appears to be out of step with the shift of research facilities. The world's most sensitive optical telescopes are still in the private sector, and, according to the report, the majority of talented astronomers are at the universities. However, the size of the expenditures for most of the programs recommended by the Greenstein committee report is so great they would almost certainly be made part of national centers. Although 60 percent of the observing time at the Kitt Peak center is reserved for visiting scientists, namely, those based in universities, many astronomers fear that the obligation of a national center to accommodate all qualified observers will throttle opportunities for intellectually exciting observations that require large blocks of time. Only recently the Kitt Peak National Observatory formalized the procedure of including visiting astronomers as well as staff astronomers on the committees that allocate observing time.

No doubt the universities still hold the major national resources of manpower and technology, at least in optical astronomy. In radio astronomy, on the other hand, the preeminence of the National Radio Astronomy Observatory is widely acknowledged. But the arguments for balance in the Greenstein report seem more directed toward preserving islands of total freedom in the universities than improving the scientific payoff of the national centers. It appears that neither the distribution of funding nor research priorities between the public and private sectors has yet reached equilibrium.

The Greenstein report is an excellent presentation, so specific that it lays itself open to criticism. The recent developments on the frontiers of astrophysics are presented in a style that is quite readable for the layman, and the section on exobiology—probably the most optimistic assessment of the likelihood of intelligent extraterrestrial life ever presented by a committee of eminent scientists—is almost lyrical. Every recommendation, with the possible exception of the optical program, appeared to be well-justified by the reasonable hope for new discoveries and the timeliness for exploiting the advances of technology.

A few years ago, astronomers could observe the universe at only two wavelengths—optical and radio. The recommendations of the Greenstein report would allow them to tune-in to the stars at virtually any region of the electromagnetic spectrum. The only wavelength, in a manner of speaking, that the astronomers may have overlooked is the current mood of the Congress.

—WILLIAM D. METZ

Narcotic Antagonists: The Search Accelerates

Narcotic antagonists—nonaddictive drugs that block the euphoric effects of opiates—have long intrigued investigators seeking new answers to the problem of heroin addiction, but the development of such compounds has been hindered by the inadequacy of available research funds. Last year, however, the federal government initiated a concerted effort to conquer drug abuse and began prodding the drug industry to accelerate research programs directed at the development of such compounds. Earlier this month, the government signaled its own commitment to the antagonist concept by awarding more than $2 million in grants for preclinical and clinical testing of the most promising candidates.

The accelerating program has already produced some tangible results. Two once-heralded antagonists have been extensively tested and shown to be only marginally adequate for clinical use. A third compound has received less testing, but appears to be a more promising candidate for general usage. Several longer-acting and more potent antagonists are in the preliminary stages of testing, and promising new methods of administration are also beginning to be investigated. Most important, perhaps, it has recently been shown that one of the antagonists exhibits great potential for preventing abuse of such drugs as methadone and paregoric.

The first important narcotic antagonist was cyclazocine—3-(cyclopropylmethyl) - 1,2,3,4,5,6-hexahydro - 6,11-dimethyl - 2,6-methano-3-benzazocin-8-ol—developed by Winthrop Laboratories, New York City. A 1- to 4-mg oral dose of cyclazocine produces clinically effective opiate antagonism for at least 24 hours, but patients must be built up to this dosage gradually because of cyclazocine's unpleasant initial side effects, which include dizziness, headaches, and hallucinations. These effects are disproportionately intensified as the dose is increased, and they may also reappear when cyclazocine use is discontinued.

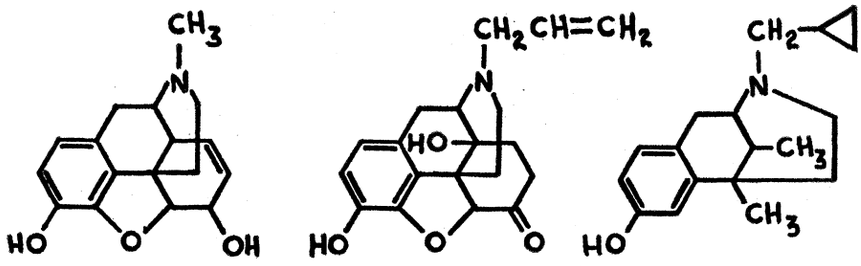
Several investigators have suggested that the side effects might be caused by *d*-cyclazocine in the racemic mixture normally used, but recently completed clinical testing at the National Institute of Mental Health's Addiction Research Center (ARC) in Lexington, Kentucky, indicates that the pure *l*-isomer also produces the side effects.

Efforts to avoid these side effects led many investigators to the use of naloxone (*N*-allylnoroxymorphone) and closely related compounds. Originally synthesized in the private laboratory of Mozes Judah Lewenstein and subsequently developed by Endo Laboratories, Garden City, New York, naloxone was the first "pure" narcotic antagonist; that is, it has no pharmacological properties of its own, but it abolishes or prevents the hallucinations, euphoria, respiratory depression, nausea, constipation, convulsions, and other effects produced by narcotics. It also abolishes such effects when they are caused by other narcotic antagonists.

Clinical studies at several institutions have shown that a 1- to 5-mg parenteral dose of naloxone produces opiate antagonism for 2 to 4 hours, and a 3-g oral dose provides antagonism for as long as 24 hours. Large oral doses are very expensive, however, since naloxone is synthesized from thebaine, an opium alkaloid whose importation is rigidly controlled. Parenteral doses are impractical because of the limited duration of action in such a form, and naloxone thus seems unlikely to find clinical use.

