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NEWS AND COMMENT

Sloan-Kettering: The Trials of an Apricot Pit—1973

These are bad times for reason, all around. Suddenly, all of the major ills are being coped with by acupuncture. If not acupuncture, it is apricot pits. . . . —LEWIS THOMAS, president, Memorial Sloan-Kettering Cancer Center, in an address delivered 11 October 1973.

At the Memorial Sloan-Kettering Cancer Center on the upper east side of Manhattan, some perfectly respectable scientists are taking a new look at some thoroughly unrespectable cancer remedies. Inevitably, they are generating a fair amount of controversy in the process.

One of the unorthodox remedies Sloan-Kettering researchers are evaluating—and one that has caused them considerable embarrassment recently—is a drug called Laetrile. Laetrile, known chemically as amygdalin, is derived from apricot pits. According to its proponents, who are legion, Laetrile often cures cancer. And, they claim, in those cases in which it fails to actually cure, it gives terminal cancer patients a sense of well-being and surcease from pain that allows them to live out their days in relative peace. According to its detractors, who also are legion, Laetrile does nothing of the sort. In the eyes of the National Cancer Institute, the Food and Drug Administration, and the American Cancer Society, Laetrile therapists are quacks.

And, Sloan-Kettering's new president, Lewis Thomas, shares the view that much of what has been claimed in the name of Laetrile goes beyond the bounds of reason. But the institute's searching look at Laetrile is another story altogether.

Preliminary results of one Sloan-Kettering study suggest that Laetrile might actually have some anticancer activity in mice. Understandably, that study is provocative. The fact that it was meant to be kept confidential and that it came to light through a leak adds a touch of intrigue to the drama.

The story apparently began about 2 years ago, when investment banker Benno C. Schmidt, who is also on the board of Sloan-Kettering, became President Nixon's number one adviser in the national war against cancer. There are a lot of people in this country who believe in Laetrile. Many of them buy it for themselves or their dying friends or relatives on the black market. Many go to Tijuana to get it at a clinic operated by a pathologist named Ernesto Contreras. These people began writing Schmidt letters.

"Since I've been chairman of the President's cancer panel, I've had literally hundreds of letters about Laetrile. Some people ask me whether it is any good. Others flatly state that it cures. A great many say that, in any case, it alleviates pain. When I answer these people and tell them that Laetrile has no effect, I would like to be able to do so with some conviction," Schmidt said in a conversation with *Science*. His curiosity piqued, he began asking questions.

He took it up with the National Cancer Institute. People there told him they had looked into the matter long since and found no basis for any claims that Laetrile is good for fighting cancer. The American Cancer Society, which lists Laetrile in its book, *Unproven Methods of Cancer Treatment*, concurs. Schmidt asked a couple of leading cancer scientists what they knew about Laetrile. They, too, told him it has no value. But when he asked for evidence, he recalls, "I couldn't get anybody to show me his work."

The research that has been done on Laetrile by so-called reputable scientists

has been minimal, although over the course of years several distinguished committees have been put together to evaluate the data put forth by advocates of the drug. These committees, including one which studied data for the Food and Drug Administration only 2 years ago, have consistently reported that the available evidence is wanting. In short, they find that Laetrile "scientists" frequently do poor science. But the nagging question that remains, and that Schmidt believes should be answered, is what one would find out about Laetrile if it were studied by good scientists conducting rigorous experiments.

Schmidt last year turned to his home territory—Sloan-Kettering. He brought the subject of Laetrile up with Lloyd J. Old, an investigator who has a reputation for doing good work without bias. Old, who had, in fact, been looking at Laetrile in dogs with cancer, was responsive. Schmidt raised the subject of Laetrile with Robert A. Good, who was in the process of leaving his laboratory in Minnesota to move to New York to become director of the Sloan-Kettering Institute for Cancer Research, the research division of the cancer center. Good, who says, "I'm willing to look at anything," was also interested. Now, a multidisciplinary team of Sloan-Kettering scientists is working under Old's leadership to see what it can learn about Laetrile.

In spite of initial hesitance to discuss the project, Sloan-Kettering officials, including Thomas, Good, and Old, agreed to talk about it with *Science*. The institute willingly got into Laetrile research for a couple of reasons. Thomas said, for example, "This institution can answer the Laetrile question fairly quickly." In this day, with its high demand for quick answers, that in itself has merit. Another explanation of the institution's decision to go ahead is that it has chosen to investigate a number of unexploited cancer remedies that, for one reason or another, its scientists believe are worth a second look. "One can always look at unproved methods for possible leads," says Old, who also clearly states that he is by no means suggesting that all quack cancer cures should be reevaluated or that Sloan-Kettering is saying the ones it is looking at will pan out. It is just that he believes there are valid scientific reasons for reinvestigating some and that the scientific community cannot afford to ignore them simply because they did not originate in well-established laboratories. "If one of our young scientists came up with the theory behind Laetrile," he says, "we would almost surely support further research to test it out."

