Meetings

Narcotic Antagonists in Opiate Dependence

The use of narcotic antagonists in the treatment of heroin addiction was the subject of a symposium sponsored by the National Institute of Mental Health and the Department of Psychiatry, New York Medical College on 4 June 1970, in New York.

Narcotic antagonists were introduced into the treatment of opiate dependence in 1965 after extensive studies of the conditioning aspects of addiction. Himmelsbach (*1*) showed that autonomic changes persist in opiate addicts for as long as 6 months after withdrawal. Environmental contingencies, frequently associated with the repetitive injection of opiates, were shown to possess qualities of a nonspecific conditioned stimulus to reactivate neural mechanisms that mediate abstinence from opiates (*2*). Wikler and Pescor (*3*) showed that the natural syndrome of morphine withdrawal could be conditioned. It was the interaction of physical dependence and conditioning to environmental factors that was the basis for relapse after withdrawal from opiates (*4*). The conditioning factors in relapse were also seen as the reason why psychotherapy had been unsuccessful in treating addicts, for the opiate-seeking behavior of the addict is determined largely by processes of which neither he nor the therapist is aware (*5*).

Within this framework and from the standpoint of behavior theory, Wikler (*4*) suggested that successful treatment would require extinction of both conditioned abstinence and opiate-seeking behavior for lack of reinforcement. *N*-allylnormorphine (nalorphine, Nalline) would not be suitable for carrying out such extinction because early studies showed that, for chronic spinal dogs, this narcotic antagonist had to be given every 3 hours to block the effects of morphine given every 6 hours and to prevent the development of tolerance and physical dependence to morphine.

The application of this concept was made possible by observations by Martin and his co-workers (*6*) that former addicts maintained on cyclazocine were protected against both the narcotic effects of opiates and those properties which produced dependence. Wikler predicted that such addicts who assay self-administration of opiates would soon extinguish the operant aspects of their drug-seeking behavior for lack of reinforcement and because of associated reduction of conditioned abstinence and anxiety.

After initial successful reports by Jaffe and Brill (*7*), Martin *et al.* (*6*), and Freedman *et al.* (*8*), more extensive clinical trials were undertaken. At this meeting, the ongoing clinical trials with former addicts on cyclazocine were reported by Laskowitz (Lincoln Hospital, Bronx, N.Y.); Petursson (Manhattan State Hospital, Ward's Island, N.Y.); Resnick, Fink, and Freedman (New York Medical College); Jacobsen (Lillian Wald Clinic); and Jaffe (University of Chicago). These trials, since 1968, showed an overall acceptance and continued treatment rate of 40 percent of more than 450 adult male addicts. Sixty patients have been maintained in treatment for more than 1 year, and 20 for more than 3 years. The initial trials in many units were marred by the experimentation necessary to establish an adequate daily dosage (now set at 4 to 8 mg) and duration of antagonism to heroin (22 to 28 hours for 4 mg given orally), as well as the need to develop rehabilitation facilities.

Almost all former addicts report continued experimentation with opiates, with decreasing frequency the longer they continue using cyclazocine, but without readdiction, provided they maintain a daily intake of cyclazocine. A rate of readdiction of 20 percent was associated with discontinued use of cyclazocine.

A daily intake of cyclazocine was accompanied by a variety of agonistic drug actions, chiefly irritability, insomnia, and illusions, which were reported early in treatment. Adaptation occurred rapidly. Resnick described a successful 4-day schedule for increasing the dosage of cyclazocine to 4 mg by the concurrent use of oral naloxone to antagonize the agonistic effects of cyclazocine. In some patients, rhinitis, muscle aches, and malaise persisting for 12 to 36 hours was described after withdrawal. Simeon (New York Medical College) reported antidepressant activity for cyclazocine in clinical trials in in-patient and out-patient depressives (*9*).

A second narcotic antagonist, *n*-allylnoroxymorphone (naloxone) was reported in clinical trial by Zaks and Fink (New York Medical College), Kleber (Yale University), and Kurland (Maryland Psychiatric Research Institute, Baltimore). Single intravenous doses of naloxone are effective in antagonizing opiates for 3 to 5 hours. Intravenous doses of 0.7 to 1.0 mg effectively antagonize 50 mg of heroin. When given orally the drug's potency is significantly less. Zaks reported that 3.0 g/day was required by addicts to achieve 24-hour antagonism to injected heroin (25 mg/2 ml per 2 minutes). Kleber and Kurland successfully treated 30 former addicts with dosages of up to 400 mg daily. The outstanding characteristics of naloxone were its specificity as an antagonist and the absence of any agonistic effects. Because of short supply and expense, however, these trials have been limited and have been performed with only a few subjects. The clinical use of parenteral naloxone in anesthesia, which provides extensive data on safety and efficacy was reported by Foldes (Montefiore Hospital, New York) and Kallos (University of Pennsylvania).

Reviewing the clinical data, Freedman and Yolles (National Institute of Mental Health) concluded that these trials, particularly with cyclazocine, supported the clinical applicability of the conditioning hypothesis and suggested that an ideal antagonist would be one that exhibited antagonistic efficacy for weeks or months, without agonistic actions.

Harris (University of North Carolina), Blumberg (Endo Laboratories), Villareal (University of Michigan), Archer (Sterling-Winthrop), and Gray (Lederle Laboratories) reported that other *n*-allyl and cyclorphan derivatives of opiates were now in animal assay for their potency in antagonizing opiates. Jacobsen (Endo Laboratories) and Yolles (University of Delaware) described studies aimed at the development of long-acting formulations by delaying absorption from material implanted in body tissues; in successful trials in animals absorption has been extended over 2 to 3 weeks.

