Depo-Provera Debate Revs Up at FDA

Claims of cancer risk with the contraceptive pose tough, nagging problems for FDA, the State Department, and Third World countries

In September, a special panel of scientists is expected to begin deliberations on a problem that has plagued the Food and Drug Administration (FDA) for 15 years. The panel has been asked by FDA Commissioner Arthur Hull Hayes, Jr., to recommend whether a drug called Depo-Provera should be approved for use as an injectable contraceptive.

The final decision, which will ultimately be made by Hayes, is expected to have major economic and social implications. Although the verdict will be based on considerations for American women only, it will take on international importance. Population control groups predict that the ruling will have far-reaching consequences because of FDA's influence abroad. The State Department has a large stake in the decision because its Agency for International Development (AID) is a major supplier of contraceptives for Third World countries. AID has faced a predicament ever since the Depo-Provera debate unfolded. It has been asked by developing countries to furnish the drug, but has a policy not to export drugs that are not FDA-approved.

Population Crisis Committee

Thai women line up for Depo shots while FDA ponders the drug's fate in the United States.

The controversy over Depo-Provera has pitted a mighty group of supporters against an unusual conglomeration of opponents. Siding with its manufacturer, The Upjohn Company, are the World Health Organization (WHO), the International Planned Parenthood Federation, the Population Crisis Committee, many other family planning organizations, and the American College of Obstetrics and Gynecology. Opposing the drug are several vocal but nonaligned groups. The principal foe is the Health Research Group affiliated with Ralph Nader. But other critics, each for its own reasons, include the liberal National Women's Health Network and right-to-life groups.

For years, women around the world have wished for a contraceptive that would be reliable, long-lasting, convenient, reversible, and free from serious side effects. Family planning professionals have shared this desire too—particularly those concerned about developing countries and their struggle to reduce population growth and the number of women dying in childbirth or from illegal abortions. In short, the development of a better contraceptive would provide millions of women with an important alternative to current methods.

In 1967, the Upjohn Company believed it had achieved this breakthrough. That year, it applied for federal approval of a new drug called Depo-Provera. The drug's attributes were remarkable: a single injection stopped ovulation for 3 months or longer, its effectiveness was comparable to that of the Pill, and its users did not need much education. By most indications, Depo-Provera was a strong and promising entrant into the multimillion-dollar market for contraceptives.

But the excitement that ensued over the next few years was dampened by doubts about Depo-Provera's long-term safety. Although more than 80 other countries have already approved the drug, the fate of Depo-Provera has wavered uncertainly in the United States.

The main dispute concerning the drug centers on animal data which critics contend demonstrate that Depo-Provera, a medroxyprogesterone acetate, is a potential human carcinogen. In tests commissioned by Upjohn, both beagles and monkeys that were exposed to high doses of the drug developed more tumors—some of which were malignant—than the controls. These two species are required by FDA as bioassays for contraceptives.

It was a 7-year beagle study sponsored by Upjohn that first set off alarms about a potential cancer risk. Malignant breast tumors developed in two of 16 dogs. These tumors, adenocarcinomas, were not seen in the control animals although other types of malignant and benign tumors developed in them.

Proponents of Depo-Provera argue that the results of the dog study are virtually worthless because the beagle is highly susceptible to spontaneous breast tumors. They say the drug response in the two animal species is not analagous to humans. In fact, in recent years WHO and the British Committee on Safety of Medicines concluded that the beagle is an inappropriate model to test progestogens, such as Depo-Provera.

The Depo-Provera dispute intensified in 1978 when Upjohn released results from a 10-year study of 52 rhesus monkeys. Two animals in the group developed endometrial cancer which was not found in the controls. A panel of Upjohn scientists and consultants concluded that "the two neoplasms were likely related to treatment with Depo-Provera and were not spontaneous lesions." But the company attempted to explain away this adverse conclusion by asserting that the

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reaction of monkeys to progestogens was different from the reaction of women, a claim also made by WHO. Endometrial cancers in monkeys develop from a condition unlike that found in women, Upjohn and WHO said. In addition, the drug is approved for use within the United States as a treatment for some forms of endometrial cancer, a fact that casts even more doubt on the significance of the monkey study, Upjohn said.

