keeping their backs posturally upright. They need help with tights, but shoes, socks, and stockings may be put on by pulling the foot backwards. Hot baths help as the patients will float out into a good posture and the heat will soothe, but to get out of the bath they must turn over and kneel in the bath and not pull themselves out forwards.

To avoid a recurrence patients are told to take a forward strain on their backs by bending their knees and hips but not their backs before lifting, and if they cannot reach the object to be lifted they must get on one knee and still keep their backs posturally upright. They must also treat all objects to be lifted as if they were heavy—that is, they must not lift a weight carelessly off the floor but face the weight and lift as instructed.

Patients visited at home and found immobile in bed usually have a lumbar strain. A pillow is put under the lumbar region. While they hold the head of the bed traction is applied to their legs until their muscle spasm relaxes and the pain goes. They are then rolled out of bed and shown how they can manage if they stay upright. Many of these patients, lying across a pillow,

will turn and manipulate their own backs, usually at night, but the more courageous are hung on a door and manipulated.

This treatment could have been deduced by realising how strong a leverage action is exerted to slip back one vertebra over the one below if the muscles do not hold during a forward strain. This is not easily noted, because x-ray films of the vertebral column are notoriously unreliable and such movements that the vertebrae sustain, although enough to irritate the spinal nerve, are readily passed as “within normal limits.”

Having manipulated well over 2000 backs in this way (patients with unstable backs come back for each relapse) and as only a few are off work for more than a week (some go straight back to work), I would like to recommend this technique for the treatment of backache.

Reference

¹ Doran, D M L, and Newell, D J, *British Medical Journal*, 1975, 2, 161

Today's Treatment

Diseases of the central nervous system

Pharmacological basis of treatment

JOHN C GILBERT

British Medical Journal, 1975, 4, 33-35

In introducing and summarising a subject as complex as the pharmacological basis of treatment of disorders of the nervous system brief reference has to be made to the general direction of progress, the problems, and the discoveries which gave the subject impetus.

Progress in treating some disorders has been long delayed by inadequate experimental methods and by the lack of suitable animal models of human disease. Experiments involving electrical stimulation of the dental pulp, or the radiant heat tail-flick test and mouse hot-plate test of nociception in animals, have proved to be useful models for testing potential analgesics for man, but some types of pain do not appear to have equivalent sensory stimuli in animals and different types of pain require different drugs for their management in man. Measurement of seizure thresholds, inducing the seizure activity by leptazol or electroshock, has its value in determining the anticonvulsant activities of drugs but the features of the seizures are not identical to those of an epileptic attack. No animal model can be claimed to be representative of schizophrenia in man. Given this sort of impediment, the development of therapeutic drugs has been a checkered affair and some drugs are in current use not so much as a result of logical study as of empirical observa-

tion. For example, the narcotic analgesic pethidine aroused interest originally because of its atropine-like effects and its tussible value as an antispasmodic. It was only later that the effects of pethidine on the central nervous system (CNS), resulting in sedation, analgesia, and euphoria (features commonly associated with morphine administration), were noted, suggesting its possible therapeutic use as an analgesic.

While the mechanisms of action of many drugs used in treating diseases of the nervous system are not clear, some modify quite distinct chemical transmission processes and the metabolic pathways sustaining these processes have been identified.

Myasthenia gravis

The metabolic pathways involving acetylcholine—its synthesis through choline acetyltransferase and its destruction through acetylcholinesterase—are well established, and the treatment of myasthenia gravis relies heavily on inhibitors of acetylcholinesterase because of the role of acetylcholine as a transmitter at the neuromuscular junction. Myasthenic patients tend to show an increased response to neuromuscular blocking drugs which competitively antagonise the action of acetylcholine at the motor end-plate and a decreased response to depolarising blocking agents such as suxamethonium.

The symptoms of myasthenia are compatible with diminished activity at the motor end-plate, and evidence suggests that this results more from a decrease in the amount of transmitter released after presynaptic events than from abnormal (reduced) sensitivity of the end-plate nicotinic receptor region to the transmitter impinging upon it. In either case prevention of destruction of acetylcholine by inhibition of the postsynaptically sited esterase

Department of Pharmacology, University Medical Buildings,
Foresterhill, Aberdeen AB9 2ZD

JOHN C GILBERT, PHD, reader in pharmacology

ameliorates the symptoms of myasthenia, and the use of drugs such as pyridostigmine which have this effect and which are only slowly metabolised is logical. While pyridostigmine has a long duration of action, however, the more rapid rate of hydrolysis of edrophonium makes its duration of action short, and it is more suitable for use in diagnosis. The fatigue and muscle weakness of the myasthenic patient may be exacerbated and cause a crisis either by pathological processes or by overdose of the anticholinesterase drugs used in treatment. The short action of edrophonium is again useful in discriminating between the two. The drug can temporarily alleviate the symptoms of the myasthenic crisis but it enhances the sweating, excessive salivation, and colic associated with the muscarinic effects of the cholinergic crisis.

