contemporary fashion the morphologic and biochemical data collected over the last few years. The chapters trace the comparative development of insulin-like proteins in invertebrates, the first beta cells in lower vertebrates and the complicated gastroenteropancreatic interplay in the higher vertebrates, especially in mammals. Somatostatin and pancreatic polypeptide, which both appear in the islets of Langerhans in the D cells and perhaps in other special cells not yet labeled, are discussed. The confusing and at times disappointing pathologic findings in the human diabetic pancreas, probably mainly of adult maturity onset, are reviewed and correlated with the newer immunologic and viral data that have recently been collected and bear directly on the pathogenesis of the juvenile-onset type of diabetes.

It is interesting to compare the previous volume by Lazarus and Volk in 1962 to the present volume, especially the components dealing with physiology. The beta cell has emerged from being a difficult-to-examine isolated site of the insulin deficiency in diabetes to probably the best characterized of any cell in the body (the red cell and white cell are probable exceptions, but how easy they are to obtain for study!), but still the precise cause of both common forms of diabetes remains to be clarified.

More and more, juvenile-onset diabetes appears to be a result of a spectrum of autoimmunity, ranging from pure autoimmunity in the kindreds with multiple autoimmune endocrine deficiencies to that with little autoimmunity and related to possible direct viral destruction of beta cells. Most cases probably lie in between, with viral damage as a possible initiator of the autoimmune event. In maturity-onset diabetes, progress has been even slower. As discussed by Volk and Wellmann, a decrease in islet mass is present in almost all diabetic patients, as well as an increased incidence of degenerative findings in and about the beta cells, especially in older patients and those with long standing diabetes. Westermark and Wilander[4] have recently corroborated this observation. With the finding, originally by Goldstein,[5] of Hamilton, Ontario, and subsequently by G. M. Martin et al., of the University of California, and Rowe et al., in Seattle, that fibroblasts and other cells from diabetic patients do less well in tissue culture, a ubiquitous cellular lesion is suspect: perhaps the degeneration of the beta cell is characteristic of the total animal. With all the other evidence for premature aging in diabetic kindreds, such as atherosclerosis, osteoporosis, senile cataract and perhaps even the increased vascular basement-membrane thickening noted by Siperstein and his colleagues[6] in offspring of two parents with maturity-onset diabetes, the cellular defect in the diabetic pancreas might simply be an early aging and death of the beta cells as well. Perhaps all persons at age 150 or over might have diabetes, as well as having gray hair, or, for that matter, no hair!

The *Diabetic Pancreas* is a unique volume, selectively and succinctly reviewing the literature of the past and adding and integrating former and present morphologic knowledge with much of the large body of physiologic and biochemical data that have only recently been collected. It will stand for a long time as the source book on the beta cell.

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SOUNDING BOARD

HOW THE PROPOSED DRUG REGULATION REFORM ACT WILL DISCOURAGE THE SEARCH FOR NEW DRUGS

THERE is much about the Drug Regulation Reform Act of 1978 that can be improved, but I will confine my comments to the *disincentives* that it would create for the research and development of new drugs in this country. I don't think anybody questions that there are such disincentives in the provisions of the bill. But are they important? Do they outweigh the advantages the bill provides the public?

The pharmaceutical industry thinks the disincentives are important. These disincentives have their origin in four provisions of the bill. The first is revealing all the safety and efficacy data created by a drug's sponsor and submitted to the FDA. This provision means revealing scores of research protocols and case report forms, which are the very framework of discovery of safety and efficacy of a new drug, the result of months or years of painstaking, creative work on the part of many people. They will, obviously, be protocols approved by the FDA, so they represent an official roadmap to success for a competitive compound — a roadmap obtainable for the price of Xeroxing. I think this policy will give innovative companies an incentive to do as much work as possible overseas to get a good head start.

