Hayes has also disqualified himself from making decisions on drugs made by Merck Sharpe & Dohme, as well as the Ciba-Geigy Corporation. Merck paid him $12,000 last year to organize and participate in lectures around the country on cardiovascular ailments and drugs, and he received $300 from Ciba-Geigy to deliver a single lecture on hypertension therapy. All decisions involving these firms will be made by Edward Brandt, Jr., the HHS assistant secretary for health.

Once a decision on prescription inserts is made, a slew of additional questions await resolution by Hayes. Among them are:

- Proposed regulations to implement legislation on medical devices approved in 1976, in the wake of disclosures about the Dalkon shield and faulty pacemakers. The Health Industry Manufacturer's Association has complained that a requirement for reporting of virtually all device problems is too burdensome, and that certain restrictions on the sale of devices are unjust. Hayes is likely to grant some relief.
- FDA appointments. Hayes must find persons to direct the Bureaus of Drugs, Veterinary Medicine, and Medical Devices. He recently hired Thomas Scarlett, a former HHS lawyer, as general counsel. Scarlett came to the FDA from a private Washington law firm, where he represented food and drug firms including The Salt Institute, Knoll Pharmaceutical Co., Richardson-Vicks, and the Generix Drug Corp. Scarlett says he will not take part in the FDA's deliberations on the sodium content of foods.

Hayes' success in bringing about reform at FDA will depend in part on how sharp a change he intends and the manner in which his reforms are presented. Surveys taken by the Yankelovich, Skelly, and White polling firm after the election show that public support for vigorous food and drug regulation remains extremely high, almost the only exception to the general appeal of deregulation. So he may have to tread carefully.

Thus far, Hayes has demonstrated a willingness to hear from spokesmen of groups on both sides. Participants report that he affects an inquiring, almost deliberately bland style. His coolness will undoubtedly stand him in good stead in the months ahead.—R. JEFFREY SMITH

Aspartame Approved Despite Risks

New FDA commissioner's first major decision reveals his distaste for regulatory delay

The most important decision made thus far by Arthur Hayes, Jr., as the new commisisoner of the Food and Drug Administration (FDA), was to approve the use of aspartame, a low-calorie sweetener, in foods. The decision ends for the moment a controversy about aspartame's safety that bedeviled the agency for 8 years.

At issue were long-standing allegations by John Olney, a scientist at Washington University in St. Louis, that ingestion of the additive might cause nerve cell and brain damage, and possibly brain tumors. Even Olney concedes that the evidence to justify these claims is not great, but the food law places a strong burden on the manufacturer of an additive to establish that no significant risk exists. In Olney's view, aspartame's manufacturer—G. D. Searle & Co.—had not gone far enough to prove this.

Last year, a special panel of expert scientists appointed by FDA discounted the risk of nerve and brain damage, but agreed with Olney's claim that a link between aspartame and brain tumors could not be ruled out. It recommended that approval be withheld pending further study. Hayes disagreed with this conclusion, but it is noteworthy that two of the three panelists reversed their opinions after reading his decision, and now approve of the additive's prompt release into the marketplace. Notwithstanding this erosion of support, Olney says he is upset by the approval and expects to challenge it in court.

Had Hayes accepted the panel's report, Searle might have brought a lawsuit. But accepting it still would have been the more cautious and therefore probably the easiest choice. Hayes' rejection of that course is probably illustrative of his philosophy. "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," he says. "The question is, are you really trying to assure a zero risk? Though the expectations of the American public are very high, I do not think most people expect zero risk. I'm not prepared to say there is no risk from aspartame—I'd say that for very few things. But I thought it had been demonstrated that there was not a significant risk."

His decision clears the way for the use of aspartame in breakfast cereals, chewing gum, powdered beverages, whipped toppings, puddings, gelatin, and as a table-top sweetener. The additive, formed by a synthetic combination of two naturally occurring amino acids, will not be used in soft drinks because Searle has yet to find a way of keeping it stable for the duration of a soda's shelf life. Consequently, analysts expect it to occupy only about a quarter of the market presently held by saccharin. As such, the approval of aspartame does little to lessen the political pressure behind the moratorium on a saccharin ban.

Olney, a professor of psychology and neuropathology, became interested in aspartame because of his research on the effects of additives on the brain. One of the aspartame hazards that he points to involves an estimated 15,000 persons who suffer from phenylketonuria, a genetic disorder that prevents them from metabolizing phenylalanine, one of aspartame's two major components. Victims of the disorder, almost always detected shortly after birth, experience brain damage and mental retardation unless they are immediately placed on a phenylalanine-restricted diet. There is general agreement that special labeling required by the FDA for all products containing aspartame should be sufficient to warn these persons away.

Where Olney and Hayes split is on the risk to a fetus, in which the disease cannot be detected. In most instances, according to the FDA's calculations, a pregnant woman would have to consume a huge amount of aspartame—akin to

