FDA and Panalba: A Conflict of Commercial, Therapeutic Goals?

Last month the National Academy of Sciences–National Research Council sent a final report to the Food and Drug Administration (FDA) on its review of the therapeutic claims made for 80 percent of the medicines Americans use. The review—carried out by 30 NAS–NRC panels, each responsible for particular categories of disease—concluded that manufacturers were unable to provide substantial evidence to back up one or more claims made for a significant proportion of the preparations.

Five NAS–NRC panels reviewed anti-infective agents that combine one antibiotic with another in fixed ratios, or an antibiotic with one or more sulfonamides. In addition to finding about 40 such products to be ineffective, by reason of being no more effective than their components used singly, the panels judged at least 50 combinations to be dangerous. The hazard was said to be not merely to the individual user, but to the public at large, because these agents can permit resistant strains of bacteria to proliferate. The mixtures held to be hazardous as well as inefficacious are the "pen-streps" (penicillin and streptomycin), the "pen-sulfas" (penicillin and sulfa), and Panalba (tetracycline and novobiocin).

Panalba is one of the most popular items manufactured by the Upjohn Company of Kalamazoo, Michigan, a prominent member of the Pharmaceutical Manufacturers Association (PMA). It was expected that the FDA, which received the NAS–NRC judgment on Panalba well before the final report on the entire efficacy review was released, would move to take it off the market; and it was predicted by Commissioner Herbert L. Ley, Jr., in testimony on Capitol Hill, that such a move would face a prolonged legal challenge. The FDA *did* move to take Panalba off the market, and Upjohn *did* file a lawsuit, in federal court in Kalamazoo.

The Panalba case is significant not only because of its impact on the continued sale of a drug termed hazardous in the NAS–NRC study but because it raises much deeper issues bearing on the "rights" of drug companies, physicians, the government, and patients. The case and congressional criticism have also highlighted what a U.S. senator called "serious ethical questions" on the part of the drug company, a conflict of interest within the American Medical Association, a remarkable flip-flop in FDA enforcement attitudes, and an abortive, late-hour intervention by HEW Secretary Robert H. Finch on behalf of the drug company.

The narrow issue before Judge W. Wallace Kent was whether to grant the petition of the company—which was supported by PMA—for an injunction against the Food and Drug Administration to force the agency to grant an administrative hearing. For Upjohn, the overriding point was its "right" to such an administrative hearing—a procedure which would allow Panalba to remain on the market while the hearing was conducted and the matter perhaps litigated in the courts—and also the "right" of physicians to prescribe as they wish. As for PMA, the lawyer acting in its behalf argued that the FDA had to be prevented from making "an authoritarian official determination of what is good for medicine." He called the Panalba action "truly a test case" both for "the doctors in this country and the drug industry."

Herbert L. Ley, Jr.

The government saw things differently. In court a Department of Health, Education, and Welfare lawyer argued that the case will control "the future of patient care in the United States." And FDA Commissioner Ley said in congressional testimony that the struggle over hazardous and ineffective combinations of antibiotics was at bottom a "conflict between commercial and therapeutic goals."

Judge Kent ruled on 11 July. On the crucial issue of an administrative hearing he held that the company was not entitled to one "as a matter of right." But this defeat for Upjohn—and the industry—was considerably softened. To take one example, the judge said that the FDA could not now stop sales of Panalba (which, in the United States alone, were running at a rate of $1.5 million a month in 1968). Instead, he said, the agency first must act on objections filed by Upjohn to the decision of the commissioner to refuse to certify Panalba as safe and effective. Once the commissioner had acted on the objections (he rejected them on 9 August), he still would be barred from decertifying Panalba for 30 days (after which, presumably, the company could carry the case to a court of appeals that would have to decide whether to allow sales to continue).

The public-interest forces involved in the Panalba struggle were unusually formidable. They included an unbroken rank of medical scientists specializing in the treatment of patients with infections; a strong law that Congress enacted without audible dissent; an agency determined—albeit belatedly—to enforce the law; the NAS–NRC verdict; and the chairman of two actively concerned congressional subcommittees, Representative L. H. Fountain (D–N.C.) and Senator Gaylord Nelson (D–Wis.).