Under Good's direction, Sloan-Kettering has been reorganized to achieve what it calls "the most effective integration of its component programs for the investigation and treatment of cancer." Thus, Good and his cohorts singled out eight fields* relevant to cancer research and organized multidisciplinary groups around them instead of conforming to conventional disciplinary lines. The idea is that having biochemists, molecular biologists, pharmacologists, and so forth, working together on the same problem will provide a measure of flexibility and variability in research that one might not otherwise have. According to the Sloan-Kettering brass, who are extremely enthusiastic about the new administrative structure, this is part of what it will take to resolve certain questions—such as the value of Laetrile—with dispatch.

Basically, the idea that has been put forward for years to explain Laetrile's alleged ability to kill cancer cells is that it releases lethal doses of cyanide when it is taken up by a tumor. "Certainly there is some old literature showing that cyanide has anticancer activity," Olds notes. "The question is whether this is so and, if it is, how you can harness the enormous toxicity of cyanide."

The question has yet to be answered fully, but there are now some data to suggest that, rather than cyanide, another chemical—mandelonitrile—may be at work. One of the scientists on Old's team looked at Laetrile in human tumor tissues and found that they appear to be "incapable of generating cyanide from amygdalin. It was therefore suggested that mandelonitrile might indeed be the putative therapeutic agent resulting from amygdalin," according to a confidential working report. The possibility is being investigated.

Mandelonitrile is at least as toxic as cyanide, Sloan-Kettering researchers point out. The idea behind their work is fairly simple. It may be that there is an enzyme peculiar to tumor cells which is capable of cleaving mandelonitrile from amygdalin, thereby selectively releasing a lethal molecule from one that is nontoxic. (As far as is known, amygdalin itself is relatively safe, even in large doses.) Were this to be the case—and no one is saying at this point that it is—one might have an exploitable system by which to deliver drugs to cancer cells. But here Old is cautious and emphasizes that, so far, the evidence is very, very preliminary, that there is no reason to believe that it would be a dramatic, single approach to cancer in any case, and that it is by no means the only idea the institute is exploring.

"It is so easy," he says, "for all of this to be overblown."

Much of the research at Sloan-Kettering that gave anyone reason to believe that there might be something to Laetrile was done between September 1972 and June 1973 by Kanematsu Sugiura, who performed three sets of experiments "to determine the effects of amygdalin . . . upon mice with spontaneous mammary tumors." Said Sugiura in an internal report to his colleagues, "The results clearly show that amygdalin significantly inhibits the appearance of lung metastases in mice bearing spontaneous mammary tumors and increases significantly the inhibition of the growth of the primary tumors over the appearance of inhibition in the untreated animals."

The conclusion Sloan-Kettering scientists draw from these data is that Laetrile is worth further study, even though there is no convincing scientific basis for its use in human beings as yet. Old explains that the model system in which chemicals are evaluated is important and may partially explain why he and his colleagues are seeing some activity, whereas other investigators (other than committed Laetrile scientists) have found none.

Much of the screening that is done is done with strains of mice bearing transplanted tumors. That is, a tumor of a designated type is cut from one animal, chopped up into tiny bits, and then surgically transplanted, bit by bit, into other animals, each of which is genetically identical to the other. The idea is to evaluate whatever agent is being screened in a consistent model system. Today, there are many scientists who are beginning to question the virtue of this procedure as the sole method for detecting new approaches, saying that transplanted tumors may be quite unlike natural or spontaneous ones, that they may possess special enzyme systems which control their response to chemical agents, and that

* Cell surfaces, oncogenic viruses, immunobiology, molecular biology, aging, human cancer, therapy, and communication of scientific information.

they may be anything but representative of tumors in man. Other scientists, of course, swear by the transplanted tumor models, which unquestionably have been invaluable in identifying the cancer drugs we have now. It is a matter of considerable controversy.

In any case, the Sloan-Kettering crew has opted to use spontaneous tumors, in addition to transplanted ones, in their search "to detect novel approaches to cancer." They therefore looked at Laetrile in mice genetically predisposed to spontaneous development of tumors. One drawback of the system is that it is time-consuming. "You must wait 8 to 10 months for the animals' tumors to appear," Old comments. And it is expensive to house and feed colonies of mice while waiting. But, obviously, Old and his colleagues think it is scientifically worthwhile.