On the basis of the same animal data, Sidney M. Wolfe, director of the Washington-based Health Research Group is convinced that Depo-Provera is "a dangerous drug." The beagle, he says, does provide an acceptable experimental model. "Industry did not object to the validity of such dog studies as long as they yielded negative results, but protested only when some of their products caused tumors in these studies," Wolfe wrote in 1976 to the Department of Health, Education, and Welfare to protest pending FDA approval of the drug.

In Wolfe's opinion, the monkey study was clearly positive, an alarming finding because a cancer-causing effect was now demonstrated in two species. Wolfe's 1976 letter said that any substance, with few exceptions, which conclusively causes cancer in animals should be considered "a potential cancer hazard in man."

The FDA still believes the two species were valid models to test progestogens. Former FDA commissioner Donald Kennedy told a congressional hearing on Depo-Provera in 1978: "FDA has required tests in both the beagle and monkey because the beagle is highly susceptible to spontaneous mammary tumors, while the monkey is relatively resistant. The human female falls between the beagle and monkey in spontaneous mammary tumor incidence." He testified before the Select Committee on Population, "No contraceptives currently approved

NASA Student Rat Project Questioned

There has been a minor conflict within the National Aeronautics and Space Administration (NASA) over a student experiment that is scheduled to be flown on one of next year's space shuttle flights. The project, involving rats with artificially induced arthritis, is moving full steam ahead and is tentatively scheduled to go up next April. However, the head of NASA's life sciences division, Gerald A. Soffen, has serious reservations about the quality of the experiment and believes that if it is allowed to fly it may bring down the wrath of antivivisectionists, who have made NASA animal experiments a special target in the past couple of years.

Although Soffen is supposed to have the final say on which animal experiments go into space, he has no authority over this one which is in the charge of the shuttle office.

The rat experiment was selected 2 years ago, in the first year of NASA's new Shuttle Student Involvement Project. The SSIP holds a yearly contest for high school students in conjunction with the National Science Teachers Association. Three winning experiments have so far been flown on the shuttle: one that observed the flight of insects in zero gravity; one looking at the effects of diet, exercise, and zero gravity on lipoprotein profiles of astronauts; and one that examined the effects of space travel on astronauts' trivalent chromium levels.

The arthritic rat project, conceived by Daniel Weber from Hunter College High School in New York City, is the first mammalian experiment scheduled to be flown on the shuttle. Weber's hypothesis is that zero gravity will have a beneficial effect on the inflammation by reducing hypercalcification of the bone that is associated with it. The plan is to inject three rats with Freund's complete adjuvant to induce inflammation and send them up for 5 days in the shuttle along with three noninjected control rats. The rats' movements will be photographically monitored for 8 hours a day. Enzyme, serum, calcium, and phosphorous levels will be measured before and after the flight. Daniel is currently working on the project with NASA consultant Emily Holton of Ames Laboratory, a specialist on bone loss in space, and with Pfizer Inc., which is supplying the drug and the rats. General Dynamics Corporation is designing and building a cage at a reported cost of over $50,000. Everyone involved is very enthusiastic about the project.

Except Soffen, who says he "hit the roof" when he heard about it. Soffen consulted two arthritis experts—Ira Goldstein, head of the Rosalind Russell Research Laboratory at the University of California at San Francisco, and John Dekker of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. In a May memo to his superiors, Soffen summed up the objections as follows: first, that the hypothesis was faulty and bore no relation to human arthritis. The number of animals was too small to yield meaningful results; the reaction of adrenaline due to the stress of a zero-G environment may have a positive effect itself on the disease and therefore could confound the results; and the test could just as well be done on the ground using immobilized or suspended animals. Goldstein, contacted by *Science*, pronounced the proposed project "very naïve" and said it was unlikely any useful information could be gained from it.

David Larson, senior researcher at Pfizer who is working with young Weber, does not think any of the criticisms are valid. He says there are enough rats because a highly susceptible strain (Wistar Lewis) is being used, and that the amount of stress-induced adrenaline they produce will not be enough to alter the course of the disease. He believes that the project will enable participants "to clearly say something changed or didn't change as a result of the weightless condition."

Another defender of the project, Alan Ladwig of the shuttle office, concedes that it is not "great science," but contends its primary purpose is educational. (The only formal scientific review of the project came during the judging, but Ladwig says a new layer of scientific review is being added for future student experiments.)

