Children

Measures recommended to prevent the development of CHD apply as much to children as to adults since all of the major risk factors found in adult life can occur during childhood. All those concerned with the care of children should be active in the prevention and management of these factors.

General practice

General practice should provide the main means of identifying those at high risk of CHD. Mass screening for CHD and its associated risk factors is not recommended, but the efforts of general practitioners should be supported by a general health education policy which involves hospital and community physicians and their supporting staff. Selective health examinations should be carried out in those groups known to be at high risk for CHD, and interested general practitioners should be encouraged to extend health examinations to other groups of patients when this can be done by using existing facilities and services.

Wider implications of recommendations

It was not the purpose of the working party to consider the implications of their recommendations for research or for government. Nevertheless, some areas may deserve further consideration by other bodies. With regard to the overall allocation of resources, the achievements of acute coronary care, coronary ambulances, and coronary artery surgery cannot bring about a major reduction in the overall burden of heart disease in the community. This must come from preventive measures.

Education—Bringing about the recommended changes in behaviour relating to diet, physical activity, and cigarette smoking will require the sustained education of the community at all levels, but particularly the young. A comprehensive public and professional educational programme will be needed together with the co-operation of food manufacturers, educational authorities, and the mass media. Apart from formal health education, much can be done by medical practitioners and other health workers who understand the problem and are prepared to provide positive advice to individuals and the community about the risk factors for CHD.

Smoking—The reduction of cigarette smoking will require fiscal measures by the government and the control of advertising. These measures may be at least as effective as general health education and possibly more so.

Diet—There are considerable implications in the dietary recommendations for national food policy, for the producers and the manufacturers of food, and for the regulations concerning food labelling. Nutrition practices and catering in schools, hospitals, the armed Forces, and other organisations may have to be reviewed.

Physical activity—Any improvement in patterns of physical activity can come only from leisure-time pursuits. Adequate and convenient recreational facilities are required if the recommendations are to be effective.

Reference

- ¹ Joint Working Party, *Journal of the Royal College of Physicians of London*, 1976, **10**, 213.

Today's Treatment

Psychological Medicine

Drugs used in psychological medicine: pharmacological basis of treatment

JOHN C GILBERT

British Medical Journal, 1976, **1**, 882-884

A wide spectrum of drugs is used to treat psychological disorders and a strong element of serendipity has often triggered major discoveries in this field. For example, searches for new analgesic drugs led to the discovery of a potent antipsychotic agent, haloperidol, and it seems almost bizarre that studies of an antihelminthic drug should lead to introducing that drug, disulfiram, for treating alcoholism. For some of the drugs, after years of clinical use fully justified by empirical observations, laboratory studies have thrown light on mechanisms of action and in several cases relatively specific pharmacological receptors have been implicated. For most drugs, however, it is difficult to postulate one mechanism of action with confidence.

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Depression

MONOAMINE OXIDASE INHIBITORS

The first controlled clinical trial of a drug for treating depression appears to have been started some five years after the chance observation that patients suffering from tuberculosis who were treated with iproniazid experienced elevation of mood. During the intervening five years the powerful tranquillising effect of reserpine was found to be accompanied by central catecholamine and serotonin depletion, and, significantly, reserpine sedation was reversed by monoamine oxidase (MAO) inhibitors, drugs which caused a rise in the monoamine content of the brain. The discovery of MAO inhibitor antidepressants highlights the importance of monoamine metabolism in the brain and the manner in which pharmacological and neurochemical studies may lead to a rational approach to treatment.

Noradrenaline is synthesised in neurons of the brain from the amino-acid tyrosine via another important monoamine dihydroxy-phenylalanine (DOPA), and after synthesis it becomes stored in synaptic vesicles within the nerve terminals. When a wave of depolarisation

tion invades the adrenergic nerve terminal a sequence of events rapidly occurs which probably involves calcium ions and the transient binding of synaptic vesicles to the membrane of the terminal so that noradrenaline is released. The transmitter diffuses across the cleft of the synapse outside the nerve terminal and acts at receptors located in the postsynaptic membrane to trigger the next neuron or group of affected neurons to respond.

Two points merit special emphasis. Firstly, any noradrenaline which is present in the nerve terminal but not bound within the synaptic vesicle and also noradrenaline which leaks out of the vesicles under normal circumstances are susceptible to enzymic destruction by either catechol-O-methyl transferase or by MAO within the terminal. Secondly, in contrast to the state of affairs for the transmitter acetylcholine, termination of noradrenaline action at the receptor depends not so much on enzymic destruction as on removing the chemical messenger from the receptor sites. This process is regulated by the rate of uptake of noradrenaline back through the axonal membrane into the adrenergic terminal.

The importance of MAO inhibitor drugs such as phenelzine and nialamide lies in their ability to prevent the enzymic destruction of transmitter outside the synaptic vesicles but within the nerve terminals. The clinical effect of this action, shown as an elevation of mood, occurs at a time when, by analogy to animal models, the concentration of monoamines in the brain has been significantly increased.

