Wise (*29*) on growth surfaces of *Pinna carnea* and *Nucula annulata*. *Nucula annulata* = *Nucula proxima*; G. R. Hampson, *Proc. Malacol. Soc. London* **39**, 333 (1971).
37. A. C. Taylor, *J. Mar. Biol. Assoc. U.K.* **56**, 95 (1976). Similar structural changes within the shells of numerous molluscs, such as the Pennsylvanian gastropod, *Shansiella carbonara* [R. L. Batten, *Am. Mus. Novit.* **2501**, 1 (1972)] and the Recent bivalves *Modiolus modiolus* and *Pholadomya candida* (*13*) may result from periods of anaerobiosis.
38. J. D. Taylor, W. J. Kennedy, A. Hall, *Bull. Br. Mus. (Nat. Hist.) Zool.* **22**, 255 (1970).
39. It has been suggested [(*33*); J. G. Carter, personal communication] that the simple prism and nacre combination originally arose spontaneously as a consequence of the precipitation of calcium carbonate contemporaneously with organic matrix under a certain set of physicochemical conditions. Subsequently, because of some selective advantage in this structural combination, perhaps strength [J. D. Taylor and M. Layman, *Palaeontology* **15**, 73 (1972)], this condition became stabilized. In our discussion, we imply that simple aragonitic prisms represent an altered form of nacre resulting from alternating processes of shell deposition and shell dissolution. We hypothesize, therefore, the "spontaneous" formation of only one structural form (nacre), with simple aragonitic prisms representing a secondary structural type resulting from physiologically controlled anaerobic processes.
40. J. G. Carter and R. C. Aller, *Lethaia* **8**, 315 (1975).
41. If such structural changes have occurred, aragonitic (myostracal) prisms associated with sites of muscle attachment may represent vestiges of early ancestral shell structural forms.
42. We thank J. D. Taylor, J. D. Hudson, C. MacClintock, M. A. Crenshaw, K. K. Turekian, K. M. Waage, R. A. Berner, J. G. Carter, M. R. Carriker, D. Jablonski, and R. E. Dodge for discussions and critical reviews of the manuscript. We thank A. S. Pooley, E. Tveter Gallagher, and A. Krishnagopalan for technical assistance with the scanning electron microscopy, W. C. Phelps for preparation of specimens, and W. K. Sacco for his assistance in photograph reproductions. Supported in part by NOAA grants 04-6-158-44056, SGI-77-17, and 04-7-158-44034 and EPA grant R804-909-010. Contribution 106 from the Ira C. Darling Center, University of Maine, Walpole 04573.

NEWS AND COMMENT

Creative Penmanship in Animal Testing Prompts FDA Controls

Inaccurate science, sloppy sciénce, fraudulent science—these are the greatest threats to the health and safety of the American people. Whether the science is wrong because of clerical error, or because of poor technique, or because of incompetence, or because of negligence, is less important than the fact that it is wrong. For if it is wrong, and if the FDA did not know it was wrong, then the protective regulatory barrier between a potentially dangerous drug and the patient is removed.—SENATOR EDWARD KENNEDY (D-Mass.), in congressional hearings on preclinical testing.

In the wake of recent evidence of massive deficiencies in scientific data that were crucial for the approval of hundreds of chemicals and drugs now used in the United States, the federal government is about to impose sweeping new rules for the conduct of laboratory testing on the safety of such products.

The new rules, which are known as the Good Laboratory Practice (GLP) regulations, to be imposed in January by the Food and Drug Administration (FDA), will cover nearly every facet of the operation of nonclinical, or animal, laboratories, from the care and feeding of test animals to the storage and retrieval of raw scientific data. All types of testing for toxicity with animals, whether to determine the potential of a substance to cause birth defects, cancer, mutations, or degenerative disorders, are likely to be covered by the rules.

Nearly 400 corporations, contract laboratories, and universities—each of which provides information to the FDA in support of the safety of a new food or drug—will be affected. Several parts of the new requirements are regarded as so strict that universities either will not want to comply with them or will not be able to afford compliance, and thus will be excluded from the lucrative market of testing for toxic effects of regulated products. A study that found university labs to be the worst performers of the tests has killed chances that their labs would be excused from compliance.

Industry officials have forecast that the regulations will increase the cost of such testing by at least 20 percent, and even the FDA places the overall cost for their implementation at each testing facility at an average of $150,000. It is no surprise, then, that the proposed GLP's have not been kindly received. Nearly 200 comments, almost all of them negative, were sent to the FDA by laboratory researchers and industry officials from every corner of the United States, as well as from France, England, Germany, and Belgium.

