Anxiety and pain over Valium, Darvon

In a nation of prolific drug-takers, incidents of bad side-effects and even death may be expected to occur occasionally. But the often-elusive point at which a drug's benefits outweigh its risks, and vice versa, continues to fuel arguments among scientists, consumers and certain drug manufacturers. Hanging in the balance of such debates may be the health and safety — perhaps the lives — of hundreds of thousands of people.

Two prescription drugs that currently occupy the spotlight of controversy are Valium (diazepam) and Darvon (propoxyphene). The effectiveness and potential dangers of Darvon as a pain-killer are under investigation by both the Senate and the Food and Drug Administration. And the possibly addicting properties of Valium — generally considered non-addictive, physically, in the past — are being suggested by a growing number of researchers, at least one of whom is calling for severe restriction in the use of the drug.

The problems with Valium are particularly disturbing for two reasons: Researchers and clinicians have failed to recognize its apparent addiction capabilities until now — 16 years after its first clinical use; and even though its use has declined in recent years, Valium is still believed to be the most frequently prescribed drug in the United States. Valium, along with Librium, accounted for the bulk of the 128 million prescriptions filled for "sedative-hypnotics" in 1976 (SN: 2/25/78, p. 119).

If Valium is indeed addictive, it does not represent an unprecedented case. "Amphetamine, introduced clinically in 1935, was not realized to be addictive until about 1958," notes Mark L. DeBard, director of emergency services at Greene Memorial Hospital in Xenia, Ohio. Phenobarbital was also thought to be non-addictive until many years after its first use, he says.

In the January AMERICAN JOURNAL OF PSYCHIATRY, DeBard describes an apparent case of "diazepam withdrawal syndrome." He tells of a 56-year-old man who, each time he was taken off Valium over a several-year period, developed hallucinations and seizures before lapsing into coma. DeBard concludes that "a physical dependence seems to develop in some patients who use the drug on a chronic basis. More severe withdrawal symptoms seem to be associated with a longer period of use and higher doses, but there is marked individual variation."

However, there is also growing evidence of a low-dose Valium withdrawal syndrome. In a clinical survey of patients taking 15 milligrams to 40 milligrams of Valium a day (DeBard's patient was on 80 milligrams a day), David E. Smith reports that he found 50 persons who exhibited withdrawal symptoms. "Interestingly, 45 of these patients had a history of alcoholism, although they were not using alcohol at the time of their diazepam withdrawal," Smith, medical director of the Haight-Ashbury Free Medical Clinic in San Francisco, writes in The Journal (Jan. 1), a drug and alcohol publication based in Toronto.

Smith and his colleagues "recommend periodic, therapeutic holidays at a reduced or zero dosage level for approximately five days" for long-term Valium takers. DeBard, though, wants even more stringent limitations. No outpatient should take the drug for longer than one month, he says, and doctors should not abruptly discontinue Valium treatment for long-term and/or high-dose patients.

Darvon's narcotic-like potentials have long been known; the questions surround its safety and effectiveness — and the answers are conflicting. Estimates by some witnesses before a Senate committee have ranged from 1,200 to 4,000 Darvon-related deaths per year. Manufacturer Eli Lilly & Co., however, says the drug causes no problems when taken by itself in proper dosages. FDA officials say they know of no deaths caused solely by regulation doses of Darvon but add they have begun a review of the drug's properties. □

Skylab: Can the end be controlled?

The National Aeronautics and Space Administration concedes that it will have no way to direct the Skylab orbiting workshop to a specific spot or swath on the earth when the massive object reenters the atmosphere a few months from now. The agency's only present hope — and it is a slim one — is that it may be possible to make the object reenter a few orbits earlier or later, thus perhaps yielding a final descent over a minimum of populated land area (SN: 2/3/79, p. 71). Even that is a touchy business, relying on the proper functioning of key elements in Skylab's attitude-control system, and NASA is not sure it will try the idea even if it looks feasible from advance studies.

One non-NASA researcher, however, believes that there may be a better way to influence the final orbit than by the space agency's currently envisioned method. In fact, says Marshall H. Kaplan, professor of aerospace engineering at the Pennsylvania State University, it may even be possible to make slight shifts in the general descent route with as little as an hour to go — during the final orbit itself.

