

How the drug-receptor interaction is linked to analgesia is unknown. Inhibition of acetylcholine release in the CNS by morphine may be pertinent, but morphine has also been found to increase brain serotonin turnover in some experiments with rodents. Moreover, it has recently been suggested that the analgesic action depends on release of dopamine from some sites so that the amine acts on receptors at other sites in the CNS.

Epilepsy

Most of the drugs used to treat epilepsy are structurally related, but no unitary hypothesis can be upheld that explains their anticonvulsant effects. A bewildering array of neurochemical and neurophysiological events can be invoked as antiepileptic mechanisms, but few of these survive close scrutiny. The many reports of abnormal folic acid metabolism in patients receiving phenobarbitone, phenytoin, and primidone have focused attention on the possibility that convulsant actions of folic acid and its derivatives are reversed by treatment with the anticonvulsants. If so an abnormal excess of folic acid and derivatives might underlie the aetiology of epilepsy in some cases. In line with this suggestion are reports that attempts to correct folate deficiency induced by anticonvulsant treatment by administering folic acid by mouth have often interfered with the control of the seizures. On the other hand, there are reports of failure to reverse the drug-induced fall in cerebrospinal fluid folate concentrations by giving oral folate, which suggests that the compound has limited access to the CNS owing to the impermeability of the blood-brain barrier. This makes interpretation of the clinical effects of folic acid difficult, and at the moment the

relation between folic acid and anticonvulsant activity and epilepsy itself must remain open to question.

Much evidence suggests that anticonvulsants alter membrane permeability (phenobarbitone) and ion transport, sometimes by inhibition of carbonic anhydrase activity (acetazolamide) and sometimes by effects on ion pumps specifically (phenytoin, ethosuximide), so that the diffusion or active transport of sodium ions is inhibited. Nevertheless, the relevance of these effects to anticonvulsant activity has yet to be established.

On the physiological side inhibition of post-tetanic potentiation by phenytoin has been reported and this could prevent the spread of seizure activity and underlie its potent anticonvulsant action. The activities of enzymes (adenosine triphosphatases (ATPases)) bringing about the hydrolysis of adenosine triphosphate in the CNS are receiving increasing attention and several authors have mentioned the possible role of the ATPases in regulating neurotransmitter release. Such a function could link the physiological action of, for instance, phenytoin with its Na^+, K^+ -ATPase-inhibiting action, and the recent observation that all anticonvulsants so far tested inhibit a magnesium-activated ATPase located in nerve terminals of the CNS may prove to be important in relation to the anticonvulsant actions of the drugs.

Hence much has to be learned about the pathophysiology underlying any particular disorder before a rational approach to treatment can be attempted. In view of the difficulties inherent in experimentation and the enormous gulf that exists between the discovery of widely diverse effects of a drug, and the identification of one of these as directly responsible for therapeutic action, it is hardly surprising that the mechanisms of action of the drugs remain largely matters for speculation.

Letter from . . . Chicago

Drug censorship

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Of the various bureaucracies that regulate American medicine none has exerted a more direct effect on clinical practice than the Food and Drug Administration (F.D.A.). A creation of Congress and a section of the Department of Health, Education, and Welfare, the F.D.A. is mandated by law to protect the public against drugs that are unsafe or ineffective. This watchdog role has often brought it into conflict with a variety of interests, and its history has been a long series of crises. Lately the F.D.A. has once more been caught in a cross fire and stands accused of being both too strict with new drugs and too lenient with the drug industry.

The cause of this paradox lies in the political nature of the agency. Whereas in Britain the medical profession retains some control over the introduction of new drugs, the United States has set up rigid legal constraints within which new therapeutic

agents must be evaluated. These arrangements make the approval of new drugs a subject of controversy, and factors other than scientific or clinical evidence play a considerable role. Indeed, the first principle new F.D.A. employees must grasp is the need to survive. They soon learn that every ruling on a drug is a potential target for a newspaper exposé or a Senate subcommittee hearing. To appreciate the issues, however, requires a knowledge of the long history of government attempts to regulate the pharmaceutical industry.

Pharmacological Disasters

In 1902, after the St. Louis disaster in which 10 children died from a tetanus-contaminated diphtheria antitoxin, Congress passed a Virus, Serum and Toxin Act regulating the manufacture and inter state movement of certain pharmaceutical products. In 1906 Congress approved a Pure Food and Drug Act, largely through the efforts of Harvey W. Wiley, chief chemist in the Department of Agriculture, who travelled around the country with his famous poison squad and led a crusade against drug fraud, impure meat, and improper slaughter conditions. Wiley became the first commissioner of the F.D.A. His tenure ended

prematurely in 1908, when his intention to look into the safety of saccharine brought him into conflict with President Theodore Roosevelt, who eased him out of his position.

A succession of pharmacological disasters punctuates the subsequent history of the F.D.A. Cataracts developed in people who took nitrophenol as a weight-reducing agent, and chronic toxicity in women who used a thallium-containing depilatory. In 1936 as many as 76 people died from taking a sulfanilamide elixir which contained diethylene glycol. In 1938 Congress passed a Food, Drug, and Cosmetic Act requiring safety testing of all new drugs by the government. But further episodes occurred, such as the cataracts caused by the anticholesterol-aemic agent MER-29 and the persistent promotional campaign for chloramphenicol despite clear evidence that the drug could cause fatal agranulocytosis.