It has been repeatedly documented that a hypertensive state may occur in patients receiving MAO inhibitors at the same time as drugs like phenylephrine, an α -adrenoceptor agonist contained in some common cold remedies, or food containing tyramine. These compounds are also normally destroyed in the body by MAO in a number of tissues so that inhibition of the enzyme permits the compounds (directly or indirectly) to cause constriction of blood vessels at the periphery, increasing the peripheral resistance and the blood pressure.

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants are increasingly prominent in treating depressive illness. Imipramine, discovered first, is still clinically important and laboratory and clinical studies of it and related compounds tend to support the monoamine theory of affective disorders. According to this theory tricyclic antidepressants act by potentiating the effects of noradrenaline and serotonin in the brain.

Evidence suggests that imipramine and desipramine block the re-uptake of noradrenaline by peripheral nerves and also the uptake of noradrenaline and serotonin (5-hydroxytryptamine) into brain tissue. It has also been reported that the drugs potentiate the response of neurons in the brain to these two neurotransmitters. The most generally accepted explanation of these observations is that tricyclics block the mechanism mediating the re-uptake of the transmitters by neurons in the brain and this would delay the removal of the monoamines from receptor sites on the postsynaptic membrane resulting in potentiation of transmitter action. In fact, while desipramine acts in this manner, imipramine may not, but it is metabolised to desipramine (desmethylinipramine) *in vivo*.

Another tricyclic, iprindole, has recently been reported not to block either noradrenaline or serotonin uptake although its chemical structure and pharmacological effects are similar to those of imipramine and its demethylated metabolite. Studies in which the drug was released from fine pipettes directly into neurons of the cerebral cortex and caudate nucleus of rats by microelectrophoresis have suggested that iprindole, as well as some other tricyclics, selectively blocks "masked inhibitory" monoamine (and acetylcholine) receptors and this is proposed to account for the potentiation of the effects of the monoamine.

So the original concept that tricyclic antidepressants as a group act by inhibiting noradrenaline or serotonin re-uptake has to be looked at again in the light of results for different members of the group and the question remains to be answered: what is the relation between neurons in the brain which are responsive to noradrenaline and serotonin and the processes giving rise to depression and to its treatment?

LITHIUM CARBONATE

The pharmacological basis for treating depressive illness cannot be left without mention of lithium carbonate in current treatment. Lithium is acknowledged to be an effective prophylactic in some phases of depressive illness but the reason for this action is obscure. One effect of the lithium ion is to substitute for potassium ions in the system commonly referred to as the sodium pump.

The molecular basis for the pump, which may force sodium ions out of the cell to the exterior and potassium ions into the cell, in spite of considerable concentration gradients in the opposite direction, includes an enzyme activated by sodium and potassium ions together. When lithium substitutes for one of these the enzymic activity and the pumping efficiency are reduced. This permits sodium and lithium ions to remain in the cell and water must accompany these to maintain osmotic forces within certain limits. This process of cellular hydration has been assumed by some to account for the prophylactic action of lithium in depression. Just how the two are related is not apparent. In animals pretreatment with lithium may result in inhibition of the release of noradrenaline from brain slices stimulated *in vitro* and one mechanism suggested for the inhibition is that lithium facilitates the re-uptake of the transmitter. The significance of such an effect in relation to depression is difficult to assess and it is clearly opposed to the generally accepted mechanism of action of antidepressants like desipramine which inhibit the re-uptake system.

Reference has also been made to a relation between serotonin synthesis in the brain and depression. Serotonin synthesis is geared in the brain to free tryptophan concentrations and these depend upon the plasma concentration of tryptophan, much of which is bound to plasma proteins. The free plasma tryptophan of depressed patients has been reported to increase from about 6%, to 10%, on recovery, and, while lithium did not influence this, it apparently reduced the total plasma tryptophan concentration and it has also been shown to increase brain serotonin. Increased brain serotonin synthesis may not, however, be a prerequisite for recovery from depression.

ANXIETY STATES

The observation in the early 1960s that benzodiazepines had a taming effect on wild monkeys was a significant advance. Because of the comparatively low risk of dependence and tolerance to the benzodiazepines as well as to the low incidence of adverse reactions, this group has overtaken the barbiturates in the role of sedatives. The mechanism of the sedative action of diazepam, chlordiazepoxide, and other members of the group is not known.

