (phase III).	36	2,700
		84 to completion of all toxicology§	400
	If usual phase II contraceptive toxicological studies are required, the following numbers of animals will be required for study of one compound: 800 rats, 160 dogs, 160 primates, for 1 year.	(36)	(315)
	If usual phase III contraceptive toxicological studies are required, the following numbers of animals are required for study of one compound: 240 rats for 2 years, 64 dogs for 7 years, and 80 primates for 10 years.	(84)§	(400)
7 to 8	Phase I clinical studies. It is assumed that 15 compounds will have proved satisfactory in the toxicological studies. A single dose will be administered to a small number of women to cause abortion in the 1st or 2nd month of pregnancy. The best compound will be selected for phase II and phase III clinical studies. With a one-dose level and costs of $660 per woman per menstrual cycle, for 3-cycle studies the total cost for 15 compounds is $300,000. Therefore, costs for a two-dose level are:	9	600
			600
9 to 10	Formulation, tableting, and cost of material for phase III clinical studies, including cost of material for long-term toxicity.	3	300*
8 to 9	Phase II and phase III clinical studies of the best compound will be combined. A requirement of 1,000 women studied for 10,000 cycles is assumed.	48	500
Total time and cost to time of NDA filing		120 to 204§	6,780
Preparation of NDA and FDA master file		6	50
Grand total (toxicity studies of Table 1 not included)		126 to 210‖	6,830
Grand total (toxicity studies of Table 1 included)		210	18,330

* Costs for formulation, stability, and analytical work (including usual overhead) can be calculated in general on the basis of $150,000 for any new drug in a conventional dosage form or $270,000 for a new drug in a novel dosage form (for example, Silastic implant). The costs given here were calculated on this basis. Allowance should be made for costs of some work on rejected compounds. † When the usual FDA toxicological-study requirements for contraceptives (see Table 1) are given as a possible alternative, the duration of the study and the associated extra cost are given in parentheses. ‡ Drugs found to cause abortion in generations F_1, F_2, and F_3. § Two-year studies in rats, dogs, and primates are necessary for NDA, but ongoing 7-year study in dogs and 10-year study in monkeys are required (see Table 1). ‖ The development time is calculated, not by summing all times in the time breakdown, but from the CPM chart, following the longest course of development.

so; other criteria (such as tests of potential mutagenesis, more sophisticated metabolic studies, and so on) will be added as logical consequences of accumulated new knowledge. Costs escalate enormously. Therefore, as a foundation for projections, we need to review the origin and magnitude of present expenditures on contraceptive research and development.

Recent research expenditures for development of new contraceptive agents. From the late 1950's until the early 1960's the U.S. Government spent very little on the development of new birth control agents. The overwhelming portion of the cost of developing the oral contraceptives was met by three pharmaceutical companies. No published figures are available for these initial development costs. In any event, retrospective calculations are useless in the light of present-day requirements and knowledge.

A more realistic starting point is the second half of the last decade, in which the situation started to approximate present-day circumstances. To my knowledge, the present-day expenditures of the pharmaceutical industry for research in the area of reproductive physiology have never been collated. An incomplete personal survey among five pharmaceutical companies (Lilly, Ortho, Searle, Syntex, and Upjohn) has shown that their cumulative 5-year expenditure (1965–1969) in this field amounted to $68 million. My survey did not include all of the major American pharmaceutical companies active in this field, nor did it cover any European firms; thus it is likely that the industry contribution during those 5 years probably exceeded $100 million. This is an enormous figure by any standards. It is unrealistic to expect that larger sums or, in fact, even the same sums will be spent by this private sector in the future when the eventual recovery of such expenditures (see, for instance, Tables 3 and 4) becomes more and more distant and problematical. Furthermore, this 1965–1969 expenditure relates entirely to scientific work on birth control, whereas a substantial portion of government funds is devoted to ancillary activities (sociological and demographic studies).

The most encouraging recent initiative of the U.S. Government has been the establishment of a Center for Population Research as part of the National Institute of Child Health and Human Development. However, its present quantitative limitation must be recognized immediately. According to the director of the center, P. A. Corfman (*14*), of the total 1970 budget of $15.6 million, specific research projects account for $12.9 million, with $9 million of this going for the development of contraceptives. The only other significant government source of funds is the Agency for International Development, whose budget (*15*) for the development of new methods of fertility regulation was negligible (about $100,000 in 1968) until 1969, when approximately $5.9 million was obligated for such purposes; the estimated figure for fiscal 1970 is $6.5 million.

Among private groups working in the area of fertility research, two of the most important are the Population Council, with an annual research budget of about $2 million, and the Ford Foundation, which has been spending $4.5 million to $7 million annually since 1966 in support of research and training in reproductive biology (*16*). An unstated proportion of this amount is allocable to research directed specifically toward the development of new contraceptive agents.

These cumulative expenditures are a reference point in evaluating the estimated research costs given below and the likelihood that the required funds will, in fact, become available.