The counterforces also were unusually formidable. Predictably they included the PMA, whose members make 95 percent of the prescription drugs sold—and consistently enjoy profit rates higher than those of any other industry, according to Federal Trade Commission records; the American Medical Association, which derives almost half of its income from drug advertising in its *Journal*; and two leading Washington law firms, Covington & Burling, repre-

NEWS IN BRIEF

● **SOVIET PHYSICIST TO TOUR U.S.:** In October a well-known Soviet physicist, Pyotr Kapitsa, is expected to tour a half dozen American universities and also visit the National Academy of Sciences (NAS) in Washington. Kapitsa, who heads the Institute of Physics in Moscow and aided in the development of Sputnik I, will be visiting the United States for the first time following a visit to Canada where he will lecture at the University of Alberta. In the U.S. he is expected to visit Harvard, Cornell, Stanford, Caltech, Rockefeller University, and the Bell Telephone Laboratories in Washington, as well as the National Academy of Sciences. The 75-year-old physicist, well known for his work in magnetism and low-energy physics, will lecture on a number of topics, including the education of scientists in the Soviet Union. Kapitsa, who has been allowed to attend many international scientific meetings, is regarded in the Soviet Union as an outspoken scientist who is openly critical of some Soviet policies, but loyal to Communist ideas in his public statements and writings. His travel plans have been confirmed by the Soviet government, and an NAS official told *Science* it was likely that the Soviet scientist would be able to come to the U.S. During the 1920's, Kapitsa worked at the Cavendish Laboratory in Cambridge, England, and is widely recognized for work in magnetic research.

● **STUDENT LOAN BILL HELD UP:** Among items of unfinished business awaiting Congress when it returns from its summer recess after Labor Day is an emergency bill aimed at increasing availability of bank loans to college students who are now finding it hard to obtain loans for college because of high interest rates. On 12 August the Senate acted to pass a measure that would have allowed the federal government to pay lenders "incentive allowances" in addition to the interest of up to 7 percent guaranteed under the 1965 higher education act. The House failed to act before the recess, despite prodding from the Administration, which had hoped that the measure would clear Congress in time to help students obtain loans before the opening of the new academic year. Educators estimate that failure to pass the bill may prevent 150,000 to 200,000 students from getting loans.

senting Upjohn, and Wilmer, Cutler & Pickering, representing the PMA. But there was also in the Panalba case the intervention, on the company side, of Robert H. Finch, Secretary of HEW, which was triggered by Representative Garry E. Brown (R–Mich.), of Kalamazoo, and—odd as it may seem, and up to a certain point in time—of the FDA itself.

In defending Panalba the Upjohn Company has ignored invitations to testify before the interested congressional subcommittees. It preferred a day in court, where lawyer Stanley L. Temko of Covington & Burling warned that a halt in the sale of Panalba would inflict "irreparable injury" on Upjohn. The drug accounts for 12 percent of the firm's domestic gross income.

The PMA had a broader concern: If the sale of Panalba could be halted without the years of delay that might accompany a grant of a hearing, the FDA would have a clear legal track to stop the sale of the pen-streps and the pen-sulfas. In addition, there would be ominous implications for other drugs that, even if not shown to be actually hazardous, had never been shown to be effective—but that nonetheless produce hundreds of millions of dollars a year for the companies that manufacture them.

For many physicians—Upjohn says that 23,000 regularly prescribe Panalba—the stakes were of a different order, having to do with the claim to an unrestricted "right" to prescribe, even if that "right" is founded on advertising, promotion, and other forms of nonscience. Panalba, Temko told Judge Kent, is one of the medicines most often prescribed, and since it entered the market in 1957, he said, 750 million doses have been administered. Indeed, fixed-ratio combinations of one kind or another—including Panalba and the pen-streps and the pen-sulfas—account for 83 (more than 40 percent) of the 200 most popular prescription products.

For patients, the important issues were not profits, wounded egos, or even high prices (Panalba is not sold under a generic name) but a risk of adverse reactions that is at least doubled by the use of two antibiotics when one suffices. "The real 'gut' issues of the antibiotic combination controversy are exceedingly simple," Commissioner Ley said in a speech in February. "Are we in this country dedicated to a rational, scientific basis of antibiotic therapy or are we dedicated to contributing unnecessarily to the 1,500,000 hospital admissions annually attributed to adverse reactions to drugs?" This view was solidly supported in the medical-scientific community. Five NAS–NRC panels, appointed at FDA's request to review all available evidence on the efficacy of anti-infective agents, concluded that mixtures are ineffective as fixed-ratio combinations because none is more effective than its components used separately. In fact, all 30 members of the panels concluded unanimously that these products "no longer belong in the therapeutic armamentarium" and should be removed from the market. The panel chairmen and Dr. Louis Weinstein, author of the "Microbial Diseases" section of the authoritative *Pharmacological Basis of Therapeutics*, in affidavits filed with Judge Kent, said that scientific literature contains no adequate, well-controlled studies to support the claims made for antibiotic combinations. This is the position held "without exception by the outstanding experts in the antibiotic field," said panel chairman William M. M. Kirby, a professor of medicine at the University of Washington. According to another panel chairman, Dr. Heinz F. Eichenwald of the University of Texas, Dallas, "There are few instances in medicine when so many experts have agreed unanimously and without reservation." None of this was any surprise, because the experts had been denouncing fixed-ratio antibiotic products from the time the FDA allowed them to enter the market, starting almost two decades ago. The combinations, of course, have the appeal of "convenience" to practitioners who prefer "shotgun" therapy to painstaking diagnosis. But such alleged advantages come at the price of preventable injury to patients who get an antibiotic they do not need, or who cannot get enough of a component they do need without also getting more of another potent agent they do not need.