Secondly, the bill provides for a longer, more formal, complex process of approval than the present law does, 360 days instead of 180, in addition to a 30-day period up front in which the Secretary decides whether or not he will even accept an application. The industry worries about this lengthening and formaliz-

ing, and when an industry worries, there is less incentive to invest in a more doubtful future.

Thirdly, the bill provides that if a second comer wishes to market a drug, he may rely on the data of the original applicant to do so, provided he waits five years. In its early drafts, the bill contained no waiting period; the five-year provision was added in recognition of a source of disincentive. So the five years is an arbitrary measure of disincentive, too short by industry standards, but long enough by the government's.

The fourth provision changes the present Investigational New Drug (IND) system radically. It proposes a two-step process whereby an applicant wishing to investigate a compound in man could do so initially in a Drug Innovation Investigation; in this phase the FDA would confine its interest to patient safety, would not attempt to rule on the scientific validity of research protocols. This, says the FDA, would be a great boon to the sponsor, permitting him to explore efficacy in a larger number of compounds reasonably quickly and without undue burden. It is this provision that the FDA cites when asked how this bill encourages the development of new drugs. Such encouragement, by the way, is one of the important avowed purposes of the bill, featured in its second paragraph and in every pronouncement that HEW made about the bill at its introduction.

But the innovative phase does not seem to be much different from the present system, in which the FDA's interest is also almost entirely the safety of subjects, not the scientific validity of the proposed studies. It does provide an opportunity to generate some efficacy data, as opposed to the present policy, which unofficially discourages such data, but I do not think this is an important incentive.

So if the proposed innovative phase is not much better than the present IND system what is it better than? It is clearly better than the provisions for Drug Development Investigations, the second phase provided for by the bill.

A group of us at the blackboard a month or so ago tried to trace the course of a new drug through this second phase. It took us an hour, and it proved a discouraging course, starting with a 60-day wait for the Secretary to decide whether the investigations may begin. That 60 days is to be spent by the FDA in evaluating potential risks to patients, of course, and whether these risks are outweighed by benefits, a difficult evaluation when benefits have not yet begun to declare themselves. Also, in those 60 days the Secretary must decide whether the overall study plan is adequate to meet objectives and whether the parts of the study plan — the proposed investigations — are adequate.

I can understand these latter provisions; the FDA has in the past seen study plans so flawed that they simply could not be expected to meet objectives. So they respond in the way that professional regulators must; they reach for a regulation to assure the adequacy of study plans, and then they require that any deviation in protocol be approved. These provisions are more rigid, more formal and more time-consuming than the present system, in which the FDA frequently provides helpful advice on study plans; they will interfere with the way in which this business of discovery really works. New insights come unexpectedly, and they require quick turns.

In the present system, if the FDA reviewer delays an IND application because he is concerned, let us say, about the electrocardiogram of dog No. 3, the sponsor can bring his dog expert, the FDA brings its experts, and, given a satisfactory outcome, the FDA can, as likely as not, conclude on the spot that the study can begin. That will not happen under the new law; a letter of approval will be needed, and experience tells us to expect many weeks of delay.

The FDA knows that the present system can work informally, but not in every FDA division, so the new law tries to create a standardized system. The trouble is that the proposed system standardizes things in the wrong direction, and it mandates by law what now sometimes works pretty well without it. And it deprives the agency of simple solutions. Often now, technical points of difference about protocols, and just plain misunderstandings, can be settled by a telephone call.

Industry wonders, too, why a bill that so tightens the investigative phase in every respect, with prior approval of all protocols and even of changes in the protocols, must then insist on a 390-day period to consider the application. If nothing were being changed about regulating the investigational phase, I could understand doubling the approval phase, to reflect better the pace at which approval takes place now. Or the other way around, if the 180-day approval phase in the present law remained the same in the new law, I could see why we should have provisions for stretching out the investigative phase. But why make both changes?

The bill has other examples of overkill, provisions written for the past, when indeed there was no public participation, no postmarketing surveillance and no real give-and-take on study plans and protocols. Now all these procedures are developing well as a result of the hundreds of policy decisions, regulations and improvements to working relations that have filled the years from 1962 to 1978, especially the past few years.