Future Birth Control Developments in the Female

All of the contraceptive methods that have been introduced during the past 20 years have been designed for the female. The reason is not just that she is more receptive to new approaches, presumably since unwanted pregnancies affect her much more directly than they affect the male, but rather that our knowledge of the female reproductive cycle provides more hints about rational approaches to contraception than our knowledge of the male process does. Furthermore, it is possible to interfere with the female cycle at numerous stages, starting with ovulation and ending with embryogenesis. Rather than scan our overall knowledge of such approaches [discussion of which can be found throughout the scientific literature (*17*)], I have selected one such method in order to subject it to a type of critical systems analysis. Such a detailed presentation for one agent, which so far has not appeared anywhere in the literature, should be very useful in research and budget planning for other contraceptive methods as well. Most importantly, such an analysis will draw attention to the weak points in our present system of developing contraceptive drugs and, in fact, other drugs as well. The set of recommendations listed later in this article is largely an outcome of the analysis. As an important example of future contraceptive methodology in the female, I have chosen a "once-a-month" pill with luteolytic or abortifacient properties, or both, since such an agent has at least four advantages over agents now being used.

1) Administration of one pill a month is clearly more convenient than daily administration of pills. This is true both for major fertility control programs in developing countries and for highly motivated individuals in advanced countries.

2) Periodic short-term administration of a drug may be expected to give rise to fewer long-term side effects, primarily because the agent is intended to act more specifically on a well-defined biological process.

3) Since the agent will be effective in incapacitating the corpus luteum irrespective of whether fertilization has or has not occurred, it does not matter whether the woman is pregnant or not.

4) Ideally, the agent might be active any time during the first 8 weeks after fertilization, so that it could also act as an abortifacient. It could then be taken bimonthly. In case of drug failure, another agent (for example, prostaglandins?) should be available for subsequent chemical abortion, or else surgical termination of the pregnancy should be available as a backup measure.

A critical path map for the development of such an agent is shown in Fig. 1, and a more detailed description of the individual steps, together with estimated costs, is given in Table 3. Three major additional comments are required for a full evaluation of this chart. The first refers to the teratology studies, which are extremely important in any agent affecting embryonic development. The unsupported assumption is made that the FDA would permit phase I clinical studies without previous teratology studies in animals. Irrespective of the correctness of this an assumption, such studies and the subsequent phase II and phase III clinical research can be performed only in a location where, in case the method fails, surgical abortion can be employed. Indeed, the work leading to

eventual determination of the clinically effective dose will require progressive lowering of the dose until a level is reached in which failure is observed. From an investigative standpoint, it would be desirable if human pregnancies resulting from such drug failures were permitted to proceed beyond the 14th week before surgical abortion was undertaken, so that the fetus could be examined for evidence of malformation. This would be a difficult requirement insofar as availability and cooperation of patients was concerned. In the absence of such cooperation one would have to depend on monkey data, which are obviously less informative.

The second comment on Fig. 1 and Table 3 pertains to the time estimates. These are ideal figures, and the aggregate of about 126 to 210 months (Table 3, next-to-last row) may not be realizable, because it involves almost perfect coordination and even telescoping of various steps in the CPM scheme. For instance, the preliminary toxicological studies (Fig. 1, steps 4→7) on 25 compounds will involve rejection of several compounds because of serious toxicity, as well as rejection based on phase I clinical data (steps 7→8). The estimate of 6 to 18 months for the time required for the initial toxicological studies leading to the selection of the final compound is, therefore, very optimistic. In any event, it is this time analysis which offers the first justification for the title of this article, since the middle of the 1980's is already an optimistic target date even when one ignores the time required for the new agent to receive the final stamp of government approval (under current regulations) and be disseminated to the public.

The third comment refers to the cost estimate. For reasons given in Table 3, there are major uncertainties with respect to the ultimate cost of toxicologic study, since this depends so much on factors such as the choice and cost of the animals, as well as on the frequently changing government regulations. A further and greater uncertainty is the estimate for phase III clinical studies (Fig. 1, steps 8→9). Much larger numbers of menstrual cycles may be required in response to demands (*18*) that virtually all actual and potential side effects of such drugs should be known prior to government approval for marketing. This may be the single greatest hurdle and uncertainty in any planning of new contraceptive developments; for this reason I make a very special recommendation later in this article. Irrespective of the final cost figure ($7 million to $18 million in Table 3), it must be emphasized that allocation of such a sum by a government or private agency in the form of grants to various nonindustrial laboratories would be insufficient to accomplish the desired goal of producing an agent ready for wide public use. The reason for this statement is that the cost and time estimates in Fig. 1 and Table 3 are based on the availability in