The issues raised by the antibiotic combinations have, with extraordinary clarity, exposed a conflict between profit and principle in the American Medical Association. For at least a dozen years AMA's respected Council on Drugs has condemned fixed-ratio preparations as "irrational." On 16 May, by unanimous vote, the Council endorsed the stand of the NAS–NRC. In 1960 a former chairman of the Council, Dr. Harry F. Dowling of the University of Illinois, told an AMA meeting that none of the antibiotic combinations "is justified." Even as he spoke, the *Journal of the American Medical Association* (*JAMA*)

was carrying 18 full pages of advertising for antibiotic combinations. In 1961 Dr. Ernest B. Howard, now executive vice president of the AMA, assured the late Senator Estes Kefauver that the Board of Trustees "has reached a decision that the mixtures . . . will be gradually withdrawn from the *Journal*, during the next two to three years." Although 8 years have gone by, such ads remain abundant in *JAMA*. At a hearing on 6 May, Senator Nelson wondered if the reason was "that advertising these drugs provides an important source of revenue." Kirby took pains to display two recent full-page ads in *JAMA* for Panalba, which, he said, are fortified by the "implied endorsement" of the AMA. Early this year, the AMA, which was seeking tax-reform legislation to exempt profits from its ads on the ground that they are "educational," had a choice before it: to continue to run ads that, as Nelson put it, "promote bad medical practice," or to publish a unique "white paper" signed by all five chairmen of the NAS–NRC panels. They were so concerned about their findings that they wanted the medical profession to be alerted by *JAMA* because of its wide circulation. However, the request to *JAMA*—made by Duke C. Trexler, executive secretary of the NRC—was, he said, refused "bluntly, flatly," and without explanation by Dr. John H. Talbott, editor of *JAMA*. The refusal was "indefensible," Dr. John Adriani of New Orleans, chairman of the Council on Drugs, told Senator Nel-

NAS–NRC Verdict on the Benefit–Risk Ratio of "Combinations"

Panalba, the drug at issue in the Kalamazoo court case, is one of the fixed ratio combinations criticized by the NAS–NRC review. The tetracycline component of Panalba is effective against a broad spectrum of infections. The other ingredient, novobiocin, has a spectrum of antibacterial activity conceded by Upjohn to be covered by several other safer and more efficacious drugs. Indeed, a review panel of the NAS–NRC found the benefit-to-risk ratio so lopsided that it recommended removal of novobiocin from the market. The vote on the injectable form was 6 to 0, and on the oral form, 5 to 1. Although the panel said that oral therapy is not indicated in serious infections, the FDA, in May, decided to let novobiocin remain on sale "for those serious infections where other less toxic drugs are ineffective or contraindicated." This new, severely restricted labeling is in a special, boxed warning emphasizing "the rapid and frequent emergence of resistant strains, especially staphylococci," as a risk in the use of novobiocin.

That the same dread threat of "staph" epidemic exists with the "pen-streps" has been emphasized by Dr. Calvin M. Kunin, a NAS–NRC panel chairman who heads the Department of Preventive Medicine at the University of Virginia. The "widespread" and "indiscriminate" use of the pen-streps, he told Senator Gaylord Nelson's Senate Subcommittee on Monopoly, has caused a proliferation of resistant organisms throughout the world and "has almost led to disaster," thus threatening injury "not merely to the individuals receiving such combinations, but to all society."*

The boxed warning for novobiocin also warns, on the basis of NAS-NRC findings and FDA's own studies, but with Upjohn's concurrence, of "the high frequency of adverse reactions, including hepatic dysfunction and rashes." In testimony on 27 May, FDA commissioner Ley told the Subcommittee on Monopoly, "Approximately one out of every five patients who receives the novobiocin component of Panalba is expected" to have an allergic or hypersensitivity type of reaction. Most such reactions are "merely irritating," he continued. "You can't sleep for several nights or a week, or you may break out in a very unpleasant, uncomfortable rash." There "must be literally hundreds of thousands" of such reactions a year, Ley estimated. In addition, a "smaller proportion" of Panalba patients "experience temporary but very severe liver damage as a result of the novobiocin component." Finally, he said, "a still smaller number" suffer blood disorders. These accounted for 11 of the 12 fatalities among Panalba users that Upjohn has reported to the FDA. But the agency emphasizes that adverse reactions to all drugs "are grossly under-reported." In the case of the pen-streps, yet another NAS–NRC panel chairman, Dr. William L. Hewitt, professor of medicine at the University of California, Los Angeles, said that, in addition to occasional reports of "dramatic streptomycin toxicity," there are, more importantly, "possible countless instances" of a cumulative, hidden threat to the hair cells in the ear, and thus to the sense of hearing.