The volume and vehemence of this opposition are tangible indications that the GLP's constitute a major new initiative for the FDA. Until a short time ago, the agency's efforts to ensure the authenticity of test data it received were restricted to audits and lab inspections initiated only after an employee in one of the agency's divisions spotted something unusual in the report provided to the FDA by the corporate sponsor of a new product. According to Ernest Brisson, the associate director for compliance in charge of the FDA's new Bio-research Monitoring Program, the limited scope of these audits and inspections reflected an "assumption that the conduct and findings of studies submitted to the Agency represented scientific research of the highest quality. Reports were assumed to be accurate accounts of well-controlled scientific studies, and we, therefore, made our regulatory decisions accordingly."

Then, after an improbable series of events (see box), FDA investigators discovered, in Brisson's tactful words, "that the scientific integrity of some individuals and establishments engaged in research is open to question." Specifically, in three notorious cases presented in 1976 to Senator Edward Kennedy's Subcommittee on Health, massive deficiencies were found in scientific data submitted to FDA and the Environmental Protection Agency (EPA) by G. D. Searle & Co., of Skokie, Ill., Biometric Testing, Inc., of Englewood Cliffs, N.J., and Industrial Bio-Test Laboratories, Inc., of Northbrook, Ill. According to Brisson, FDA inspectors found that in several instances, gross lesions in test animals were not properly examined or reported to the FDA, and experiments were designed in such a way as to obscure whatever toxic effects the products may have had. "We also encountered creative penmanship which causes test animals to appear and disappear throughout the course of a study," he said, "[circumtances that] make us wonder who is running the show, a toxicologist or a magician."

Such findings are particularly disturbing in light of the fact that in the Industrial Bio-Test (IBT) case alone, tests were submitted that led to the approval of nearly a hundred products by the FDA and 123 pesticide ingredients by the EPA. IBT data also were relied upon by the EPA and ultimately the corresponding agencies of several foreign countries, in setting the accepted levels of tolerance in foodstuffs for 160 pesticide products. So pervasive are the deficiencies, according to FDA and EPA officials, that every one of the thousands of tests re-

ported by IBT in this decade has been called into question.

As a result of these findings, the FDA decided that a new approach to laboratory monitoring was necessary and an agency task force set about writing the GLP regulations. The rules that were developed signal a major departure for the FDA from past regulatory practice, because, instead of being oriented to problems with specific studies or investigators, they are oriented toward the reliability of the scientific process itself. By establishing rigorous procedural standards that must be applied to every study that a laboratory does, the FDA hopes that in good part the laboratories will regulate themselves; that is, that the studies will be reliable if the process is. Among the procedural requirements that would be imposed are these: test equipment must be cleaned, tested, and calibrated, repaired, and maintained; test and control substances must be examined to determine identity, strength, quality, purity, and stability; studies must follow written "protocols" that clearly identify—in advance—their objectives, procedures, and the information to be reported; and all data must be entered, signed, and organized so that they are easily accessible to the appropriate laboratory specialists. According to L. J. Servano, the director of Laboratory Animals Resources at the Oak Ridge National Laboratory, these regulations "seem to state what is obvious to any well-trained scientist or research administrator." According to Brisson, however, they are spelled out in the GLP's because deficiencies in each of the requirements were found in tests performed by Searle, IBT, and Biometric Testing.

In another significant departure from past regulatory practice, the FDA no longer will rely on an assumption of good faith compliance with the requirements. As a result of the 1976 congressional hearings, the agency was given $16 million and 600 positions to inspect preclinical and other laboratories, and has plans now for 240 on-site inspections of laboratories each year. Many of the GLP regulations are explicitly designed to facilitate these inspections, such as those covering maintenance and retention of data. Under the GLP's, the FDA also wants access to the reports of internal auditors, who would be organized into a "quality assurance unit" and given the responsibility for ensuring to laboratory officials that the GLP's are being followed. Although FDA investigators place a high priority on the establishment of the units and would make them a focal point for their inspections, industry and laboratory spokesmen oppose the requirement bitterly. According to the Pharmaceutical Manufacturers Association, if internal audits were required and were subject to FDA inspection, the reports would "probably be less candid and complete than at present. The net effect [would] be to deprive management of an effective tool to help assure the quality of studies."