Table 4. Cost and time data for the development of a male antifertility agent.*

Step identity No.	Function	Duration of function (months)	Cost (including overhead) (thousands of dollars)
1	Start of project.		
1 to 2	Chemical synthesis of compounds for biological screening (four chemists at $45,000 per chemist per year).	60	900
1 to 3	Use of compounds synthesized, in modified Jackson bioassay, to discover compounds affecting fertilizing capacity of sperm stored in epididymis, followed by studies in primates.	18	150
2 to 4	Synthesis of compounds found active (the number is assumed to be 25) in bioassay screen.	24	225
2 to 5	Radioactive labeling of best compound from steps 1 to 3.	3	10
3 to 6 to 8	Preformulation, formulation, and tableting for phase I.	12	200
3 to 7	Continued animal pharmacological studies.	24	200
5 to 8	Studies of biochemical metabolism of the labeled compound prepared in steps 2 to 5.	9	25
4 to 8	Toxicological studies (in an assumed 25 compounds) for phase I clinical studies: these include LD_{50}, 90-day toxicity, and teratological studies in 4,000 rats, 1,500 rabbits, 800 dogs, and 500 primates.	24–36	1,700
8 to 9	Formulation and tableting for phase II clinical studies.	3	50
8 to 9	Phase I clinical studies with 15 compounds. The study for each compound will involve groups of five males and three widely spaced dose intervals for 6 months. Evaluation of sperm mobility, fertilizing capacity, and effects on spermatogenesis will be required.	9/compound (maximums, 48)	450
8 to 9	Toxicological and teratological studies for phase II clinical studies (in an assumed five compounds): 1-year toxicity studies in 800 rats, 160 dogs, and 160 primates, and continued teratological studies.	24	315
9 to 10	Formulation and tableting for phase III studies, including cost of material for steps 9 to 12.	3	300
9 to 11	Phase II clinical studies. Expansion of phase I studies to 50 to 100 men to obtain quantitative dose requirements for five compounds.	24	500
9 to 11 to 12	Continued toxicological studies for phase III clinical studies with one compound. These include 2-year studies in 240 rats, 7-year studies in 64 dogs, 10-year studies in 20 primates, and continued teratological studies with one compound.	96	400
9 to 12	Phase III clinical studies. Increased numbers of men in trial (possibly 1,000) with studies of mechanism of action, of return of fertility upon cessation of dosing, and of any fathered offspring from accidental pregnancies.	48	800
Total time and cost to time of NDA filing		144 to 240	6,225
Preparation of NDA and FDA master file		6	60
Grand total		150 to 246	6,285

* See footnotes to Table 3.

...ne organization (that is, research divisions of large pharmaceutical companies) of all the manpower, facilities, and logistic support required for the type of activity and schedule outlined in the CPM chart. If these facilities have to be created de novo and the required infrastructure had to be supported exclusively from funds allocated to such a project, then the final cost would have to be multiplied several times. Finally, whatever the overall cost estimate, it should probably be at least doubled because, as has already happened in the case of oral contraceptives of the types now being used, an agent may be rejected at a late stage of the phase III clinical trial.

Prostaglandins. The importance of abortion as a means of population control has been emphasized many times (*19, 20*). In areas of the world (Japan and eastern Europe) where population growth was reduced dramatically within a short period, this was done principally through surgical abortions. Clearly, the availability of a chemical (that is, nonsurgical) abortifacient would be highly desirable. Therefore, aside from the hypothetical abortifacient agent described in Fig. 1 and Table 3, which, it appears from present leads may well turn out to be a steroid, some mention of the prostaglandins (PG) is warranted, especially since they are chemically distinct from the steroids and offer another illustration of the long time sequences involved in birth control research.

The isolation of the prostaglandins and elucidation of their chemical structure were effected by Bergström and his collaborators (*21*) in Sweden in the 1950's. By 1957 one pharmaceutical firm, the Upjohn Company, had already started a program in this field; after 13 years, the cost has reached multimillion-dollar proportions. However, no drug containing any of the prostaglandins has yet been introduced into medical practice. Luteolytic effects of $PGF_{2\alpha}$ in the pregnant rhesus monkey have been reported (*22*), and two European clinical studies (*23, 24*) have appeared on the use of $PGF_{2\alpha}$ and PGE_2 as abortifacients after intravenous infusions in women at various stages of pregnancy. The degree of success ranged from 14 abortions in 14 patients to 3 abortions in 11 patients; the differences were probably associated with differences in infusion rates and concentrations. The side effects were generally diarrhea and vomiting (*25*). In spite of extensive press coverage and optimistic headlines (*26*) accompanying these initial clinical trials, it must be recognized that these are only preliminary leads and that many problems requiring time-consuming work must be overcome before the prostaglandins can be considered practical candidates as abortifacients. I shall cite a few of the more obvious ones.

1) The prostaglandins act on almost all body systems (*21*), and, while their use as abortifacients will involve only short-term administration, extensive clinical work will be required to determine possible side effects in a representative group of women.

2) A great deal of research has been performed in the past few years, in academic and industrial laboratories, on synthesis of the various prostaglandins. While various successful approaches have been reported, none has as yet lent itself to large-scale synthesis, and the availability of adequate amounts of various prostaglandins is still a bottleneck.

3) The requirement for intravenous infusion limits use of the prostaglandins to hospitalized patients. Such a drug would still represent an important advance in developed countries, where surgical abortions are carried out in hospitals, but alternative means of administration must be developed if one of the prostaglandins is to be used in the manner and on the scale envisaged for the type of agent described in Fig. 1. Intramuscular administration (*24*) is a possibility, but major emphasis in future research must be placed on development of an effective oral form. Until now, there has been no success in producing biological activity after oral administration with any of the naturally occurring prostaglandins, and work with synthetic congeners or special formulations would be required. This would put such compounds only at the beginning of the CPM chart of Fig. 1, and thus subject them to most of the time and cost estimates outlined in Table 3.