The basic question here seems to be whether student shuttle experiments should conform to the standards of professional science or whether their role in educating and stimulating scientists of the future is sufficient to justify their presence on the shuttle. Probably no one would raise much of a fuss if a marginal bug project made it into outer space, but with the eyes of the newly hyperactive animal welfare community trained on its every move, NASA would do well to see to it that any experiment involving vertebrates has solid scientific justification.

—CONSTANCE HOLDEN

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for marketing have shown a similar carcinogenic potential in the beagle assay."

Renate Kimbrough, an epidemiologist and medical officer at the Centers for Disease Control, contends the animal studies are "clearly of concern." She disagrees with Upjohn and WHO that different mechanisms of cancer development in animals and humans negate test results. "It's not a valid argument." She says, for instance, that human endometrial cancer is not always preceded by hyperplasia, the particular condition cited by Upjohn and WHO. Kimbrough remarks that, furthermore, the development of cancer in a certain animal organ does not mean that it will occur in the same organ in a human.

She wonders why Upjohn did not do additional animal studies, if it discounts the significance of the cancers in beagles and monkeys. An Upjohn spokesman, Joseph Heywood, says that the monkey study was not repeated because of the availability of studies in humans. But the beagle study has been repeated, and the results—as yet unannounced—will be presented by the company to the FDA later this year.

Upjohn and others say that the true test of safety can be found in the available epidemiological data. The company says that its clinical trials involving more than 11,000 patients treated for as long as 8 years have not revealed any increase of uterine cancer. Upjohn says that in Thailand, where more than 86,000 women have received the drug since it was approved in 1965, there has been no recorded increase in endometrial cancer. Gordon Duncan, who administers and coordinates Upjohn's international research program in fertility says, "There's no evidence of a cancer risk potential in any women. That's a flat statement. The studies are negative."

WHO does not go as far as to say that the studies are negative. But it argues in favor of the drug because "extensive clinical and epidemiological studies among women using Depo-Provera have thus far demonstrated no life-threatening side effects," according to a bulletin published this year by the WHO Special Programme of Research, Development and Research Training in Human Reproduction. The drug appears to be an "acceptable" and "important" option.

Robert N. Hoover, deputy chief of the National Cancer Institute's environmental epidemiology branch, disagrees sharply with Duncan's judgment. "There is essentially no good epidemiological study Depo-Provera to date," says Hoover, who will testify before the Board of Inquiry on behalf of the FDA. Hoover says, "The human evidence is so bad you can't make a statement whether it's carcinogenic." In his opinion, for example, the studies so far have been too small. The WHO bulletin acknowledges that "the potential long-term effects (over more than 15 years) are not yet known. . . . Further research is needed."

David Thomas, a professor at the University of Washington at Seattle, says the epidemiological evidence is "reassuring," but concedes that this assessment "is not based on strong evidence." Thomas should be able to provide more definitive answers during the next several years. Funded by a $1-million contract by WHO, he is currently conducting an international case control study to explore the question of potential cancer risk associated with various contraceptives, including Depo-Provera. The study will include women from nine countries who have developed cancer of the ovary, endometrium, breast, cervix, and liver. Thomas says the preliminary data on breast cancer and Depo-Provera look "reassuring." The analysis on any endometrial cancer risk will not be completed for three to four more years.

In addition to a cancer risk, Sidney Wolfe believes Depo-Provera is unsafe because its contraceptive effect is not always reversible. WHO says that in one study, 90 percent of previous Depo-Provera users eventually became pregnant, a rate similar for former Pill users. But the bulletin goes on to caution that women who have not had children and may desire them later should "use other methods." Wolfe charges that the 90 percent figure is an overestimate because too few women have been monitored to check if they conceived.

All in all, the controversy over Depo-Provera's alleged cancer risk and its side effects has vexed the FDA for more than a decade. Its varied actions illustrate its problems with the drug.

At one point, in 1974, FDA sanctioned the use of Depo-Provera for a very limited population of women—primarily those who found other methods unacceptable or difficult to use and those who were institutionalized. But a month and a half later, after a congressional hearing was held to examine allegations that the drug was associated with cervical cancer, the agency stayed the order.