The agency plan, now being studied at NASA's Marshall Space Flight Center in Alabama and Johnson Space Center in Texas, would use Skylab's attitude-control system (ACS) — gyroscopes and small gas jets — to shift the object into a position with minimum atmospheric drag a few days before the final descent and hold it that way for several orbits. The idea is that the more time spent in the low-drag position, the more orbits Skylab could complete before descending to an altitude where the denser atmosphere would finally pull it down. The possible gain comes from the fact that, since the orbits are tilted relative to the equator, Skylab follows a sine-wave pattern over the earth's surface, with each wave pattern displaced slightly from the one before. A delay of several orbits would thus place different portions of the earth along the "ground track" below.

A problem is that the object may well start tumbling more strongly than the ACS can handle (if, for example, one or more of the gyros run out of room to turn in a given direction) at an altitude of about 130 miles, several orbits before final reentry begins. This could leave such large uncertainties in estimates of the final descent path as to make the effort pointless.

Kaplan believes that it may be possible to influence Skylab's behavior at a lower altitude, and without using the gyros. Despite the workshop's asymmetrical shape, Kaplan thinks that it may reach a position of aerodynamic equilibrium — and thus stop tumbling on its own — less than 100 miles above the ground. If so, a few "tweaks" of the ACS gas jets might reveal how Skylab would respond as it descended further, giving a chance to apply the life-prolonging low-drag technique at lower altitudes with proportionally smaller uncertainties, perhaps even in the final orbit. Each minute of change in the impact time, says Kaplan, would shift the impact point about 300 miles along the ground track.

Such low-altitude maneuvers would involve hurried calculations that some NASA engineers doubt are even possible, but Kaplan is developing the idea under a six-month, $35,000 NASA contract. In the end, help may come from either idea, or neither, or both. □

DSDP gets to the core—longest ever

Like children exclaiming over a new toy, scientists at the Scripps Institution of Oceanography recently announced the successful testing of a new piston coring technique that has recovered "the world's longest undisturbed piston core."

The new equipment, tested in the Gulf of California during Leg 64 of the Deep Sea Drilling Project, is much more than just a toy to be forgotten after a few weeks. It will allow scientists to examine the climate-related physical properties and stratigraphy of the hundreds of thousands of years' worth of soft sediments covering the ocean floor. Such studies were impossible with the jumbled samples obtained by routine drilling and limited by conventional piston coring techniques.

The excitement of the success was conveyed in a cablegram received at Scripps from co-chief scientists David G. Moore and Joseph Curray: "The ability to routinely recover undisturbed samples of the upper one to two hundred meters of sediments at DSDP sites is a major technological achievement which will provide previously unattainable and immensely valuable information on the properties of nonlithified [soft] ocean sediments."

The 152-meter core represents 300,000 to 500,000 years and is a significant step over the 30- to 40-meter cores obtained by conventional piston coring methods. Piston cores, as implied by the name, are taken when a hollow cylinder is driven or dropped through a sediment. In previous piston core techniques, the corer was lowered on a wire line from the ship and allowed to "free fall" into the sediments. Thus, relying on the force of gravity, only short cores could be retrieved.

The new device, developed in a 28-week crash program by Scripps engineers Stan Serocki, Mike Storms and Don Cameron, operates from the end of the drill string, or pipe, used for routine drilling. Hydraulic pressure, borrowed from the high pressure pumps used to circulate fluids in the pipe during drilling, punches the barrel rapidly into the sediments. A 5-meter sample is then withdrawn up the drill pipe by a wire line. The device can be repeatedly dropped down the drill string and retrieved, stopping only when it hits hard rock. According to Moore, the hydraulic piston corer will become a standard tool to complement routine DSDP drilling, which manages to churn up the sediments so much that they are useless for stratigraphy studies.

The coring was scientifically as well as technologically successful. The diatomaceous samples are distinctly laminated — the layers are undisturbed by bottom crawlers because of the anoxic conditions in the Gulf—and varved—showing annual layers. A varve, for example, might consist of a set of sediments formed by eroded material carried from the land by summer winds and by diatoms which bloom when winter upwelling carries nutrients to the surface. Comparing the content and properties of varves may allow researchers to infer yearly climatic changes. Knowing they might be able to recover varved samples, Scripps scientists pushed completion of the corer for Leg 64.