4) If intramuscular administration and, especially, oral administration of prostaglandins become realities, then outpatient use will presumably be their widest application. This in turn implies the definite possibility of incomplete follow-up and raises the specter of potential teratogenesis if abortion should be unsuccessful. Irrespective of possible FDA requirements, teratological studies in primates must be performed at some stage.

Male Contraceptive Agent

The condom and withdrawal prior to ejaculation are the only practical contraceptive measures that are currently available to the male. As has been pointed out by the World Health Organization scientific group (*3*), "an agent that could safely and effectively inhibit fertility in the male, without risk of interfering with spermatogenesis and libido, would find practical application in fertility regulation." The report then proceeds with a long list and associated bibliography of chemical agents that have been shown to have some effect on the fertility of male animals, notably rats, and concludes, "none of the chemical agents is suitable for use in man, owing to known or potential toxicity. Similarly, immunological processes present hazards when used in man, and they suffer from a lack of specificity. *Consequently, no systemic method of fertility control in man is available at present*" (italics mine).

The CPM chart (Fig. 2) and accompanying Table 4, therefore, contain a longer estimate than those of Fig. 1 and Table 3 for the time needed for discovery of suitable leads that may give rise to compounds warranting clinical investigation. It would be highly desirable if several programs (each of them costing about $3 million) of the type outlined in Fig. 2 under steps $1 \rightarrow 2 \rightarrow 4 \rightarrow 8$ and $1 \rightarrow 3 \rightarrow 7$ were instituted in several laboratories at the same time in order to increase the chances that a useful agent might emanate from such research. Nothing will stimulate future research on a practical male contraceptive agent more than the discovery of viable and significant chemical leads, but, even in that event, 1984 appears to be an exceedingly optimistic target date for development of a male contraceptive pill ready for use by the public.

Three other difficulties associated with the development of a chemical contraceptive drug in the male must be recognized. First, our basic knowledge of the reproductive biology of the male is even less advanced than our knowledge of that of the female, and a great deal of fundamental work needs to be done, much of it probably in subhuman primates.

Second, the actual clinical work has so far not drawn the attention of planners in the birth control field. The human spermatogenic cycle, from spermatogonium to ejaculate, lasts approxi-

mately 12 weeks. It is likely that testing, including preliminary treatment control and posttreatment recovery observations, might last up to 6 months, depending on the point where the drug in questions attacks this sequence. Pilot testing could presumably be carried out in groups of five males, at each of three widely spaced dose levels for each agent (Fig. 2, 8 → 9). Observations should combine evaluation of the effect on spermatogenesis or sperm motility, or both, with observations of organ toxicity and other side effects. At present there appear to be available, in the entire United States, facilities for evaluating only two drugs at a time. The complications would be even greater in phase II and phase III clinical studies. Women can easily be assembled for clinical studies through their association with Planned Parenthood clinics and individual obstetricians or gynecologists; there exists no simple mechanism for assembling similar groups of males for clinical experimentation. The prisons and armed forces are the only convenient sources, and results would have to be based largely on examination of masturbation sperm samples rather than on an evaluation of fertility control in an average population.

This leads to the third difficulty—namely, the male's generally lesser interest in, and greater reservations about, procedures that are aimed at decreasing his fertility. If the agent were to be administered orally, men would probably be even less reliable about taking a tablet regularly than women have proved to be, and efficacy could probably be determined on a large scale only through long-term studies of married couples.

The single greatest objection to the oral contraceptives now being used is to the essentially continuous administration of a potent agent to fertile women for many years. Clearly the same objection would be raised in the case of a male contraceptive pill if it had to be taken day after day by fertile males for many years. However, if both a female and a male contraceptive pill were available, then the two partners could alternate (say every 3 to 6 months) in their use of a pill and thus avoid continued exposure to one [illegible] likely to work only in educationally advanced and highly motivated groups, and it is probable that the female partner would bear the principal burden of [illegible].

"Orwellian" Approaches

Some laymen, legislators, and scientists concerned with the economic and environmental effects of rapid population increase have started to imply that drastic government-imposed birth control procedures may have to be introduced during the next decade if voluntary use of conventional methods fails to stem the tide. I would like to use the adjective "Orwellian" for such externally imposed extensions of voluntary fertility control, which Berelson (*27*) has reviewed extensively, together with incentive programs, tax benefits, and many other proposals. Clearly the most all-encompassing and frightening concept is the first entry in Berelson's list of involuntary fertility control methods—addition of a temporary sterilant to water or staple foods. I would like to consider briefly some of the practical problems associated with the development of such an "Orwellian" agent, which reduce the concept to an absurdity.

1) The substance would have to be active in either the male or the female, but only in their reproductive years, and active over an enormous dose range, since food and water intake of, say, a 20-pound child and a 200-pound adult are very different. It would have to be tasteless. It must be specific for man.

2) If added to food, the substance would have to be incorporated by the supplier rather than by the consumer in order to ensure universal administration. Even then, a dissenter could simply eliminate a given food from his diet and thus escape the contraceptive effects, unless it were a food that is universally required (for example, salt). In any event, the contraceptive additive would have to be stable during processing (baking, heating, sterilization), and during exposure to oxidants or light in the course of packaging and shipping.