Universities, in particular, object to those parts of the GLP's which are designed primarily to facilitate FDA monitoring. Eighty-six universities, including such places as the Massachusetts Institute of Technology, the University of Chicago, the University of California, the University of Tennessee, and Carnegie-Mellon University, conducted animal tests on regulated products that were submitted last year for FDA approval. According to a member of the faculty at the University of Georgia's college of veterinary medicine, the "excessive paperwork, analytical 'rechecks,' and multiple supervisory evaluations would frustrate our researchers to the extent that they would have little interest in the type of research covered by these regulations." Similarly, a faculty member at the University of Texas said the regulations would lead to "unnecessary expense, personnel, and paperwork." Indeed, because of intimations in an FDA statement published along with the proposed GLP's last year that the regulations may not be appropriate for every type of testing institution, many universities expected that they would be exempt from the GLP's in the final version. The Association of American Medical Colleges, for example, wrote to the FDA to express the view that peer review in the academic community already accomplished whatever monitoring was appropriate. "The regulations are not appropriate for the short-term, ad hoc studies that constitute the bulk of this genre of university investigations," the association added.

According to knowledgeable FDA sources, however, the universities'

As Luck Would Have It . . .

Deficiencies in the animal test data provided to the federal government by G. D. Searle & Co., a major pharmaceutical manufacturer, and by Industrial Bio-Test Laboratories, Inc., became apparent to the FDA after a series of events that, in the words of Adrian Gross, the associate director of nonclinical studies in the FDA's Bureau of Drugs, "occurred purely by chance."

Suspicions about the data submitted by Searle first arose in 1972, when a cancer researcher in Nebraska submitted an article to the *Journal of the National Cancer Institute* (NCI) about a study he had done of Flagyl, a drug manufactured by Searle and approved by the FDA. NCI routed the study, which showed that Flagyl caused cancer in test animals, to Gross (who is a pathologist) for prepublication review. Gross then reviewed the data that Searle had submitted prior to the drug's approval, and the FDA notified Searle of some deficiencies in their report. Eventually, in 1974, Searle submitted a new version of the same study to the FDA. "Instead of changing the summary to more accurately reflect the data, however, the data had been changed to more accurately reflect the summary," Gross said. According to knowledgeable sources, the case has been referred to the Justice Department by the FDA with a recommendation for prosecution of potential criminal violations.

The deficiencies at Industrial Bio-Test came to light after an even more improbable set of circumstances. In 1975, FDA officials received a tip from an employee of Syntex Corp., a drug manufacturer in California, that there were problems with tests that Syntex had submitted to the FDA. An FDA official, instead of pulling a file on Syntex, pulled one by mistake on Industrial Bio-Test, an independent laboratory that had done a study for Syntex on an antiarthritic drug called Naprosyn. On reading it, he found enough deficiencies to warrant an inspection, Gross said, "and what we found there is enough to make your hair stand up." IBT, which conducted studies for the federal government as well as private firms, currently is under investigation by the FDA, Environmental Protection Agency, the National Cancer Institute, and the inspector general of the Department of Health, Education, and Welfare. Preliminary information indicates that IBT consistently bid under the prices of other laboratories for animal studies, and accepted more work than it could handle, several sources said.—R.J.S.

hopes of exemption from the GLP's may be short-lived. The GLP subcommittee of the FDA's Toxicology Monitoring Task Force has just completed its revision of the original proposals, the sources said and, in the revision, universities remain subject to compliance with all the requirements for toxicity testing (basic research, such as pharmacological screening, remains excluded from the GLP's). The revisions still must be approved by the task force itself, an intra-agency steering committee, and by FDA commissioner Donald Kennedy, but none of these parties is expected to excuse the universities from complying with the standards.

A major factor in the subcommittee's decision was a report that would surprise many consumer advocates: On the basis of a pilot monitoring and inspection program conducted between March and May 1977 at 42 laboratories around the country, the report concluded that, when measured against the standards the FDA was proposing, corporate laboratories come out on top, followed by contract labs, and at the bottom, labs at institutions of higher learning. Of the five universities included in the study, none had better than a 50 percent compliance score. Perhaps more than coincidentally, each scored lowest in those portions of the regulations that universities have protested most vehemently: the quality assurance unit, use of standard operating procedures, data storage, and record retention. As a result, Carl Blozan, the FDA operations research analyst who prepared the report on the pilot program, concluded that universities were the "most lax in animal study control." He also found that universities conducted the same types of studies as other testing institutions. Therefore, he told the subcommittee, university laboratories should be included in the GLP's.