The application of implants of antagonists in the prophylaxis of opiate dependence in high-risk populations, particularly juveniles, the development of an "immunization" procedure, and the need for more extensive laboratory studies were discussed by Martin (Lexington), Fink, and Cochin (Boston University).

In the present chaos of treatment and prophylaxis of heroin addiction, therapeutic trials with narcotic antagonists represent a unique opportunity to test a rational theory of relapse in opiate dependence, a means for prophylaxis, and a way to reduce the incidence of juvenile dependence on opiates, and of opiate-related deaths.

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References and Notes

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10. This meeting was conducted in the course of development of a long-acting narcotic antagonist—part of the addiction research program which is supported by contract with the New York State Narcotic Addiction Control Commission.

Immunological Surveillance

The intriguing suggestion that adaptive immune responsiveness evolved as a general vertebrate protective surveillance mechanism to eliminate spontaneously arising neoplasms was made by Thomas more than 10 years ago. Burnet has since championed and extended this concept, proposing that primordial lymphocytes developed the capacity to recognize and to react destructively against anomalous "not-self" surface characteristics on altered somatic cells. The operation of such a "policing" system would require the prior phylogenetic development of both an extensive genetic polymorphism of detailed topography, including histocompatibility (H) antigens on cell surfaces, and a diversity of immunoglobulin cell receptors which would make possible a continuing subtle distinction between "self" and "not-self," between normal and abnormal, and between what is permissible and what is to be eliminated.

The central position of this concept in immunologic thinking led to the organization by the National Institute of Allergy and Infectious Diseases of an international conference on Immunological Surveillance, held at Brook Lodge, Augusta, Michigan, on 11 to 13 May 1970. As in the two preceding conferences in this series there were no formal presentations, but rather a continuous discussion was developed among the 30 invited participants, who represented a broad spectrum of experience in carcinogenesis, in developmental biology, and in cellular and tumor immunology.

At issue were general questions such as whether vertebrates are indeed equipped with surveillance mechanisms to detect and destroy spontaneously arising neoplastic cells; whether surveillance is mediated principally by cellular immune mechanisms; whether the immune machinery is amenable to augmentation of or interference with its tumor surveillance efficacy; and whether there is a relationship between strong and weak H antigens and tumor antigens.

It was conceded that surveillance mechanisms probably do exist in higher organisms, but there was no firm consensus that they necessarily operate solely by processes involving adaptive immunity. Among the evidence in favor of an immunologic basis for the surveillance mechanism, Good cited the "experiments of nature" involving immune deficiency diseases, noting that patients with thymic deficiencies, such as ataxia telangiectasia and the DiGeorge syndrome, have far higher incidences of solid epithelial and gastric tumors than would be expected from purely statistical considerations. Patients with agammaglobulinemias also display a higher than normal incidence of leukemias. Furthermore, individuals who have been subjected to sustained therapeutic or prophylactic immunosuppression, such as recipients of renal homografts and even those undergoing milder treatment with 6-mercaptopurine (for psoriasis), constitute a high-risk group in terms of the increased incidence of neoplasia. Allison reviewed the evidence for inhibition of tumor growth in mice inoculated with polyoma virus being mediated by cellular immunity and for heritable resistance in some mouse strains against leukemogenic viruses being abolished by immunosuppression and then restored by adoptive transfer of lymphoid cells. He took the view that immunological surveillance delays oncogenesis, and that inherited resistance of some strains of mice to leukemogenic viruses is due to the immune response of the host rather than to a limitation of the capacity of the virus to transform host cells.

The case against immunological mechanisms playing a significant role in surveillance was marshaled by Prehn. Attention was focused on the following points. (i) Tumors that escape the surveillance mechanism would be expected to be those least antigenic to the host, nevertheless most neoplasms do bear tumor specific antigens. (ii) Tumor induction in an "unpatrolled" environment should be accompanied by the appearance of stronger antigens; yet tumorigenesis in tissue culture and in diffusion chambers rarely involves the expression of new antigens. (iii) Papillomas raised in the skin of BALB/c mice grafted to C3H mice that had been thymectomized, irradiated, and treated with antilymphocyte serum regressed while the skin was accepted—in this instance surveillance did not appear to involve an immunologic mechanism. These situations are the opposite of what would be expected of a surveillance mechanism involving immunity against new surface antigens.

The surface topography of somatic cells which might serve as targets for surveillance and which might be important for cell interactions in differentiation was charted by Boyse. He constructed a new model in order to explain the origin and possible modulation of structural membrane moieties which might be antigenic to the host lymphoreticular system—a synthesis based primarily on his own studies. Normal cell populations exhibit extensive phenotypic diversity of cell surface structure, including specified sets of species, strain or individual specific antigens. Examples of this include the thymocyte-lymphocyte specific, Ly-A, Ly-B, and mouse specific lymphocyte (MSLA) antigens, the plasma cell specific (Pca) antigen, and skin specific (Sk) antigens. Such a phenotypic diversity of cell surface structure could be due to the selective activation of "private" sets of genes different for each tissue. Another order of diversity might be due to unique arrangements of relatively few gene products in the assembly of the surface topography so that the cell need draw on only a small number of genes to achieve an extensive diversity of surface dis-