Are the hazards posed by Panalba and the penicillin combinations offset by therapeutic advantages? The FDA and the NAS–NRC say they are not. This is all the more troubling because of a report—which first emerged on 13 May in a hearing of the House Intergovernmental Relations Subcommittee—that the amount of novobiocin in Panalba is sufficient to do harm but insufficient to do good. The report was made by Dr. Max B. McQueen who, as a medical officer in the FDA's Division of Anti-Infective Drugs, analyzed a series of studies of Panalba that Upjohn itself sponsored but failed to submit to the FDA as required by law, and which were discovered in its files by an agency inspector.

These studies showed that the amount of novobiocin that becomes available in the bloodstream is not only a subtherapeutic dose but is occasionally even zero. McQueen's report was included in an affidavit filed with the federal court in Kalamazoo. In another affidavit, Winton B. Rankin, Deputy Commissioner of the FDA, told of a meeting on 1 May at which Dr. Fenimore T. Johnson, director of product research for Upjohn, admitted—despite the company's claims that Panalba was superior to its components used separately—that the company "had substantiated evidence of the efficacy of novobiocin but not of the combinations."—M.M.

* The NAS–NRC panel on the fixed-ratio penicillin-sulfonamide combinations ("pen-sulfas") said, "Reactions to these drugs are common, and . . . can be severe and even fatal. . . . Another troublesome aspect . . . is that it is difficult to detect the drug causing an untoward reaction when multiple drugs are used." In addition, the panel warned that the pen-sulfas often *decrease* antimicrobial effectiveness because of antagonism among the components, a problem averted by their separate use as determined by the need of the individual patient.

son. "It boils down to this," he said. "They need every dollar they can get." The *New England Journal of Medicine* was offered the "white paper" and, on 22 May, published it.

Congressional committees have continued to play a pivotal role in drug politics, particularly by putting pressure on federal agencies. Last March, for example, Roy D. Sanberg, an inspector for the Food and Drug Administration, went to Kalamazoo to search Upjohn's files in the Panalba case. He discovered a series of controlled studies which the company had sponsored in 1960 and earlier. FDA regulations required submission of materials such as these in 1964 and 1966. Nothing was known of Sanberg's discovery until 13 May, when an analysis of them by the FDA's Dr. McQueen was put into the record of a hearing by Representative L. H. Fountain's House Intergovernmental Relations Subcommittee. At a hearing of the Senate Subcommittee on Monopoly, Senator Gaylord Nelson said that Upjohn's failure to offer the studies raised "very serious ethical questions." William Goodrich, the FDA counsel, testified that there was a possibility of "regulatory action of a criminal nature." Upjohn's explanation was that "no valid conclusions could be drawn" from the studies.

One of the studies, conducted by Dr. Bennett W. Billow, was a double-blind trial of 50 persons who were moderately to severely ill with a pneumonia treatable with tetracycline. Dr. Billow found that Panalba was no more effective than its tetracycline component used alone. Dr. E. L. Foltz conducted four in vitro crossover studies to compare efficacy by measuring blood levels after use of Panalba, novobiocin alone, and tetracycline alone. For Panalba, the results were unfavorable. They showed, Dr. McQueen said, that Panalba produced "lower blood serum levels for both novobiocin and tetracycline than the levels attained by the use of either used alone."

In earlier hearings, Fountain was critical of Dr. Ley, who, on 1 July 1968, was promoted from director of the Bureau of Medicine to FDA Commissioner. The subcommittee probed Dr. Ley's handling of chloramphenicol sodium succinate, the injectable form of the antibiotic most commonly known by the Parke-Davis trade name of Chloromycetin. Fountain was appalled by the FDA's "lack of vigor in protecting the public, and especially children," against the continued marketing of a drug with a labeling recommending sites for injection, the efficacy of which had not been established and which could result in irreparable harm and even death. He told Dr. Ley that his performance in this case "appears to border on indifference." The commissioner has said privately that the hearings turned him into a hard-liner on efficacy, not only because of the sting in the Fountain charge but also because of sharp work by the subcommittee staff that exposed weaknesses in his executive echelons, of which he had been insufficiently aware.