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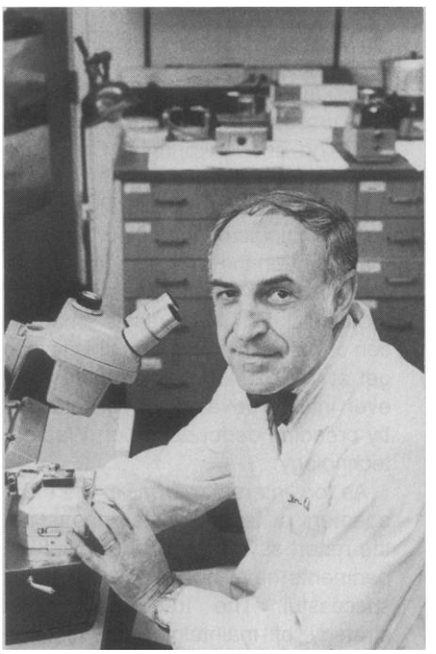
drinking 6½ gallons of diet soft drink or eating 600 tablets at a single sitting—before the fetus would be endangered. There are, however, several thousand women who reach child-bearing age each year whose natural blood levels of phenylalanine fluctuate wildly, and in whom a smaller dose of aspartame could endanger a fetus. Hayes and the FDA panel of experts, which was composed of Walle Nauta, a neuroanatomist, and Vernon Young, a nutritional biochemist, both at the Massachusetts Institute of Technology, and Peter Lampert, a neuropathologist at the University of California in San Diego, all agreed that this risk exists. But they said that the women are probably more vulnerable to the effects of phenylalanine that exists naturally in milk, beef, and other foods. Because it is impossible to keep the women from consuming these foods, it makes little sense to keep aspartame off the market, they argue. They do not challenge Olney's response that, in a few cases, ingestion of aspartame could be the single factor that pushes the blood level of phenylalanine past a threshold and into the danger zone.

A second hazard he cites is the possibility that increased exposure to aspartic acid, aspartame's other major component, might cause nerve cell or brain damage. Although studies show this effect at high doses in animals, both Hayes and the FDA expert panel discounted the risk in humans because a comparable dose would never be consumed. Fetuses are not at risk because aspartic acid cannot cross the placenta. Olney claims, however, that some people are more sensitive to the chemical than others and might therefore be at risk, although he can point to only a single study of nine persons that supports this conclusion. Hayes responds that Olney's interpretation of it is "scientifically incorrect." But in the final FDA decision, Hayes admitted to some concern about the predictions of human exposure. "Prudence dictates that these estimated use levels be compared to actual use levels to ensure the validity of the safety assessment," he wrote. Consequently, Searle will be required to monitor use and keep FDA informed.

The final hazard, and the one on which the FDA panel initially sided with Olney, is the possibility that ingestion of aspartame might cause brain tumors. Searle commissioned two long-term feeding studies in rats and one in mice. All of the parties agreed that the study in mice is negative, but vehemently disagreed about the other two. One included 272 rats, a number that Olney and the FDA panel said was too small. In addition, the control group of rats in that study had a higher incidence of brain tumors than the group exposed to aspartame, a result that the panel termed bizarre and which in its view justified dismissal of the study results. Searle, Hayes, and the FDA's Bureau of Foods said this was merely a statistical anomaly and concluded that the study was definitively negative.

In the other study, a group of 320 rats



Herb Weitman/Washington University

John Olney

Disagrees with aspartame decision

exposed to aspartame experienced 12 brain tumors, while the control group had only one tumor—a disparity that may be intuitively interesting but which all parties agree is not statistically significant. Olney terms the study suggestive of an aspartame-tumor link, using a number of arguments that the FDA panel accepted, but which Hayes rejected. The important point is that two of the panelists, Nauta and Young, are convinced by Hayes' rebuttal to their conclusion about the study. Lampert, the third panelist, refused comment.

One other study was a subject of controversy in the review of aspartame's safety: an experiment at Searle's laboratories with rats exposed to the chief chemical to which aspartame is metabolized in the body. Again, no increase in tumors was detected in the group of rats exposed to the chemical. But Olney has uncovered an internal FDA report that tends to call this conclusion into question. The report, based on an inspection of Searle's internal records, says that supervisors of the study excised a tissue mass on one of the test animals and made incisions over tissue masses in two others; failed to autopsy an animal with a tissue mass; and failed to detect three tumors and two other possible signs of tumors. Literally dozens of discrepancies were found between Searle's documents and the data submitted to FDA. Most important, a former Searle employee told the FDA that the chemical was improperly mixed in the rats' food during the study, a factor that could substantially reduce the amount of the chemical they consumed. He later recanted this story during an in-depth interview with FDA officials, shortly after a former colleague at Searle had visited his new place of employment. The director of the tests, who had left Searle by the time of the inspection, refused through his attorney to be interviewed at all by the FDA. Even though questions about the feed mixture could not be resolved, FDA's Bureau of Foods decided that the study conclusions were valid. Hayes agreed.

Olney says his interpretation of all these studies "is not that aspartame is a proven neuro-oncogen, but that currently available evidence on the issue is contradictory, inconclusive, and of dubious reliability." Hayes told *Science* that there is a distinction between saying that "the data are not there" and "gee, it would be nice to have more, but I really feel I can still decide." He notes that the Ajinomoto Co., Inc., in Japan, which markets aspartame overseas, recently completed an additional study in rats of both aspartame and the metabolite that showed no increase in brain tumors. Although he acknowledges that the study has not been analyzed in depth or sent out for comment, he says it provides additional support for the approval. Olney has not seen a detailed report yet, either, but notes Ajinomoto's potential conflict of interest.

The decision shows that Hayes is inclined to take a different view toward food additives than the two previous commissioners, Jere Goyan and Donald Kennedy. Their criticism of saccharin stemmed in part from their belief that it was only of psychological, not physiological, benefit to the public. Hayes says that psychological benefits can be just as important.

More generally, it provides a case study of how the FDA may resolve difficult issues under his tenure. "In the best of all possible worlds," Hayes says, "Searle would have conducted additional tests of its own. I wish they had, sure. On the other hand, I didn't feel there was justification for saying, okay, let's wait a few years."—R. JEFFREY SMITH