Not to be slighted, other parts of Leg 64 also scored successes. Because the Gulf of California is a young (3½-million-year-old) ocean basin, it can serve as a model to understand the earlier stages of formation of the Atlantic Ocean. For example, the Guaymas Basin between Baja California and Mexico offers a unique chance to examine zero age crust. Although, theoretically, zero age crust could be drilled at the Mid-Atlantic Ridge, practically it is not possible because of the lack of sediments necessary to stabilize the drill pipe. In the Guaymas Basin, however, the Sonora rivers which drain Mexico dump an abundance of sediments into the Gulf. Drilling at the spreading center recovered zero age crust and encountered high geothermal activity. Researchers also found sheet-like basalts which intrude into the sediments and which seem characteristic of young spreading centers instead of the pillow basalts found at older spreading centers.

Leg 64 also gave researchers a chance to sample the ocean crust flanking the continental slope. In the Atlantic, the continental margins are smothered beneath sediments; the underlying ocean crust lies out of the *Challenger*'s reach. But the margins of the Gulf of California haven't been around long enough to build that sediment barrier. The drilling during Leg 64 provided a transect of samples of the ocean crust up to the point where it hits contlnental crust. Such samples will provide detailed history of the subsidence of the continental margin, says Moore. □

Third World drugs: Dollars and sense

The severity of health problems in developing countries was the only noncontroversial item at the conference on pharmaceuticals for developing countries held by the National Academy of Sciences last week. Speaker after speaker listed the major diseases of the tropics and recited the statistics. Reported cases of malaria increased from 3.2 million in 1972 to 7.5 million in 1976. The vast numbers of "semi-urbanized" squatters who have migrated to the periphery of tropical cities have transformed rural diseases to urban epidemics. And millions of unvaccinated children in underdeveloped countries die each year of common, preventable diseases.

A history of conflict between government and drug industry attitudes toward international health actions shadowed the meeting. Yet on some actions government, industry and academia seemed to be approaching a workable agreement.

A major complaint of U.S. drug companies is the legal requirement that new drugs may be exported for commercial use only if they have met Food and Drug Administration standards. Unapproved drugs may be produced at manufacturing facilities outside the country, but the U.S. Agency for International Development, the federal agency with the clearest mandate for foreign health assistance, will not provide funds for drugs not approved in the United States.

Besides the difficulties in testing drugs designed for foreign diseases, the drug companies argue that a drug considered unsafe under some conditions may still be desirable under others. Frank T. Perkins of the World Health Organization pointed out, "It is most important to appreciate that these drugs or vaccines are urgently needed for infections that are causing millions of deaths each year. The price of efficacy, therefore, may be side reactions in a small proportion of those needing the drug or vaccine and the level of acceptibility must be assessed in those communities in most need of the products."

Donald Kennedy, U.S. Commissioner of Food and Drugs, argued that the law should be a balance between the prohibition of U.S. companies dumping inferior or even dangerous substances in countries poorly equipped to evaluate potential risks and the right of foreign countries to use products that, "for often rather special reasons" have been deemed unsuitable for use by U.S. citizens. Kennedy said that the FDA last year submitted to Congress significant amendments to the export provisions. According to the proposed new law, drugs not in compliance with domestic requirements could be exported, under special approval, if the importing government assented after being informed of the basis of the drug's U.S. unapproved status. This is essentially the same policy already adopted by Congress for export of medical devices.

While standards for new pharmaceuticals remain controversial, the economics of getting current pharmaceuticals to developing countries appears on the brink of important advances. V. Fattorusso of the World Health Organization told the meeting that WHO is encouraging regional groups to make a list of essential drugs for governments to purchase in bulk. The South Pacific countries have already made such a list of priority medicines. Fattorusso says that coordinated purchasing would provide markets for effective drugs not in widespread use and provide an incentive for further research and development. He reports that the reactions of European drug companies have been encouraging, as long as the drugs are packaged so that they could not be sold privately or re-exported.

Present vaccine-producing facilities can be scaled up to meet global requirements, Perkins reports on the basis of a recent meeting in Geneva with major vaccine manufacturers. WHO proposes to increase the profitability of vaccine production by realistically estimating future demands, placing advance orders and accepting a research and development component in the price. WHO suggests that developing nations considering their own production of vaccines should first establish a quality control facility, then build a vaccine blending, filling and packaging operation and finally, perhaps, begin vaccine production. Perkins points out that most countries would be best off stopping with the packaging facility, which could save a sizable fraction of the cost, because the amount of vaccine a single country requires is generally too small to justify economically a separate vaccine-producing facility.