Dr. Ley's performance in the early stages of the antibiotic combination controversy also drew congressional fire. For one thing, despite the urgency felt by the five NAS–NRC panel chairmen about the need to get the "white paper" swiftly before the medical profession, Ley had sat on it for 6 weeks. This period, it must be noted, was one of tense uncertainty because of the transition to the Nixon Administration. For another thing, in what Ley later told me was "a mistake," he granted Upjohn and E. R. Squibb, producer

After Kefauver, Drug Claims Tested

Until the late 1930's, a manufacturer could market a drug without first being required to demonstrate that it was safe and effective in the uses for which it was labeled. The death of 107 people in the Elixir of Sulfanilamide disaster of 1937 led to the passage of the Food, Drug, and Cosmetic Act of 1938. Now, for the first time, manufacturers were required to present premarketing evidence of safety. In 1959, Senator Estes Kefauver, then chairman of the Senate Subcommittee on Antitrust and Monopoly, began 2½ years of hearings that produced overwhelming evidence of the need for reform legislation, including a requirement for a premarketing demonstration of efficacy. President Kennedy agreed. In March 1962, in his message on Consumer Protection, he said that, of the new single entities listed since 1956 by the American Medical Association's Council on Drugs (which does not list combinations at all), more than 20 percent "were found, upon being tested, to be incapable of sustaining one or more of their sponsor's claims regarding their therapeutic effect. There is no way," he said, "of measuring the needless suffering, the money innocently squandered, and the protraction of illness resulting from the use of such ineffective drugs."

The thalidomide catastrophe rescued Kefauver's reform proposals from oblivion, and, in the fall of 1962, propelled them, as the Kefauver-Harris Amendments, through Congress without a dissent being heard. The efficacy provisions require the sponsor of a drug to provide "substantial evidence," which the law itself defines as consisting of "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." Although the efficacy provisions took effect forthwith for new medicines, a 2-year period of grace was granted for the 1938–1962 products. These include most of the drugs prescribed today—approximately 4000 formulations sold by 237 companies. The FDA directed manufacturers to search their files and report, by September 1964, if these contained information showing that any claim—whether for efficacy or safety—was not warranted by actual experience, and if promotional materials failed to disclose any necessary warning or contraindicated use, along with any side effects or untoward reactions that may have appeared after marketing had begun. In July 1966, with an order published in the *Federal Register*, the FDA required manufacturers to submit any materials in their files bearing on efficacy to the National Academy of Sciences–National Research Council (NAS–NRC), which, under a contract initiated by the then Commissioner James L. Goddard, was beginning a survey of the effectiveness of the 1938–1962 drugs. Essentially, Goddard felt that only by enlisting the NAS–NRC could he get the job done. His resources within the FDA were extremely limited, whereas, he believed, the NAS–NRC could offer the help of the country's top scientific talent.—M.M.

of Mysteclin-F, which, simultaneously with Panalba, had been declared ineffective as a fixed-ratio antibiotic combination, a period of 120 days atop an original 30 to submit "substantial evidence" of efficacy (this was before the safety issue also was raised). The companies used the extra time to solicit almost 3500 letters of support—"testimonials," Ley called them—from the profession. Some of the letters picked up verbatim phrasing suggested by the companies. A number of letters from doctors at the Oak Forest Hospital in Oak Forest, Illinois, were identical to letters from doctors at the Chicago State Hospital. The Maine Medical Association circularized its membership with a paraphrased list of guidelines for letters that had been prepared by Squibb. On 28 January, J. C. Gauntlett, a vice president and director of Upjohn, sent an appeal to doctors to protest to the FDA on the ground that it was violating "the physician's right to prescribe." Dr. Hewitt of the University of California, in his appearance before Senator Nelson, denounced Upjohn's "Dear Doctor" letter as an "ill-founded, confusing, threatening, and dangerous" method for deciding a scientific issue; as "bold, unscrupulous and selfish"; as "insulting to the intellectual and scientific training of physicians"; and as "detrimental . . . to the practice of medicine as well as to the necessary efforts of regulatory agencies to protect the public from truly unscrupulous promoters." But it may tell us something about the state of the profession to note the number of letters of support the FDA got in comparison with the 3500 "testimonials." The number was ten.

Political Overtones

The controversy had other political overtones. Since January 1967, the Third Congressional District of Michigan, which includes Kalamazoo, has been represented by Garry E. Brown. On 15 May he voluntarily presented himself before the House Intergovernmental Relations Subcommittee as a "Congressman-ombudsman" summoned by high duty to protect any constituent—personal or business—that becomes "a victim of the impersonal, remote and awesome structure of the Federal Government."* It was in this role of "Congressman-ombudsman," Brown testified, that he had arranged a meeting between a delegation from Upjohn, including its president, Ray T. Parfet, Jr., and its Washington counsel, Stanley Temko, and Robert H. Finch, Secretary of HEW. Finch's involvement had been a surprise disclosure when the hearings opened 2 days earlier.