3) Since everyone must drink water, this would seem to be the better vehicle for the contraceptive agent, but even here there would be a difficulty; incorporation would be feasible only when water was supplied through a central system, not obtained from wells. This limitation alone would probably make the method unworkable for at least half the world's population. However, regardless of the method of incorporation into the water, the contraceptive agent would have to display chemical stability on coming in contact with pipes and other metal objects; stability on exposure to light and oxidants in a holding tank or reservoir; stability on exposure to extreme temperatures during cooking or refrigeration (that is, lack of precipitation from solution); no chemical interaction with minerals in the water, and with commonly consumed foodstuffs during cooking; and no properties that would cause problems of over- or under-concentration during food processing, as in the preparation of frozen juice or soup concentrates. Even if these virtually insuperable obstacles could be overcome, let us not forget the tremendous public protests evoked by proposals to add even as simple an agent as fluoride to municipal water supplies.

4) The question of "side effects," which has gained so much notoriety in the context of the recent "Nelson hearings" on oral contraceptives in the U.S. Senate, is insoluble. No drug is devoid of side effects and, in this particular instance, the side effects of the agent would have to be minimal not only in the sex and age group in which it was supposed to be active but also in all other age groups and in the opposite sex. In contrast to any drug now used by humans, which generally is simply a contaminant of the person's microecology, the "Orwellian" contraceptive added to food or water would be a general environmental pollutant. It would have to be considered a pesticide, albeit one that is directed primarily at humans. It is exceedingly unlikely that such a compound active in man would be ineffective in at least some other animal species. In fact, since initial biological screening for such an agent would be carried out not in man but in animals, *an agent truly specific for man would completely escape detection.*

5) If such an "Orwellian" contraceptive were completely effective, then its effects would have to be reversible through the administration, presumably by license, of a second agent. The likelihood of discovering such an agent is slight, yet its availability is an absolute prerequisite for employment of the sterility agent. The other alternative would be to develop a contraceptive which significantly reduced but did not abolish fertility, the level of which then setting the birth rate. Such a property might make such an agent acceptable from a demographic, but hardly from a personal, standpoint.

In the light of these special problems,

which would have to be superimposed on the already formidable difficulties (see Figs. 1 and 2) associated with the development of any systemic, chemical agent of fertility control, it is perfectly clear that the development of such a universal birth control agent is outside the realm of possibility in this century. My conclusion should be contrasted with that of Ketchel (*28*), who makes the optimistic, but completely unsupported, prediction that, within 5 to 15 years, methods will be developed for controlling the fertility of an entire population.

Immunological approaches, though probably slightly more easily implemented in an Orwellian society than the addition of a sterilant to food or water, are still so far away (*3*) that they do not merit serious consideration within the context of this article. We are thus brought back to reality with only two reversible methods that could conceivably be introduced on a massive scale by government edict during the next two decades, provided the political realities enumerated by Berelson (*27*) and by Ketchel (*28*) are faced. In the male, this would be vasectomy, and in the female, administration of a sustained-action contraceptive of the estrogen-progestin type (*4*).

General Recommendations

The inevitable conclusion reached from the data of Figs. 1 and 2 and Tables 3 and 4 is that the pharmaceutical industry ought to remain involved in the massive effort required to bring a fundamentally new female or male contraceptive agent to fruition in the 1980's. Furthermore, for reasons outlined in detail elsewhere (*7*), most of this work has to be, and will be, done under rules and regulations established by the FDA and similar government regulatory agencies of the technologically most advanced countries. If this premise is granted, then the following four recommendations should be taken into consideration.

Implementation of the first two recommendations would stimulate research irrespective of what organization (industrial, governmental, or academic) [illegible] implement it. Implementation of the last two would provide specific incentives for continued investment by the pharmaceutical industry in contraceptive research. These need to be provided for three reasons. First, the organizational abilities of the pharmaceutical industry are a sine qua non for the development of practical birth control agents. Second, given that major advances in birth control will be based on chemical methods, then access to the large and highly productive organic chemical research groups in the pharmaceutical industry is an indispensable prerequisite (see Figs. 1 and 2, steps 1 → 2). This has already been recognized by nonindustrial groups like the Population Council and the National Institutes of Health's Center for Population Research. Third, unless some incentives in the area of contraceptive research are introduced soon, it is unlikely that the present rate of industry expenditure on research in this field (probably $15 million to $20 million per year) will be maintained; indeed the rate is likely to decline, and it may reach a noncritical level in a short time. This would be a tragedy, except in the eyes of those who dismiss or ignore the population problem. Therefore, proposals 3 and 4 are made with the purpose of ensuring industrial laboratories some likelihood of achieving a profitable recovery of their research investment and of reducing the risk inherent in 10- to 15-year research projects.

If the problems which prompted the following four recommendations are not taken into serious consideration, then birth control in the middle 1980's will not be very different from birth control in 1970.

1) *Conditional approval.* The U.S. Food and Drug Administration, as well as government regulatory agencies in other countries (for example, the Food and Drug Directorate in Canada), has two principal functions which are potentially conflicting (*29*). This conflict has particularly serious consequences for future research in contraceptive technology, *irrespective of whether such research is performed by industry or by some other sector.* A definition of this conflict and a possible resolution should, therefore, receive the highest priority.