The agency continued to ponder approval. In 1975, FDA advisory committees recommended that Depo-Provera be approved, but again, for only a small group of women. Wolfe protested. In 1978, FDA commissioner Kennedy decided not to approve the drug. The agency defended its actions by arguing that other contraceptives had come on the market since its first approval and eliminated the need for Depo-Provera, given its risks.

In an unusual action, Upjohn appealed the disapproval and asked for a Board of Inquiry to review the issue. A board has been requested only one other time in FDA history. (In that case, the panel took up the agency's decision not to approve the sweetener aspartame.)

More than 2 years slipped by before board members were appointed. During that time, the leadership of FDA changed hands three times: Kennedy stepped down, Jere Goyan came and left, and then Hayes took over. The board was finally named by Hayes last September and is chaired by Judith Weisz, a professor at Pennsylvania State University and head of the division of reproductive biology at Hershey Medical Center. The other two members are Griff T. Ross, associate dean of clinical affairs at the University of Texas at Houston, and Paul D. Stolley, professor in the Departments of Medicine and Research Medicine at the University of Pennsylvania School of Medicine. Both Weisz and FDA commissioner Hayes declined comment on the Depo-Provera issue.

The FDA's refusal in 1978 to approve Depo-Provera has had repercussions abroad. It prompted five countries—Korea, Taiwan, Egypt, Jordan, and Yemen—which had approved the drug to reverse their positions. International family planning groups complain that other countries have refrained from approval to avoid charges that they are distributing an unsafe drug. Countries that continued to sanction the drug have already weathered such criticism.

Although population control professionals believe that the drug is suitable as a contraceptive for women in general, they contend it is especially attractive and important for Third World women. The medical director of the International Planned Parenthood Federation states that over the next two decades several million women will die as a result of unplanned pregnancies. Pramilla Senanayake told a medical conference in Kenya earlier this year that women in developing countries "often live in overcrowded homes where storage and use of contraceptives such as condoms and pills pose immense problems. The overworked rural woman, moreover, has problems remembering the daily routine" of taking the Pill. Many women resent the pelvic exam necessary for IUD insertion. "Under these circumstances, the injectable contraceptive

has some distinct advantages," she said.

The approximately 80 nations that have approved Depo-Provera are split evenly between developed and developing countries. They include Belgium, where an Upjohn subsidiary manufactures the drug for overseas distribution, France, Sweden, West Germany, and Norway. Depo-Provera, however, recently received a setback in Britain. The drug is already approved there as a contraceptive for a small group of women whose husbands recently have had vasectomies or for whom no other contraceptive is acceptable. The Committee on Safety of Medicines this year recommended to the government that the drug be approved for a larger, although limited, group of women. Similar to initial FDA approval, the committee advised that Depo-Provera use be restricted to only women who find other methods unsatisfactory or who suffer unacceptable side effects from them.

Apparently for the first time in the ministry's history, Britain's top health officer went against the committee's advice and proposed not to approve the drug for greater distribution. Kenneth Clarke, the new health minister, said in a letter to Upjohn and the committee that in his opinion the risks outweigh the benefits. Opponents of Depo-Provera, including a group called "Ban the Jab," had been quite active, according to a ministry spokesman.

Upjohn appealed the minister's action, which in the past has always been interpreted as a final decision. A hearing is to be held in November.