On 26 March, the Bureau of Medicine formally recommended to Ley that FDA stop certifying Panalba as safe and effective because its novobiocin component created serious risks without commensurate benefits. On 30 April, the commissioner said in a memo to Finch that, at a meeting the next day, he would (and he did) tell Upjohn that FDA was discontinuing certification of Panalba, which would make further distribution illegal; that all outstanding stocks were being decertified and had to be recalled by the company, and that Upjohn would have to send a "Dear Doctor" warning letter about novobiocin and Panalba. The memo was routed through Surgeon General William H. Stewart, Acting Assistant Secretary for Health and Scientific Affairs; whether it reached Finch, who declined to testify, was not established. At the 1 May meeting, Temko attacked FDA's plans as "drastic and shocking." The same day, Ley sent a memo on the meeting to the Secretary.

On 5 May, thanks to the intervention of Representative Brown, the Upjohn forces met with Finch and Under Secretary John G. Veneman. The company's proposals, repeated later in the day to the FDA, were that there be no publicity about the Panalba matter, that a "Dear Doctor" letter not be sent, that certification of Panalba be resumed promptly, and that a hearing be granted without interruption to sales of Panalba. Later the same day, Veneman phoned Deputy Commissioner Rankin with an instruction: to "consider" a "possible resolution" that turned out to be identical to Upjohn's own proposals.

"The basic question before us," Ley said the next day, 6 May, in a memo to Dr. Stewart (the commissioner meanwhile had been instructed to stop addressing memos to Finch), "is whether the Government is prepared to move promptly and effectively to stop the use of a hazardous drug when the available facts and the national drug law show clearly Panalba represents serious hazards to patients who take it which are not balanced by any benefit to be expected." The commissioner said that the evidence made it impossible for him to certify Panalba to be safe and effective. He said he could not suppress publicity, as Upjohn had requested, particularly because Senator Nelson and Representative Fountain had scheduled public hearings and "are insisting that when public interest must be weighed against private interest the former should take precedence." As for FDA holding an administrative hearing, Ley said he would grant one, with sales of the drug in question continuing, if the issue is efficacy alone; but in a case such as Panalba's, he said, a hearing would be considered, with certification stopped, only if Upjohn could supply reasonable grounds for holding one—meaning "substantial evidence" of efficacy. If HEW is unable to back him, Ley concluded, "I request your instructions as to the Departmental position that I should follow."

Finch Intervenes

The Finch episode came to a climax—or series of climaxes—3 days later, on Friday, 9 May. At 9:15 a.m., C. C. Johnson, who, as Administrator of the Consumer Protection and Environmental Health Service, is Ley's boss in HEW, phoned the commissioner to report that Stewart had approved his recommendations for the course of drastic action against Panalba. Fifteen minutes later, however, William Goodrich, the assistant HEW counsel, phoned with a contradictory message: "The Secretary said we must have a hearing." Although Finch wanted it to be convened "with all possible dispatch," it could take 4 months even to get a hearing under way. Goodrich, who testified that he had acted at the request of Robert Mardian, general counsel of HEW, told the subcommittee that at this point Finch had not seen the 6 May memo in which Ley said that he could not in conscience certify Panalba to be safe and effective.

An hour later, at 10:30 a.m., W. Donald Gray, an investigator for the subcommittee, who was unaware of the events of the preceding 75 minutes, notified the FDA that he wanted to examine its files on antibiotic combinations. He was told the files would be ready for him within an hour. Shortly, however, the FDA informed Gray that there would be a delay because, it was disclosed, Finch had "an unwritten policy that requests from congressional committees regarding 'potentially explosive situations' were to be called to the Secretary's attention." Was Presi-

* In the proceedings before Judge Kent, local counsel for Upjohn was Henry Ford, Jr., of the Kalamazoo firm of Ford, Kriekrad, Brown & Staton. "Brown" is the congressman. However, he says he left the firm when he entered the House 2½ years ago. He received at least $1000 from the law firm in 1968, as disclosed in his filing, with the House Committee on Standards of Official Conduct, but he says this was entirely in settlement of his severance.

Trouble at Nevada Research Center

The University of Nevada's fast-growing Desert Research Institute (DRI)—a recognized leader in certain fields of atmospheric and arid lands research—is at a critical crossroads because of the forced resignation of its director and chief architect, Wendell A. Mordy. Mordy was asked to resign by the university regents last spring in what appears to have been the climax of an increasingly bitter struggle between Mordy and the university's new chancellor, Neil Humphrey.