In addition to looking at Laetrile in the laboratory, the Sloan-Kettering group decided it needed to know just what claims have been made for it in the clinic and what its various therapeutic effects are said to be. So, Old wrote to physicians here and abroad who are known to prescribe Laetrile for their cancer patients. He asked them whether the drug has a proved value in the therapy of human cancer and, if so, which types. He inquired about the route of administration, the dosage employed, and how rapidly one might expect to see a response. He also asked, "Why has there been so much controversy surrounding the use and effectiveness of Laetrile?"

To date, he says, the responses to his letter have been varied. The information is "not consistent," but answers are still coming in and have yet to be correlated. Nevertheless, one aspect of the situation that interests him is the suggestion that Laetrile eases pain—many clinical reports from underground users say that, once on Laetrile, patients have been able to give up mind-clouding narcotics—and increases well-being, including appetite. Even though these effects are not life-saving, to the terminal cancer patient they are anything but inconsequential.

Among the persons to whom Old wrote was John A. Richardson, M.D., a California physician who is on trial for administering Laetrile to his cancer patients. (The Food and Drug Administration has banned the interstate shipment of Laetrile. Many states, including California, have specific statutes prohibiting its use within state borders.) By some route unknown to Sloan-Kettering scientists, Richardson received a copy of Sugiura's report about his mouse studies and a memo about further research that was being planned.

Richardson's lawyer, George W. Kell, made much more of the information than Sloan-Kettering intended—indeed, far more than it will stand behind. For example, in mid-October he wrote to the California department of corrections in an effort to secure the release from prison of another client whose crime was related to prescribing Laetrile. Kell challenged the California law banning Laetrile on the grounds that it was based on faulty scientific information. "Ultimately, its invalidity will be conceded because, as may be noted from the confidential research report enclosed, it has now been established by the world famed Sloan-

Protection Sought for

A lawsuit that could help give professional workers some of the safeguards enjoyed by union members has recently been filed in Orange, Texas. There the Du Pont chemical company is being sued for $20 million by a chemical engineer, Louis V. McIntire, who claims he was fired by Du Pont for writing a book which satirized large chemical companies. Du Pont declines to comment on the suit while it is in litigation.

The importance of the case is that professional employees, most of whom are not members of unions, enjoy very little legal protection from arbitrary dismissal. If McIntire wins his case, an important precedent could be established in the interests of scientists and other professionals employed by corporations.

In a petition filed last August, McIntire claimed that during 16 years of working for Du Pont there had been no critical evaluations of his performance until he published a book, *Scientists and Engineers: The Professionals Who Are Not.** Written in collaboration with his wife, McIntire's book narrates the behavior of an imaginary chemical corporation, LoChemCo, toward its professional employees, satirizing the corporation's life-or-death powers over its scientists and the way it exploits their ideas without proper recompense. Immediately after publication of the book, the petition alleges, McIntire's supervisors began to find fault with his work.

McIntire was invited to resign but chose to be fired. Du Pont, despite repeated requests, has not provided any reason for his termination. "We claim that his right of free speech under the first amendment was violated," says W. Arthur Combs, partner in the Houston law firm of Combs & Archer which is representing McIntire. "He has been blackballed from getting other employment because he wrote a book somewhat derogatory of his employer."

The McIntire case is of considerable interest to those concerned with protecting the rights of "whistle blowers," Ralph Nader's term for professionals who, by speaking out about corporate abuses, put their duty to the public above their loyalty to an employer. Peter Petkas, former executive director of the Clearinghouse for Professional Responsibility in Washington, D.C., believes the McIntire case may help toward the development of a new theory of law to protect scientists and other professional employees. The theory would hold it a tort to jeopardize, by arbitrary dismissal or other means, a person's right to pursue his profession.

Professionals owe their present vulnerability, Petkas believes, to a lack of interest on the part of both unions and associations. Associations and learned societies have always been extremely reluctant to become involved in matters affecting employment, while labor unions have been equally reluctant to touch anything other than bread and butter issues. Also, scientists and engineers themselves have only in the last few years been willing to make public their differences with an employer or his practices. "The old work ethic of loyalty to an employer has suppressed

* L. V. McIntire and M. B. McIntire, *Scientists and Engineers: The Professionals Who Are Not* (Arcola Communications,, Lafayette, La., 1971), $4.95.