Parkinsonism

Mechanisms involving acetylcholine are also involved in the treatment of Parkinsonism, in which the use of an anticholinergic agent such as benzhexol to combat the rigidity and tremor probably has as its basis antagonism of acetylcholine at muscarinic receptors. This rationale applies equally to the Parkinsonism which can be induced by neuroleptic agents such as the phenothiazines and the idiopathic disorder, whereas the use of drugs which increase dopaminergic activity in the corpus striatum (see below) tends to be effective only in the idiopathic condition. In relation to the role of acetylcholine one hypothesis is that cholinergic transmission in the corpus striatum, which normally regulates motor activity, becomes excessive, so that antagonism of acetylcholine at its receptor is necessary to correct this abnormality. Hence side effects of treatment include those often associated with anticholinergic activity—dryness of the mouth and blurring of the vision. It is probably an oversimplification to contend that only two control pathways—the cholinergic pathway and a pathway involving the catecholamine dopamine as the predominant transmitter—are responsible for achieving a balanced control of motor activity by the extrapyramidal system of the basal ganglia, but present-day treatment of Parkinsonism is based upon this general notion.

Our increased understanding of this second pathway has led to the inclusion in therapy of levodopa, a metabolic precursor of dopamine. Interestingly, the role of the substantia nigra in the pathophysiology of Parkinsonism was suggested before 1900, but the importance of dopamine and its possible role as transmitter has been fully recognised only in the last decade. In Parkinsonism the decreased concentration of dopamine in the corpus striatum may reflect decreased activity of the dopaminergic nerves which leave neurons of the substantia nigra and connect with the striatum. Extrapyramidal symptoms such as tremor and rigidity may therefore be alleviated by replacing the dopamine, but the possibility of administering this directly is precluded because of the blood-brain barrier. Most evidence now suggests that the brain has appreciable extracellular space (some 15% to 20% of its volume), and it is neither the close proximity of the brain cells nor the special characteristics of glial cells which constitute the major permeability barrier to solutes. More probably the tight junctions of the cerebral vascular capillary bed constitute the blood-brain barrier and prevent access of dopamine to the brain. The more lipid soluble precursor of dopamine, levodopa, readily penetrates the brain and there it is metabolised to the putative transmitter by the enzyme dopadecarboxylase. This approach to treatment has been valuable and it may be improved by the use of a peripheral dopadecarboxylase inhibitor, which should not penetrate the CNS, in conjunction with levodopa. This prevents the rapid destruction of the compound at the periphery, allowing higher concentrations to be attained in the brain. The use of the two drugs together may also reduce the incidence of hypotension in patients by reducing peripheral dopamine formation. The treatment of Parkinsonism represents a rational approach to treatment as described so far, but one has to allude, too, to the

empirical observation that when amantadine, which has antiviral activity, was prescribed for influenza in a Parkinsonian patient the symptoms of Parkinsonism were alleviated. The mechanism for its therapeutic effect is not clear but amantadine modulates the release of both acetylcholine and dopamine in preparations derived from the CNS of animals so that again a cholinergic-dopaminergic control system may be implicated.

Migraine

The physiological processes of vasodilatation and vasoconstriction are finely regulated in the CNS and derangement of their control causes several disorders. Particularly complex is the balance between dilatation and constriction of the cerebral blood vessels associated with attacks of migraine. Spasm of the arteries, resulting in transient vasoconstriction and ischaemia, occurs during the initiation of a migraine attack and is followed rapidly by vasodilatation. Several chemical changes, including an increase in the concentration of serotonin (5-hydroxytryptamine), accompany the initiation stage. This monoamine is present in relatively high concentrations in the hypothalamus. While its role as a central transmitter, in controlling body temperature, or in sleep processes is not established unequivocally, there is little doubt that drugs which antagonise the actions of serotonin at some receptors in the CNS are effective in the prophylaxis and treatment of migraine.

Methysergide has to be mentioned, although it is now used infrequently as a prophylactic. Whether its effectiveness depends on competition with serotonin, thereby antagonising its action at some receptors so that a greater concentration is available at others, must remain open. Ergotamine is also a serotonin antagonist, although its direct vasoconstrictor action may be more relevant to its use in migraine, and its combination with caffeine, which both increases the intestinal absorption of ergotamine and exerts a central vasoconstrictor action, has proved useful. More recently clonidine has been used in doses that are sufficiently low to preclude any antihypertensive action. Its effects in the CNS are complex and its effectiveness in the prophylaxis of migraine may or may not depend on its alpha-adrenoceptor agonist activity.

Pain

Headache and mild pain respond to analgesic drugs such as aspirin and paracetamol that raise the threshold to pain, but the basic mechanisms are again a matter for speculation. There is strong evidence to support the contention that prostaglandins are mediators of fever and inflammation and that the antipyretic effect of aspirin depends on inhibition of prostaglandin synthesis. While the relief of low intensity peripheral pain may include the same mechanism, however, there is no strong evidence to implicate it in the analgesic action of aspirin in headache. Neurochemical and neuropharmacological studies to clarify this point are difficult, and we need to learn more about the uncoupling of oxidative phosphorylation in the CNS by aspirin—which results in increased oxygen consumption of the cells—and the consequences of the effects of aspirin on adenosine triphosphatase activities at different sites and aminoacid transamination reactions.

Similarly, electrophysiological studies of the activities of different brain regions—stimulated in the presence and absence of analgesics—are required. Such studies have suggested that the action of narcotic analgesics at least may possibly result from depression of central activating and arousal systems located in the midbrain reticular region and the hippocampus. The precise mechanism of pain relief by narcotic analgesics has not been elucidated but specific receptors may be involved in the analgesic action of morphine and related drugs which not only raise the pain threshold but also diminish the patient's reaction to it.

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

GEORGE DUNEA

British Medical Journal, 1975, 4, 35-36

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

Department of Medicine, Cook County Hospital, Chicago, Illinois
GEORGE DUNEA, M.B., M.R.C.P., Attending Physician