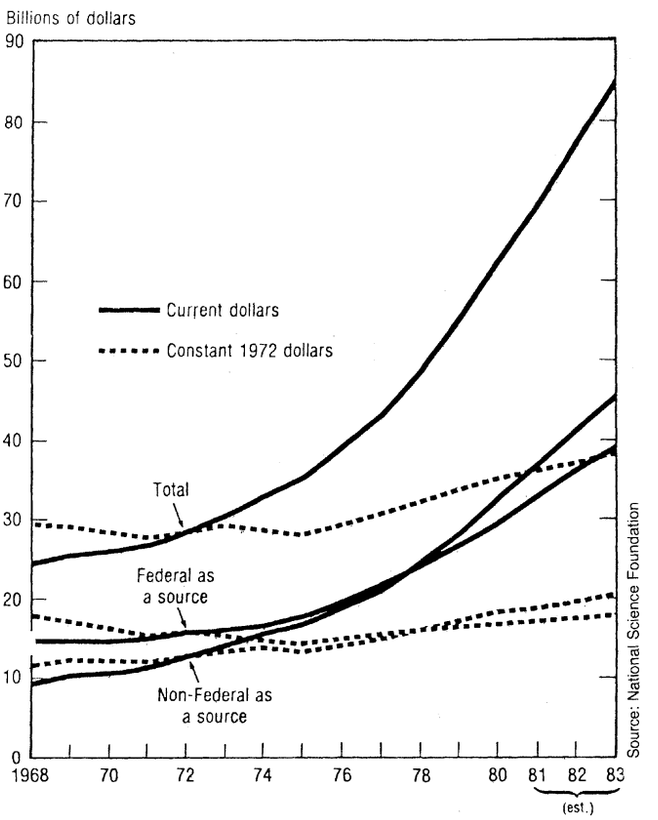
For the Agency for International Development, the Depo-Provera issue is particularly sensitive. Although many developing countries have requested assistance to acquire the drug, AID's hands are tied because of its policy not to export drugs lacking FDA's stamp of approval. Foreign governments complain that AID's position is righteous and paternalistic. The agency came under so much pressure to put up the money for purchase and to supply the drug that AID assembled an ad hoc panel in 1980 to review the scientific data and make a recommendation. The committee members, of whom at least half were population experts, advised AID to make an exception for Depo-Provera and allow its export because of the drug's outstanding merits. But AID has so far not altered its policy and still does not either export the drug or directly finance its purchase domestically or overseas.

A spokeswoman for the Population Crisis Committee, based in Washington, D.C., says that one factor that may have

Industrial R & D Rises

While attention has been focused on the ups and downs in federal support for research and development in the past few years, corporations have been steadily increasing their outlays on R & D. This trend was apparent well before Congress approved special tax incentives to encourage corporate R & D, and it seems to confound the oft-repeated myth that expenditures on research are among the first to suffer during a recession.

Fresh evidence for this continued expansion of privately funded R & D comes from the annual survey of corporate expenditures on research and development published by *Business Week*.* According to the survey, major research corporations in the United States increased their outlays on R & D



by 15.1 percent in 1981, or about 6 percent faster than the rate of inflation. And this boost occurred in spite of the fact that the economy was in the grip of a deep recession.

Moreover, according to a recent projection by the National Science Foundation, equally impressive increases are expected in 1982 and 1983. On the basis of a survey of top officials of major research corporations, NSF says it expects to see a 12 percent rise in corporate R & D spending this year and an 11 percent boost in 1983.†

Spearheading these increases are companies in sectors such as computer manufacturing and information processing, which are experiencing increasing competition from abroad. According to the *Business Week* figures, such companies generally boosted their R & D spending by at least 20 percent last year, and in some cases the increases amounted to more than 30 percent. The biggest single spenders, however, continued to be General Motors ($2.25 billion) and Ford Motor Company ($1.72 billion), with AT&T ($1.686 billion) and IBM ($1.612 billion) not far behind.

As a result of this steady expansion of corporate-funded R & D, private industry now supports more than half the total R & D in the United States; 15 years ago, it funded less than one-third.—COLIN NORMAN

Business Week, 5 July 1982. †National Science Foundation, *Science Resources Studies*, NSF 82-311, June 1982.

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swayed the agency is protest from right-to-life groups such as the American Life Lobby and National Right to Life Committee. The conservatives' objections are based on the belief that Depo-Provera is a dangerous medication and also that Upjohn sells products that cause abortion. An AID official denies that the right-to-lifers were influential.

Upjohn's Gordon Duncan says the company has persisted in seeking FDA approval because it believes Depo-Provera is "a good drug. There is a reasonable population of women who want Depo-Provera." Upjohn insists that the drug's market potential is modest.

But information about the contraceptive market suggests that the economic stakes are tantalizingly large. The international market for oral contraceptives alone totals roughly $700 million annually. Population groups estimate that a significant percentage of women who use the Pill will switch if FDA approves Depo-Provera. The drug will also attract first-time users of contraceptives. About 1.5 million women outside the United States now receive the injectable contraceptive and the figure could shoot up by as much as 50 percent within 5 years after FDA approval, according to the Population Crisis Committee.

The value of Depo-Provera sales has already reached approximately $25 million, according to market analyst Arnold Snider of Kidder, Peabody and Company in New York. He adds that contraceptives are very lucrative. Oral and injectable methods "have an incredible profit margin." They are "among the most profitable of all pharmaceuticals."