The first function, which clearly should not be abolished, is that of protector of the consuming public insofar as drugs on the open market are concerned. The FDA must protect the consumer from harm and fraud, it must maintain and enforce appropriate analytical standards, and it must generally assume the function of policeman or watchdog. This historical function of the FDA is at least partly incompatible with a more recent one—namely, its role in passing on all clinical protocols by having a de facto veto on all clinical work with experimental drugs. It is at this premarketing stage of a drug's development that the maximum flexibility commensurate with scientific caution and medical responsibility must be maintained; the agency responsible for such protocols must consider its main function to be stimulation of research and drug development rather than just a policing function.

Thus, the role of the FDA seems to have moved from that of protector to that of guarantor; Congress, the press, and consumer protective groups are responsible. Yet it must be recognized that this role of guarantor is an impossible one. No drug can be *totally* effective and *completely* safe, and no agency of government can guarantee that it will be. It is illuminating to examine the roles of other regulatory agencies. For instance, the Federal Aviation Administration certifies aircraft as meeting certain safety requirements. It does not give the traveler a guarantee that the plane will not crash.

Every contraceptive drug will have side effects, as any drug does. The FDA reviewer must recognize a drug's potential benefit as well as the hazard; yet, in deciding whether to approve a drug, his incentive to recognize the benefits is far less than his incentive to avoid the risk of approving it and later having to defend his position to his superiors under pressures from the press or Congress. Understandably, the emphasis has been on hypercaution, bureaucratic delays, and enormously escalating requirements. For every instance where such hypercaution proved ultimately justified, there are probably dozens where it led to long delays or to total abandonment of potentially important drugs.

The consumer also suffers from the delusion that drug safety and drug efficacy are all-or-none propositions. The fact that people experience side effects from "safe" drugs should be no more surprising than the fact that occasionally some people die when "safe" airplanes crash. This evaluation leads to the following recommendation: [illegible] beneficial in facilitating and stimulating research not only on contraceptive drugs but also on other drugs in preventive medicine involving long-term administration to "normal" populations.

For such drugs, the IND/NDA process as it exists is totally inadequate and should be modified. The existing phase III clinical program should be reduced to meticulously planned moderate-sized clinical studies of limited length (2 years would be adequate in most instances), which would disclose whether a new agent had any conspicuous toxicity. Efficacy could clearly be established under such conditions. The question of whether the drug had any low-incidence toxicity would remain. The oral contraceptives have taught the medical profession the important fact (well known to statisticians) that large samples are needed to demonstrate small effects reliably (*30*) and that it is extremely difficult and costly to accumulate such samples in a premarketing phase.

It is at this stage that the FDA could introduce the concept of *conditional approval* (*31*, *32*), somewhat analogous to the FAA's "Certificate of Provisional Airworthiness." During this time of use-testing, the agent could be marketed, but some of the profits from sales would be used for structured follow-up studies of sizable populations consisting of the patients put on medication. The FDA could assign a permanent monitor to coadminister such programs; this would be far superior to the present monitoring through the collection of anecdotal reports of side effects which may or may not be drug-related. Under the proposed new scheme, one avoids the need to collect, during the phase III clinical trials, tremendous quantities of information on people who are well and reacting favorably to the drug. Instead, attention is focused during the "provisional-approval-for-marketing" phase on the few individuals who do poorly, and it is possible to determine more quickly whether their reactions are drug-related. If the drug survived a well-designed follow-up study, then it could be given full approval by the FDA, and continuing large studies financed by the sponsor would not be required. As may be seen from Figs. 1 and 2, implementation of such a recommendation could markedly speed up the time required to develop a practical contraceptive agent.

2) *Appeal procedure.* As pointed out in this article and elsewhere (*7*), all clinical research performed in this country is subject to disapproval by FDA personnel. Disapproval for the initiation or continuation of clinical trials is essentially unappealable, and yet such action is frequently a result of hypercaution rather than of exceptional scientific insight. A procedure of the type outlined in my earlier article (*7*) for appealing such scientifically debatable decisions is urgently required in the field of birth control, since lack of the right to appeal is already having serious repercussions in the form of discontinuance of major research projects.

3) *Patent protection.* Consideration should be given to a possible revision of the patent lifetime of drugs in the area of birth control and in other fields where very-long-term, premarketing investigation is required. At present the life-span of a U.S. patent is 17 years. Clearly, if a pharmaceutical firm invests millions of dollars in research over a period which consumes most of the lifetime of the patent (a circumstance which may easily happen when a 10- to 15-year period of premarketing research and development is required), then a crucial incentive is removed. One possibility is to offer use-patent protection for such products for, say, 10 years, starting with the date of the *approved* NDA.

4) *Government-industry interaction.* As pointed out above, the costs of developing a new contraceptive agent have risen so dramatically that they are beginning to outstrip the financial capabilities of an individual pharmaceutical company, and to reduce greatly the company's chance to recover such costs after the drug has been approved for public sale. For instance, if 10 to 15 years of research by one company, costing $10 million to $30 million, results in development of a "once-a-month" pill, is it likely that the public, the press, or possibly even the legislature will tolerate a price in the several-dollar range for a single pill when the final manufacturing cost of the chemical ingredient may be only 5 or 10 percent of that amount? Yet unless such prices for single pills were charged, the prospects for a firm's recovering the research expenditure, let alone making a profit on the investment, would be negligible.