In 1957 the late Senator Estes Kefauver became chairman of the Senate Subcommittee on Anti-Trust and Monopoly. This committee laid the groundwork for the dramatic changes which altered the course of therapeutics in the U.S.A. In April 1961, while Senator Kefauver's bill was pending in Congress, the thalidomide disaster in Europe came to widespread attention. Public pressures resulting from this helped the passage of Kefauver's bill, which became the 1962 regulations. These required that the efficacy as well as safety of new drugs must be documented. As a result elaborate protocols must be followed before new drugs may be released to the public—protocols so strict that neither aspirin nor digitalis would have passed the scrutiny of F.D.A. investigators.

Therapeutic Stagnation

The earlier failure of the drug industry to police itself and avoid the hasty marketing of inadequately tested drugs was largely responsible for this over reaction. Recent allegations that the F.D.A. is unduly influenced by the drug industry must also be viewed against this background. But the overall result was a decade of therapeutic stagnation. During the 1960s the agency approved remarkably few drugs, and then only after considerable delays. Propranolol serves as a case in point: it was long withheld, then released only for angina, and to this day has not been officially approved for hypertension, though in this instance common usage has prevailed. Moreover, the F.D.A. has released no other beta-adrenergic blocking agents on the American market.

Arguably the overall health of the American people has not suffered from this "drug lag." Yet some patients clearly receive inferior or unnecessarily dangerous drugs when better ones are available. Cromolyn, orciprenaline, and terbutaline were released only after long delays. Beclomethasone and salbutamol are still unapproved. Only indomethacin and ibuprofen, of the many new antirheumatic drugs, may be prescribed. Several useful antihypertensive agents such as bethanidine and debrisoquine are still unavailable. Diazoxide was held up for almost a decade. And many severely hypertensive patients remain poorly controlled with the available drugs while the agency is making up its mind about minoxidil and prazosin. These, moreover, constitute but a fraction of the hundreds of investigational drugs currently under review. To acquit itself of its task the F.D.A. has expanded into a huge operation with 6000 employees and a yearly budget of over \$200 m.—a colossus that is hard to control and even harder to move. Furthermore, so long as approving a new drug renders the agency vulnerable to attack the safe course is to reject the application, or stall, or, when all fails, demand further studies.

Lately the drug lag has received much attention. The system for approving new drugs has been charged with being repressive and overstructured, the United States is said to have acquired a "conservative image" in world therapeutics, with American books on pharmacology seriously out of date, and American physicians having a surprising lack of awareness of new drugs. Moreover, if the F.D.A. comes to be regarded as pro-

tecting patients against doctors as well as against the drug industry a precedent might be set for government also to interfere with other clinical decisions.

Unending Studies

Perhaps the complaint about the F.D.A. most often voiced is that it requests unending studies while rejecting experience obtained from foreign countries or from ordinary clinical practice. Yet the law does appear to require such elaborate testing, and neither common usage nor foreign approval constitute acceptable legal evidence. Thus in a recent controversy over propranolol it was pointed out that the drug was approved for use in angina without the evidence required by law, and that if the efficacy tests were too stringent or cumbersome the law and not the F.D.A. needed changing.

In recent years, however, with the appointment of a new commissioner, Dr. Alexander Schmidt, the F.D.A. has done much to streamline procedures, eliminate delays, and in many instances has shown it can move speedily. Yet this very streamlining has laid it open to attack from politicians and consumer groups—who say the agency is negligent and under the sway of the drug industry. As a result, the F.D.A. is again embroiled in a series of crises. Last year Dr. Schmidt and his assistant, Dr. Richard Crout, were raked over the coals by Senator Edward Kennedy's Senate Subcommittee for allegedly harassing and intimidating junior F.D.A. staff scientists who opposed the introduction of new drugs. Since then critics have accused the agency of being too lax in approving propranolol for angina, diethylstilbestrol for postcoital contraception, and the Dalkon Shield as an intrauterine device. Controversy has raged over the use of lincomycin and clindamycin, and there was criticism when the F.D.A. hesitated to follow up on the University Group Diabetes Program report by proscribing the hypoglycaemic agents.

In each of these cases the debate had been heated and protracted, and some Senate subcommittee hearings have been characterized as prize exhibitions of bully-boy tactics, with added implications that physicians were gullible, poorly trained, and easily misled by the drug industry. Yet the suspicion lingers that some of these hearings have become an opportunity for ambitious politicians to obtain exposure on inflammatory issues. The comment was made that though charisma may get one elected to the Senate it will not get one through the board examinations. Unfortunately, the needs of the patients have somehow become lost in this tangle of controversy. While the problem of curbing a profit-hungry pharmaceutical industry remains unresolved, the buffeting of useful drugs between the Scylla of bureaucratic procrastination and a Charybdis of demagogic pressures serves ill the interests of the American public.

A patient suffered an injury to his elbow 13 years ago with ulnar nerve damage and partial median nerve damage also. At the time treatment was totally confined to realignment of the bones. Is it too late to undertake reconstruction or reorganisation of nervous tissue in the arm?

Thirteen years after a nerve injury there will be irreversible muscle wasting and, even more significant, secondary joint capsule fibrosis where active movement has been limited for so long; thus, even if nerve regeneration occurred after reconstruction of the damaged nerves (which is highly improbable), then it would be frustrated. Conceivably, however, rearrangement of the remaining active motor muscles, by tendon transplants or possibly tenodesis or even arthrodesis, could achieve an appreciable improvement in hand function even now. From the sensory aspect it may also help if innervated flaps of skin are transferred into functionally important but at present anaesthetic tactile areas of the hand. These sophisticated procedures would be of value only in a well-motivated patient who has a real need for improved hand function. After 13 years he may have become totally adapted to his disability.