While seemingly incongruous with the reputations enjoyed by universities and suffered by corporations, the findings might be explained by differences in the social and economic environments of all three types of institutions. At universities, several FDA officials pointed out, animal testing of regulated products is thought of as an important source of revenue, but an often dreary, unimaginative task. Adrian Gross, the associate director for nonclinical studies in the FDA's Bureau of Foods, pointed out that many of the university faculty members who obtain the testing contracts will assign the responsibilities to graduate students, "who just want to get their degrees and get out." University labs performing such commercial services also tend to be multifunctional and poorly disciplined, several other FDA officials said. On the other hand, corporate and contract labs can assign the studies to technicians, and rigorously define laboratory procedures.

The question of economics in animal testing is more complex. Typically, a routine 2-year study in which a new food or drug is fed to 200 to 300 rats can cost $250,000, or about $1,000 for each rat. A study with more expensive animals, such as dogs or monkeys, will cost double or triple that amount. On top of this, Gross said, is the "dog-eat-dog nature of the price competition in the business. Often times, bad studies are not a question of scientific incompetence but one of sheer economics. Small things such as substituting the wrong feed or reporting a greater number of animals than are used, all of which can vitally affect the reliability of the study, also can mean a tremendous savings." Brisson is more blunt: "Any way a laboratory can save a buck, it will attempt to do it, and sometimes at the consumer's expense."

University laboratories are attractive to chemical and drug sponsors as locations for animal testing because their informal working environment and multiple functions translate into a low overhead and cheaper prices. Contract laboratories are used for a variety of reasons—if the product sponsor is not wealthy enough to have its own laboratory, or if a particular technical expertise is needed—but a common reason for their use is a lack of capacity in the sponsor's laboratory to test as many new chemical entities as it develops. When a drug or chemical sponsor contracts with an independent laboratory, then, it is usually because the sponsor will not delay the testing until it could be done "in-house."

This is a crucial point in understanding the relationship between a product sponsor and an independent laboratory, according to FDA and EPA officials, because avoidance of delay is a primary cause of deficiencies in animal testing of regulated products.

The point can be illustrated by some recent correspondence between an independent animal tester, Food and Drug Research Laboratories (FDRL), of Waverly, N.Y., and a chemical company in Holland, Gist-Brocades. In a feeding study to determine the long-term toxicity of a food additive, pimaricin, FDRL lab technicians accidentally miscalculated the dosage of the additive in feed given to two of four groups of rats in a critical part of the test. As a result, many of the rats died, and the remainder were killed.

When FDRL wrote to Gist-Brocades to tell them about the groups, Gist-Brocades' officials became alarmed. Eventually, Gist-Brocades responded that "we were—and still are—seriously concerned about the loss of time caused by the error in the composition of the feeds. You will realize that a delay of about 10 weeks is almost unacceptable setback [sic], especially when time schedules for marketing a study are seriously involved." Ultimately, neither FDRL nor Gist-Brocades mentioned in their final report to the FDA that the animals had been killed and thus were not a part of the study. As a result, the FDA, which uncovered these circumstances during a recent inspection, is said to be contemplating some form of regulatory action in the case.

Currently, regulatory action by the FDA in response to deficiencies in animal tests consists of several limited alternatives: the product sponsor can be required to validate the test findings, or the test can be rejected outright. Gerald Laubach, the president of Pfizer, Inc., a major pharmaceutical firm, noted recently that the economic loss that a drug sponsor would incur in any of these circumstances is severe enough to motivate most sponsor-owned laboratories to conduct scientifically responsible tests. This accounts for the relatively high rating given to such laboratories in the FDA pilot program, he said, because the losses caused by delay or retesting of a product are incurred by product sponsors, not independent labs or universities.

To alleviate this imbalance, the new GLP's include provisions that would allow the FDA effectively to disqualify laboratories from submitting preclinical tests in support of regulated products. According to Brisson, the disqualification will be invoked through pressure on the product sponsors that contract with the labs, so the incentive for the lab to submit reliable information will be an economic one.

Most industry officials believe that disqualification is too harsh a penalty to be included in the GLP's, but the FDA is firmly committed to having the option of an administrative sanction for use against pervasive deficiencies of the type found at Searle, IBT, and Biometric Testing. In a statement published along with the proposed regulations, the FDA said, "The seriousness of the problems recently uncovered by the agency demands the use of an approach that will directly and promptly achieve compliance by all affected testing facilities. . . . Decisions about the safety of consumer products that are based, wholly or in part, on data derived from such testing are too important for the agency to accept anything less than the best scientific data that can be obtained."

—R. JEFFREY SMITH