* * *

Well, those are the disincentives as the industry sees them. The question still is whether they are really important. The Administration thinks we are overconcerned about them, that we are overestimating them, and that in fact we may not be able to perceive what is good for us.

In one sense that opinion may be right; my industry may not understand as well as it should how incentives and disincentives work. The long, long process

that brings an idea to the fruition of an active chemical compound, and then takes the compound through years of study to produce a new drug, is as complex as a natural ecosystem. You might as well ask a forest to explain how it replenishes its floor or a stream how it purifies itself as to ask the drug-development system how it works.

I'm not talking about the science of it; that's all well understood. I'm talking about the motivation behind the complex history of ups and downs that every research program goes through. Nothing is more impenetrable than the motivation of our actions; yet we must try to penetrate what motivates the search for new drugs, or we will lose our way and perhaps never find it again.

Every research program must have enthusiasts. That fact is well known. And, almost as inevitably, it must have detractors — scientists and managers in the same firm who are not as enthusiastic, who'd like to replace it with their program, their compound. The competition is for funds, for computer time and for a dozen other scarce resources.

Also, in the modern large firm, the decision to "take research overseas," as we used to say it, is different now. Research is now overseas as much as it is here. The United States is now the "overseas" to much of the research on new drugs.

Another consideration is that pharmaceutical companies are the world's greatest counters and measurers of things present and to come. By every method known to man, they research the potential market for new drug therapy. They try, in other words, to measure future economic incentive to decide present financial support.

And they try to measure *disincentives*. For the past 15 years the FDA new-drug-approval process has made up a large part of that effort. And if this bill is enacted, new worrisome questions will be asked at quarterly and annual reviews of research and development programs and of compounds in the laboratories of some 20 or 30 pharmaceutical companies. These questions will force a new compound to declare itself much too early, not just to the FDA, but to the managers of the money to be invested in it. It's as though the entire FDA approval process were moved up several years and previewed in each company by a whole new generation of nail-biting industry people guessing how many conferences, hearings, 60-day waits, formal rejections and unexplained delays lie ahead of a new compound. Everybody plays "What will FDA say?" and discouragement dominoes down through the organization.

It doesn't matter that industry may be misreading the FDA, or that it may be foolish to try to play "What will FDA say?" Experience tells the companies that the FDA will more frequently than now say, "no," or "not now," or "do more work."

So I predict that, with 20 or 30 companies trying constantly to measure research incentives and disincentives in quarterly budget reviews, fewer and fewer of the hundreds of risky, positive commitments needed will be made as companies opt for the surer and safer. The result will be a sort of cloning of the whole process as research programs, preclinical work, and clinical protocols hew close to the official, approved standard. And the change will be insidious — scarcely noticeable when it occurs.

I could be wrong. Things may work out. But that is not the modern way to decide on big changes. Ordinarily, in this age when the complexity of socioeconomic processes is well recognized, the burden is on those who would change a process to prove that they will do no harm. In this case, the process is complex and it does work, and those who are nearest to it, those who do make it work, are warning that it needs to be nurtured and cherished and can be hurt by the proposed changes. Those who do not make it work say it would not be hurt.

The question seems to be: Is the pharmaceutical industry standing up too close to its research process to understand it, or is the FDA standing back too far?

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THE ECONOMIC COSTS OF STROKE IN MASSACHUSETTS

ELIZABETH MILLS, M.A., AND MARK THOMPSON, PH.D.

The morbid and mortal harm of strokes may be reduced by public-health programs addressed to the underlying risk factors — particularly the early diagnosis and control of hypertension — as well as by medical management of the condition. The benefits of such programs are alleviation of both the human and the economic costs of stroke. Although a consideration of both cost categories is critical to effective public-health policy, only the economic consequences can be measured. Of economic costs, the more evident and readily measured are the direct costs: hospital expenses, fees for physician visits, nursing-home charges

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