Mordy was brought to Nevada in 1960 by a previous chancellor and given the task of building up the then newly-authorized research institute. Over the next 8 years he attracted several leading researchers to the staff, organized a prestigious scientific advisory board that included six members of the National Academy of Sciences, greatly increased the institute's annual dollar volume of research (to a level currently in excess of $3 million), and won the institute an international reputation in certain fields, notably cloud physics, desert biology, and water resources (see *Science*, 30 August 1968).

Last April, however, Mordy was forced to resign under circumstances that have never fully been made public. Reports in Nevada newspapers indicate that Chancellor Humphrey, at a closed meeting of the regents, stated that either he or Mordy would have to go. Humphrey reportedly told the regents that he had to fight constantly with Mordy over a variety of policy matters. The regents, by a split vote, decided that Mordy would have to vacate his posts as director of DRI and as a vice-chancellor of the university, though he was allowed to remain as research professor earning essentially the same salary.

Sources of the Conflict

University observers differ in their interpretations of what lay behind the struggle between Humphrey and Mordy. Some believe it was primarily a "personality conflict" between two strong-willed men. Others describe it as a "power struggle." And two scientists in Mordy's camp believe the clash developed from a basic philosophical disagreement. They picture Humphrey, who has a business administration background, as a man interested in balancing the books and keeping the university's political fences mended, in contrast to Mordy, whom they see as a freewheeling entrepreneur interested in building a first-rate institution but not terribly concerned about administrative niceties or about how many enemies he might be making in the process. Mordy and Humphrey are said to have clashed on a number of issues over the years—including DRI's bookkeeping practices and the operation of the university's computer center.

Whatever Mordy did to offend the Nevada administration seems not to have bothered officials of the University of Montana, who quickly signed Mordy up as a consultant to help them organize a new Center for Natural Resources. Two Montana officials sent down to Reno to investigate Mordy found that "even Mordy's worst enemies had considerable respect for what he had done."

What impact Mordy's departure will have on DRI remains to be seen. The institute was faced with a budget squeeze this year because of the nationwide cutback in National Science Foundation support, a planned reduction in funds from a Nevada-based foundation, and the failure of the state legislature to appropriate enough extra money to make up the difference. Whether DRI can continue its remarkable growth will depend largely on whether the university is able to attract another first-class director, and on whether that director is successful in persuading the state to increase its level of support. The outcome may hinge on how Nevadans answer the question of whether their relatively poor and unpopulated state needs—or can afford—a high quality research institution.—PHILIP M. BOFFEY

dent Nixon invoking "Executive privileges," the subcommittee inquired. No such claim was being made, Assistant Secretary Creed Black said—but he was unable to cite a legal basis for refusing to open the files. After lunch, Goodrich testified, Finch was briefed on the situation. The Secretary authorized that the files be opened. Goodrich phoned at 3 p.m. to tell Ley of the decision.

Once the files were examined, subcommittee chairman Fountain told the hearing, it was "apparent that the decision with respect to the marketing status of this drug [Panalba] was made by the Secretary, rather than the Commissioner." This was unprecedented: In the approximately 15 years during which a succession of Secretaries had delegated their power over antibiotic certification to the FDA, none had ever been known to try to prevent a commissioner from acting to protect patients from a serious hazard.

Plans Endorsed

At 3:10 p.m., soon after Finch knew that the documents revealing his involvement would be discovered by the subcommittee, he rescinded his earlier order to FDA to leave Panalba on the market while a hearing was being held and endorsed the commissioner's plans for Panalba.

(Finch's defenders claim that he was misled, at the meeting with Upjohn executives and counsel, into believing that the FDA had inexcusably reneged on a promise to hold a hearing. Such a hearing, of course, is available so long as the issue is efficacy alone. But efficacy had been the sole issue in the Panalba case only for a time.)

On 27 May, the Upjohn Company responded by asking Judge W. Wallace Kent for a temporary restraining order and an injunction to stop the Food and Drug Administration from decertifying Panalba without a hearing. In granting the order (after a discussion in chambers) and the injunction the judge constructed a legal structure whose intricacy awed students of food and drug litigation. A primary question was how *any* court could assume jurisdiction in a case in which the FDA had pending before it, and was required to rule on within 30 days of filing, the company's objections to the agency's declared intention to stop certifying Panalba as safe and effective. Judge Kent answered the question simply by holding that, in issuing the decertification order, the FDA in fact had completed final ad-

ministrative action. But the Food, Drug, and Cosmetic Act of 1938 says that, when administrative action is completed, a company may carry a grievance to a court of appeals; how, then, could a lower court in Kalamazoo take jurisdiction?