Kettering Institute for Cancer Research that . . ." and he went on to quote Sugiura's statement about the inhibition of lung metastases in mice. "What this means, of course, is that the State regulation outlawing Laetrile . . . is based upon the totally erroneous factual assumption that 'laetriles are of *no value* in the diagnosis, treatment, alleviation or cure of cancer.' "

Kell then made a copy of the Sloan-Kettering reports available to medical reporter Harry Nelson of the Los Angeles *Times* in the hope that Nelson would write the story. (Kell also sent a copy to *Science*.) Nelson had some doubts. He knew, he said, that if he wrote anything it would give credence to an idea that was far from substantial. He did not want to appear to be supporting the Laetrile crowd. Nevertheless, he believed that the establishment's evidence on Laetrile was also weak. Nelson established to his own satisfaction that the reports were authentic and finally decided to write the story, which appeared in the *Times* in late October.

Subsequently, the information office at Sloan-Kettering was bombarded with inquiries, especially from reporters on the West Coast, where the story received more attention than it did in the East. Sloan-Kettering issued what was little more than a perfunctory statement saying that the research was preliminary and tried to let it go at that. Spokesmen said over and over that the institute itself had not released any report, that they were sorry it had been leaked, and that they were most certainly not coming out in favor of Laetrile.

The institute's embarrassment over the situation and its extreme reluctance to discuss it are not surprising. In the first place, the Sloan-Kettering investigators are fully aware of the large Laetrile cult in this country and of the fact that desperate cancer patients will try anything. They did not want to put the prestige of their name behind a drug they were light-years from endorsing, because they knew the harm that it could do. Then, they felt there was no necessity to discuss the details of preliminary research, taking the position that first it should be published and that, in any case, there was nothing far enough along for publication.

Negative Results Found Too

Furthermore, an attempt to reproduce Sugiura's original results was unsuccessful for reasons that remain uncertain. So, as Good says, "We have evidence on both sides of the fence on this."

Also contributing to the hesitancy to talk about Laetrile was their fear that people might presume they had all gone off the deep end because they were studying Laetrile and other suspect cancer therapies. Nor did they want either the public or their scientific colleagues to get the impression that the investigation of unorthodox ideas constitutes a major portion of the institute's activities. It does not.

But the fact that the institute is paying serious attention to Laetrile and other unorthodox ideas which, it thinks, have just enough of a shred of truth to make them worth a second look, is something many people see as a step ahead for science.

—BARBARA J. CULLITON

Satirists and Whistle Blowers

what might otherwise be courageous actions on the part of an individual," says Petkas.

The clearinghouse has handled the cases of several scientists and engineers, among other professionals. McIntire was one who wrote in after reading about the clearinghouse in the Nader treatise on whistle blowing† and was put in touch by Petkas with a Houston law firm. The clearinghouse has tried to assist several university scientists active in matters of public interest who have been denied tenure, apparently because of their public positions. A typical case is that of a professor of mining engineering at the Virginia Polytechnic Institute who had spoken out against strip-mining; according to Fritzi Cohen, the new director of the clearinghouse, there was circumstantial evidence that tenure was denied because of the professor's attitude. His department says his contract was not renewed for financial reasons.

Several government scientists have also been helped by the clearinghouse, including veterinarian meat inspectors employed by the Department of Agriculture and an Agricultural Research Service scientist whose experimental animals were destroyed in the course of a dispute with his superiors. Unlike corporate employees, government scientists have the protection of the Civil Service Commission regulations. Nevertheless, it still takes a person of uncommon courage to speak out, says Robert Vaughn, a law professor at American University who has handled some of the clearinghouse's cases.

One professional society that has begun to take an active interest in the plight of members who are victimized for whistle blowing is the American Chemical Society. At the urging of president Alan C. Nixon, the ACS is proposing to set up a legal aid fund and to institute various sanctions that could be taken against a recalcitrant employer. "We are aware of many cases in industry, government laboratories, and even universities where scientists have been retaliated against when their professional standards interfered with the interests of their employers or funders. This retaliation has taken many forms, ranging from loss of employment and industry-wide blacklisting to transfers and withholding of salary increases and promotions. We are convinced that the visible problem is only the tip of the iceberg," ACS president Nixon stated at a recent conference held at Alta, Utah.

Corporations probably do not maltreat their professional employees in large numbers, but when they do, the individual has had little redress. The initiatives now being taken to safeguard professionals' rights may help to remedy the situation described by one of the characters in McIntire's book: "For all our existence as scientists, we have been deluged with the idea that if we are competent, if we demonstrate excellence in our performance, salary and status will follow. By the time we realize this is not the truth, it is too late for most of us to do anything about it."—NICHOLAS WADE

† *Whistle Blowing*, R. Nader, P. Petkas, K. Blackwell, Eds. (Bantam, New York, 1972), $1.75.