Whether the FDA will approve Depo-Provera is unclear. Commissioner Hayes may be willing to accept a greater margin of risk than his predecessors, given his voting record on aspartame. Although a Board of Inquiry advised him not to approve the sweetener, Hayes ruled in favor of the drug. He said at the time, "It is wrong, and I'm not just singling out aspartame here, to say well let's just wait further and further for more evidence or a unanimous opinion. The question is, are you really trying to assure a zero risk? . . . I do not think most people expect zero risk" (*Science*, 28 August 1981, p. 986). But Hayes' aspartame ruling may or may not be a clue to his verdict on Depo-Provera. Wolfe and others are hoping Hayes concludes the drug presents an unacceptable cancer risk.

The agency is charged with weighing the risk-benefit ratio only for American women, a fact that provides little comfort to developing countries clamoring for the drug. Kennedy, during his FDA tenure, stated that other countries must take into account their individual needs despite his verdict not to approve the contraceptive. In addition, he suggested that AID modify its export policy or that Congress initiate export reforms. He argued that if other nations request the drug and AID clearly explains FDA's reservations, AID could then be of assistance. Such a policy should help shield the United States from accusations of adopting a double standard on drug safety.

But AID continues to be faced with a delicate political situation. Cynthia Green of the Population Crisis Committee says that the Reagan Administration most likely does not want to risk raising the ire of the right-to-life groups. Kennedy perhaps put his finger on the solution when he said, "The right way to solve this policy dilemma is by an export policy that recognizes national differences, and allows national autonomy in the making of decisions about health."

—MARJORIE SUN

ISABELLE Spending Questioned

The Department of Energy's (DOE's) inspector general has raised questions about some $25 to $30 million that is being spent on the ISABELLE accelerator at Brookhaven National Laboratory. Although work on ISABELLE will be halted in fiscal year (FY) 1983, pending a decision on whether to complete the project, Brookhaven has been spending its FY 1982 money as if the accelerator were going to be completed as originally designed, the inspector general claims.

Chiding DOE's Office of High Energy and Nuclear Physics more than Brookhaven, the inspector general's report calls for a plan to guide ISABELLE activities through the rest of FY 1982 and 1983. Brookhaven provided DOE with such a plan in May, and it was approved last month. The inspector general's office says it is mollified.

There are two main issues. The first is the alleged improper guidance by DOE's high energy office to Brookhaven. DOE's FY 1983 budget submission, prepared last October, contained nothing earmarked specifically for ISABELLE. Some $23 million was included for R & D on superconducting magnets for a future accelerator. DOE should have informed Brookhaven last fall of the budget situation and to ensure that no FY 1982 money was spent on items that were so ISABELLE-specific as to be wasted if the accelerator was terminated, argued the report.

In fact, the situation was somewhat less clear-cut because the controversial ISABELLE project was not definitely excluded from FY 1983 funding until mid-January. One of the items holding up a decision was a study by the subpanel of the High Energy Physics Advisory Panel. The physicists reported in November that ISABELLE should be completed only if the high energy budget was raised dramatically. Although the proposed FY 1983 level of spending was $59 million below the amount recommended, the physicists had indicated a willingness to accept a partial budget increase as a sign of good faith toward the full amount in 1984.

The second issue is what constitutes appropriate superconducting magnet R & D? DOE's high energy office and Brookhaven had agreed that the laboratory should assemble and test a section of the full accelerator ring, specifically a sextant comprising some 100 magnets. Among other things, this would require the purchase of the full ISABELLE liquid helium refrigeration system for cooling the magnets.

The inspector general's office suggested that testing of a shorter string of magnets would be more in line with the intent of the FY 1983 Brookhaven budget, in part because making and testing too many ISABELLE magnets would commit the laboratory to a particular design that might not be suitable for an altered ISABELLE or other accelerator. The inspector general's report identified an estimated $25 to $30 million of Brookhaven expenditures that seemed to be more specific to ISABELLE than generic to superconducting magnet R & D, or that were not immediately needed.

With a management plan in hand, the affair seems to be over. The director of DOE's Office of Energy Research was "generally responsive" says the report.—ARTHUR L. ROBINSON

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