The judge met this situation with a finding that Upjohn was entitled to the extraordinary relief of a preliminary injunction. This finding, in turn, required the company to show that it probably would prevail in the administrative process or on the merits in a judicial review. However, the judge held that the company did *not* have to show a strong likelihood of success in an administrative process. The basis for this holding was the statement he made repeatedly to counsel, when the case was argued on 29 June, that he was not at all concerned with the issues of safety and efficacy, only with the legal issues. Thus, as the FDA summed up Judge Kent's ruling in a brief filed later in another injunction case, he "refused to recognize" that Upjohn "had been wholly unable to produce" adequate and well-controlled studies to demonstrate the efficacy of a potent drug it had sold for 13 years, and that his injunction would allow the firm to continue to make claims of efficacy which it had not documented. While ignoring the commissioner's explicit finding that Panalba created an unwarranted hazard, and the documentation of unnecessary fatalities in the affidavits, the court was able to hold that an injunction would in no way seriously threaten the public health—but was necessary to avert irreparable injury to Upjohn. Upjohn, the judge said, was entitled to interim relief because it had been placed in "an extremely awkward position" by the refusal of the FDA to divulge the names of the NAS–NRC panelists—"faceless judges," Upjohn lawyer Stanley Temko had called them. The judge rejected the FDA's explanation that NAS–NRC had insisted on anonymity "so as to avoid pressures from commercial sources" (8 July, in its final report, NAS–NRC listed the 180 members of all 30 panels). He also said that the commissioner had placed complete reliance on the anonymous NAS–NRC panelists—even though the commissioner said the panel reports were advisory and the final decisions were his alone.

On challenged, intricate legal grounds, a federal judge in Upjohn's home city assumed jurisdiction and allowed the company to go on for more than 3 months selling a product that the NAS–NRC and the FDA found to be a serious hazard and ineffective. In mid-August, it was disclosed that the judge is the unpaid chairman of the Kalamazoo Science Foundation, a charitable organization, half of whose trustees are connected with Upjohn.

It will be recalled that the commissioner, Dr. Herbert L. Ley, Jr., said the conflict over the combination antibiotics was "between commercial and therapeutic goals." If he is correct, the Panalba case reaches a great question of our time: In a struggle between public interest and special interest in which the stakes are needless exploitation, injury, and even death to helpless patients, can American institutions function reliably to protect the public?

—MORTON MINTZ

Morton Mintz, a reporter for the Washington Post, *is author of* The Therapeutic Nightmare. *For his reporting on thalidomide in 1962 he was awarded the Heywood Broun, Raymond Clapper, and George Polk memorial awards.*

Open University: Britain's New Venture in Higher Education

London. Adult education classes, TV and radio instruction, correspondence courses, home experimental kits—all of these are to be found in many countries today, usually as low-ranking appendages of traditional institutions of higher education. Britain is now planning to pull together all these techniques, plus some others, in an ambitious and long-planned effort to create an autonomous, high-quality university that will enable adults throughout the United Kingdom to work part time for undergraduate as well as graduate degrees.

Known as the Open University, the new institution comes up against the stigma of dubious quality often associated with after-hours instruction. But the Open University, scheduled to accept its first students in January 1971, is aiming for standards of performance that will compare well with any in this land of academic snobbery. For this purpose, its creators have gone far beyond the usual concepts of adult education and have formulated an institution that is attracting the scrutiny of educators throughout the world. Although it will operate on a national basis, the Open University will have its own central campus in a new city, Milton Keynes, about 50 miles from London. It will have a full-time faculty, initially of about 100, half of whom have now been hired from among more than 1000 applicants who already hold academic posts. (In the sciences, there were nearly 400 applicants, 72 of them at the professorial level.) The campus, now under construction, will include laboratory, computer, and library facilities, and will be the center of a fairly broad spectrum of research programs involving graduate and postdoctoral students. Tied into the campus will be several hundred local centers throughout the country, where students will meet with tutors—these will be "moonlighters" drawn from nearby educational institutions. At these centers, students will be able to listen to or borrow tape-recorded lectures, and eventually the centers will be equipped with video tape equipment. Keyed to the course of work, most of which will be embodied in correspondence materials, will be regular lectures and demonstrations on TV and radio. The correspondence materials are being specially prepared by the teaching staff and various outside groups, and work is in progress on laboratory kits that can be sent through the mail. In an effort to escape the aridity that often characterizes broadcast instruction, some 30 academics have been detailed to the BBC to study TV and radio production. Each student will be required to take 2 weeks of full-time instruction per summer at classroom and laboratory facilities that the Open University will borrow at schools throughout the country. Finally, though many staff members are equivocal about the value of