The reason for these tremendous costs and for the long experimental periods is the readily understandable one that a drug administered to large portions of the normal population must present minimal risk. The chances of developing such drugs are correspondingly smaller than those of developing other drugs, and it is only reasonable that the public (that is, the taxpayer, by way of the government) should bear part of this development cost. The very special features responsible for the extraordinary costs of birth control drugs are the very long trials required to determine toxicity (completely unlike those for other drugs and eventually concentrating largely on subhuman primates) and the very large and long phase II and phase III trials in man, accompanied by an ever-increasing number of clinical laboratory examinations. It is this aspect of the research, rather than the chemical, biological, short-term toxicological, or even phase I clinical studies, which should be funded by the public. One means of partially funding such research is implicit in recommendation 1, for conditional marketing approval (*32*) by FDA.

Another possibility is that a pharmaceutical company be given the option of applying to a government agency for full financial support of the long-term toxicity studies (which could actually be performed elsewhere under contract) and of all phase II and phase III clinical work. If the research should lead to development of a commercial product, then the company would be obligated to repay the government agency on an annual royalty basis. If all of the money was repaid and the drug was still being sold commercially, it might be reasonable to expect a continued royalty payment on a reduced basis for the life of the commercial product. In other words, during the first years of such a system, funds would only be outflowing from the government agency, whereas after a certain period an equilibrium would be reached. Under extremely favorable circumstances the flow might even turn in favor of the government agency.

Such a proposal may appear unprecedented in the drug field, but it has a striking precedent in the U.S. Government's decision to underwrite the development of a supersonic transport (SST) in this country. The socially redeeming features of the SST cannot compare with those of a drug in the birth control field, nor are the respective effects of these developments on the environment in which we live comparable. Expenditure in the birth control field of the monetary equivalent of a few SST's per year could have a remarkable effect and, at the same time, could serve as an indication of how national priorities should really be

handled. My fundamental purpose in making this proposal is not to argue the advantages of the free enterprise drug industry or to protect its profits. It is to assure the continued possibility of the development of drugs that are vital for human well-being. To assure this we must decide either to create an effective partnership between government and industry, on the model of other major technological efforts such as the space program, or to undertake the difficult and even more costly steps that would be involved in socialization of the drug industry in areas requiring long development periods.

Conclusions

1) Eric Blair (alias George Orwell) can rest easy in his grave, because birth control by governmentally imposed methods, such as incorporation of a contraceptive agent into drinking water, is totally unfeasible by 1984.

2) Fundamentally new birth control procedures in the female (for example, a once-a-month luteolytic or abortifacient agent) and a male contraceptive pill probably will not be developed until the 1980's at the earliest, and then only if major steps of the type outlined in this article are instituted in the early 1970's. Development during the next decade of practical new methods of birth control without important incentives for continued active participation by the pharmaceutical industry is highly unlikely. If none are developed, birth control in 1984 will not differ significantly from that of today.