Some effort has been made to use naloxone to overcome the side effects of cyclazocine. Max Fink of New York Medical College (NYMC) has reported that a relatively small oral dose of naloxone blocks the adverse effects of cyclazocine for as long as 24 hours, but does not interfere with its antagonist activity. William R. Martin of ARC, however, has found that the cyclazocine side effects return after 4 to 6 hours; this discrepancy has not yet been resolved.

Even if Fink's results are confirmed,



Morphine Naloxone Cyclazocine

the combination is probably unsatisfactory because of its limited duration of action. Most clinicians say they would prefer an antagonist whose effects last for several days or weeks so that its use would require less motivation on the part of former addicts in rehabilitation programs [see *Science* **173**, 503 (1971)]. Attempts have thus been made to find naloxone analogs with increased potency and duration of action.

The most rewarding of these attempts was the synthesis by Endo of a compound called EN-1639 (*N*-cyclopropylmethylnoroxymorphone). Clinical studies by Martin and Donald R. Jasinski of ARC show that EN-1639 is intermediate between naloxone and cyclazocine in its effects: a 50- to 100-mg oral dose of EN-1639 produces opiate blockade for as long as 48 hours with very few side effects. It thus appears to be the best antagonist yet tested, Martin says, and the drug of choice for clinical application.

At least two other prospective antagonists are also being investigated. Bristol Laboratories, Syracuse, New York, has developed a totally synthetic compound it calls *levo*-BC-2605 (*l*-*N*-cyclopropylmethyl-3,14-dihydroxymorphinan), and Lederle Laboratories, Pearl River, New York, is making available for testing an oripavine derivative, called M-5050, that was developed by the British firm of Reckitt and Colman. Preliminary results with the two drugs in animals indicate that both are very promising candidates for clinical studies with humans.

Another approach, also developed by Endo, is the use of the pamoate ester of naloxone. Neither pamoic acid—4,4′-methylenebis(3-hydroxy - 2 - naphthoic acid)—nor naloxone pamoate has pharmacological or antagonist properties of its own. Instead, injected naloxone pamoate serves as a depot from which naloxone is slowly released as the ester linkage is hydrolyzed. (Pamoate esters have been used in the same way previously to extend the duration of other drugs, such as penicillin.)

Fink and Alfred M. Freedman of NYMC have shown that a 6-ml injection of a mineral oil suspension of naloxone pamoate provides opiate blockade for as long as 72 hours. Martin, however, finds that with what he terms a "more reasonable" 1- to 2-ml dose, the level of blockade is barely detectable 24 hours after injection. Nonetheless, Freedman contends, the concept itself is promising, and Endo is currently preparing the pamoate ester of EN-1639.

Implantable Casings Show Promise

A logical extension of this principle is the development of a depot form of administration in which a large supply of antagonist in an implantable drug casing is surgically embedded in the body so that it will be released slowly into the bloodstream. Such casings have been suggested for use with a wide variety of drugs, particularly those used for birth control, but several problems have impeded their use. Particularly difficult is the development of nontoxic container materials that allow release of the agent at a uniform rate.

Seymour Yolles and his associates at the University of Delaware have developed two experimental depot systems specifically for narcotic antagonists. In one, a matrix of polyethylene film is the antagonist carrier; accordingly, this system exhibits a defect common to all such casings made from plastics—the polymer matrix must be removed surgically after the drug supply is depleted.

More promising, Yolles says, is the use of a polylactic acid matrix that is easily absorbed by the body after the reagent charge has entered the blood stream. Preliminary tests at ARC show that 0.5 g of a polylactate/cyclazocine blend injected into dog muscle releases the drug at effective levels for more than a week. By the end of the year, Yolles predicts, there should be available polylactate matrices that will release effective levels of EN-1639 for a month or longer.

Yolles' injectable polymers are the only implantable casings that have been examined by federally supported investigators, but other research groups are also attacking the problem. Alza Corporation, Palo Alto, California, recently announced the development of a group of proprietary synthetic polymers that can be used "with virtually any drug." These polymers have been subjected only to preliminary toxicological testing in animals, however, and none of the testing has specifically involved narcotic antagonists. Dynatech Corporation, Boston, Massachusetts, has also developed several implantable drug casings—most of them polylactates and polyglycolic acids—which it plans to test in conjunction with narcotic antagonists under a contract with the New York City Health Services Administration.

Naloxone (and, to a lesser extent, EN-1639) appears attractive for use with depot systems because its potency is much greater when injected than when taken orally. This relative difference in efficacy can also be used to prevent abuse of legitimate drugs designed for oral administration, suggests Irwin J. Pachter of Bristol Laboratories. The addition of 1 mg of naloxone to 100 mg of methadone does not affect the potency or action of methadone when it is taken orally, he says. But when the combination was injected into addict volunteers at ARC, the naloxone blocked the narcotic effect of methadone and thus caused marked withdrawal symptoms. The extreme discomfort lasts only about 30 minutes, he contends, but it is sufficiently unpleasant that no addict would knowingly inject such a preparation. Addition of naloxone to methadone could thus conceivably curb all the intravenous abuse of methadone in maintenance programs.

Similar results can also be obtained with paregoric, a camphorated tincture of opium that has long been widely used for control of diarrhea. Addicts frequently process paregoric for injection, but animal experiments at Bristol Laboratories show that the addition of 0.3 mg of naloxone to each fluid ounce of paregoric is sufficient to abolish the narcotic effect upon injection without decreasing the antidiarrheal properties. Both applications will require much more testing—and FDA approval—before their use can become widespread, but eventually, Pachter predicts, "the words 'contains naloxone' may become anathema to drug addicts."

—THOMAS H. MAUGH II