References and Notes

1. Statement by Senator Gaylord Nelson, *Congressional Record* (27 Feb. 1970), pp. S2611–S2612.
2. J. Platt, *Science* 166, 1115 (1969).
3. "Developments in Fertility Control," *World Health Organ. Tech. Rep. Ser. No. 424* (1969) (report of a WHO scientific group).
4. The FDA Advisory Committee on Obstetrics and Gynecology in its "Second Report on the Oral Contraceptives" (Government Printing Office, Washington, D.C., 1969) considers the long-term administration (up to 3 years) of synthetic progestational hormones through implants "one of the next developments in contraceptive methodology." Without belittling its potential importance in birth control or the great amount of developmental work that needs to be done for years before such formulations can be used on a wide scale, such approaches do not fall within my definition of fundamentally new contraceptive agents. Rather, they represent new modes of administering the usual steroid hormones and thus offer no basic advantages in terms of further minimizing side effects.
5. Note a long column by M. Mintz entitled "IUD hazards" in the Washington *Post* (5 Mar. 1970).
6. The mechanism of action of IUD's is incompletely understood, and suggestions have already appeared in the literature [A. Pakrashi and G. Ghosh Ray, *J. Reprod. Fert.* 19, 357 (1969)] to the effect that their use may be associated with hyperestrogenism in women and with polycystic changes in the ovaries. Little is known about possible carcinogenic effects caused by the presence of foreign bodies in a woman's uterus for many years [see W. B. Ober, A. J. Sobrero, R. Kurman, S. Gold, *Obstet. Gynecol.* 32, 782 (1968)], although the relevance to humans of tumor induction by loops and spirals in rats has been questioned [C. M. Southam and V. I. Babcock, *Amer. J. Obstet. Gynecol.* 96, 134 (1956); P. A. Corfman and R. M. Richart, *ibid.* 97, 987 (1967)].
7. C. Djerassi, *Science* 166, 468 (1969).
8. E. I. Goldenthal, *FDA Papers* 1968, 13 (May 1968).
9. ———, *ibid.* 1969, 15 (Nov. 1969).
10. E. Forchielli, R. A. Runkel, M. D. Chaplin, (Syntex Research, Palo Alto, Calif.), private communication.
11. U. S. Seal and R. P. Doe, *Steroids* 5, 827 (1965); *Proceedings 2nd International Congress of Hormonal Steroids* (Excerpta Medica Foundation, Amsterdam, 1967), p. 697; *Metabolic Effects of Gonadal Hormones and Contraceptive Steroids*, H. A. Salhanick, D. M. Kipnis, R. L. Vandewiele, Eds. (Plenum, New York, 1969), p. 277.
12. J. Hillaby, *New Sci.* 1968, 93 (10 Oct. 1968).
13. In a symposium on "the impact of drug legislation on the drug industry," held in August 1969 at the Gottlieb Duttweiler Institute for Economic and Social Studies (Zurich), J. F. Sadusk (Parke, Davis & Company, and former medical director of the FDA) compared the 167 volumes (consisting of 72 200 pages) of a recent (1968) New Drug Application to the FDA on a new anesthetic agent with the much smaller applications (for example, two volumes of 439 pages in 1959) of 10 years ago. This illustration is not necessarily offered as a special variant of Parkinson's law, but also points to the greater volume and complexity of supporting data required at present—much of it due to increased knowledge and the availability of more sophisticated techniques. Of additional interest is Sadusk's observation that the Canadian counterpart to the American FDA application (72,200 pages) amounted to 67,128 pages, whereas the Japanese (2000 pages), British (857 pages), and Swiss (159 pages) versions were much shorter. Sadusk concluded with the question: "Is the public in these countries with greatly increased requirements better protected, and what is the proof if the answer is in the affirmative?"
14. See "Proceedings of Hearings of Senate Subcommittee on Monopoly of the Select Committee on Small Business," vol. 69, 23 Jan. 1970 (Washington, D.C.), pp. 7089–90.
15. J. J. Speidel (Office of Population, AID Bureau for Technical Assistance), private communication.
16. O. Harkavy and J. Maier, *Fam. Plann. Perspect.* 2, No. 3, 5 (1970).
17. For an extensive bibliography, see "Developments in Fertility Control" (*3*), pp. 33–36.
18. As an illustration of the magnitude of such costs, one may cite a current study in 10,000 women on various medical effects associated with oral contraceptives. This study, sponsored by the NIH Center for Population Research, involves an annual cost of $1 million [see "Proceedings of Senate Subcommittee on Monopoly of the Select Committee on Small Business" (*14*), p. 7670].
19. G. Hardin, *Perspect. Biol. Med.* 10, 1 (1966).
20. The lay press [for example, *U.S. News & World Report* 1970, 37 (2 Mar. 1970)], as well as the Senate hearings [see (*14*), p. 7699], contains the unsupported statement that, if abortion were available as a backup procedure in case of contraceptive failure, then less dangerous contraceptives could be used. As yet we have no evidence that it is easier to develop a "safe pill" which needs to be only 90 percent effective than one which must be 99.9 percent effective. The history of the present oral contraceptive drugs suggests that this is not the case, because lowering of the recommended dose (that is, presumed lesser danger) may still give full protection and yet be unacceptable as a result of other side effects, such as uncontrolled breakthrough bleeding. Similarly, clinical testing of an estrogen-free "mini-pill" associated with a slightly higher rate of pregnancy than the usual oral contraceptives was recently (January 1970) suspended by the FDA because of factors that had nothing to do with efficacy.
21. For review, see S. Bergström, L. A. Carlson, J. R. Weeks, *Pharmacol. Rev.* 20, 1 (1968).
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24. U. Reth-Brandel, M. Bygdeman, N. Wiqvist, S. Bergström, *ibid.*, p. 190.
25. A. Gillespie and J. M. Beazley, *ibid.*, p. 717.
26. See, for instance, *New York Times* (28 Jan. 1970), *Time* (9 Feb. 1970), and Washington *Post* (14 Mar. 1970).
27. See B. Berelson, *Science* 163, 533 (1969), and the extensive bibliography cited therein.
28. M. M. Ketchel, *Perspect. Biol. Med.* 11, 687 (1968); *Med. World News* (18 Oct. 1968), pp. 66–71.
29. Some brief comments on this point are made in "Technology: Processes of Assessment and Choice," *Nat. Acad. Sci.–Nat. Res. Counc. Rep.* (1969) (available from Government Printing Office, Washington, D.C.).
30. At the 23 January 1970 hearings of the Senate Subcommittee on Monopoly, D. Seigel of NIH, in response to a question about the number of subjects required to determine the doubling of the risk of breast cancer, indicated [see (*14*), p. 7705] that 85,000 person-years would be needed for a statistical evaluation.
31. Such a proposal has been advocated by, among others, my colleague J. Lederberg (department of genetics, Stanford Medical School). For some relevant comments, see his article "Biomedical research: its side effects and challenges," *Stanford M.D.* 1967, No. 3, 13 (1967).
32. It is pertinent to note that the FDA has recently followed such a "conditional approval" route for the new drug L-dopa, used in Parkinson's disease.

33. I am grateful to many persons in academic, industrial, and government circles for comments, but I am particularly indebted to Drs. J. Bennett S. A. Bessler, K. Dumas, R. Havemyer, R. Hill, and E. Segre for their valuable contributions.