Several studies have indicated that diazepam and others inhibit sodium, potassium-adenosinetriphosphatase (ATPase)—the enzyme, in the brain responsible for pumping sodium ions out of cells and potassium ions in—and it has been suggested that such inhibition would result in a tranquillising effect; just how is not clear. Sodium, potassium-ATPase is found at several sites (mitochondria, membranes) in different brain cells and until the relative sensitivities of these to various concentrations of benzodiazepines encountered clinically are established the significance of the inhibition is likely to remain obscure. It is also difficult to relate this biochemical effect to numerous electrophysiological and pharmacological experiments showing that chlordiazepoxide and some other benzodiazepines consistently slow the electroencephalographic spontaneous electrical activity recorded from some brain regions in cats. This effect on spontaneous electrical activity may be related to the antianxiety action observed clinically. Interestingly, the antiepileptic action of benzodiazepines tends to be much more pronounced after parenteral than oral administration and electrophysiological studies of their effects on evoked electrical activity—the activity elicited in brain regions by implanting chemical irritants—show the parenteral route to be more effective. More recently evidence has indicated that the benzodiazepines might act by mimicking the action of glycine at receptors in brain. This simple amino-acid may have an important function as an inhibitory transmitter in the central nervous system (CNS): it can cause hyperpolarisation in motor neurons, decreasing their frequency of firing so that the co-ordination of muscle groups is affected. If the benzodiazepines act at the glycine receptor then muscle relaxation could be one result.

Whether muscle relaxation itself leads to a lessening of the symptoms of anxiety or the quelling of anxiety in patients is

partly responsible for muscle relaxant activity is a moot point, the two being very closely associated. It may well be that this phenomenon is involved in using centrally-acting muscle relaxants like meprobamate for anxiety states.

SCHIZOPHRENIA

In schizophrenia drug treatment plays a prominent part, the object being more to control the diverse symptoms which are presented by this general disorder than to treat the schizophrenia in the true sense: the two processes are by no means synonymous.

Chlorpromazine remains prominent in treatment because of the dramatic effect it can have of controlling aggression and "stabilising the mood" of some patients. The discovery of chlorpromazine and other phenothiazines again owes much to serendipity, phenothiazine itself being introduced for treating infection by worms. In spite of the vast number of papers dealing with effects of chlorpromazine on the CNS it is still not clear how the drug acts as a major tranquilliser—its main value in treating schizophrenia.

It antagonises actions of dopamine in the brain, and levodopa, the dopamine precursor, antagonises the action of phenothiazines. Since no change in the dopamine content of the brain seems to accompany chlorpromazine administration to animals, whereas the rate of turnover of the amine is increased, it has been suggested that the tranquillising action results from blockade of dopamine receptors. Such an action could increase dopamine turnover by a feed-back control mechanism. This hypothesis is at least compatible with the effect of chlorpromazine of causing extrapyramidal symptoms and a Parkinsonian-like syndrome. The major tranquilliser reserpine may also cause the syndrome, but the underlying cause in this case is depletion of brain dopamine, a phenomenon not caused by chlorpromazine. Chlorpromazine also blocks α -adrenoceptors normally responsive to noradrenaline and this effect may also be involved in its mechanism of action.

Numerous authors refer to the importance of effects of chlorpromazine on the reticular formation of the brain-stem. The lack of a general depressant effect of the drug in that region sets it aside from the barbiturate group of sedatives. The significance of the observation that chlorpromazine reduced the electrical activity evoked in the reticular formation by peripheral stimuli, however, is not clear. Unlike reserpine, chlorpromazine does not reduce the brain content of serotonin or noradrenaline, but both drugs are major tranquillisers. It may be argued that, while the pharmacological basis for chlorpromazine action remains for the moment well hidden in a maze of neurophysiological and neurochemical events, the basis for the action of reserpine lies simply in its ability to deplete the brain of noradrenaline, dopamine, and serotonin. This may well be an oversimplification but one potent action of reserpine seems unchallenged and that is its effect of inhibiting the uptake of catecholamines and serotonin by vesicles within nerve terminals in the brain. Uptake is an active process, requiring metabolic energy and evidence suggests it involves a magnesium-dependent enzyme which hydrolyses adenosinetriphosphate (magnesium-ATPase). Reserpine inhibits the process and when noradrenaline, for instance, is not taken up to be stored in the vesicles it becomes vulnerable to enzymic destruction in the cytoplasm.

Another phenothiazine derivative, trifluoperazine is proving to be particularly useful in schizophrenia because it has a long duration of action and some tests indicate it is far more potent than diazepam and other drugs in alleviating punishment-induced suppression of a response—that is, in conflict-punishment tests. Briefly, food-deprived animals can be trained to press a lever and to obtain food after a specific number of presses. Later this activity is not only rewarded by a food offering but is also punished by an electric shock so that the animal becomes faced with conflicting stimuli. The introduction of the punishment reduces the lever-pressing activity of the animals but drugs such as the benzodiazepine chlordiazepoxide alleviate the suppressant effect of the shock and increase the lever-pressing activity. This effect occurs at doses of the drug which do not significantly affect the response of the animal when there is no punishment so that it is the behaviour induced by conflict which is influenced by the drug at these doses. Trifluoperazine can be particularly potent in such tests. Its effect does

not arise simply from analgesia; morphine, for instance, has little effect.

Haloperidol was discovered during searches for more potent analgesic agents and it is still widely accepted as a useful tranquilliser and antipsychotic agent. It has potent antiemetic activity. There is evidence that it interferes with the action of dopamine with receptors in the CNS and side effects of the drug include extrapyramidal symptoms such as tremors and muscle rigidity at some dose regimens.

ALCOHOLISM

Disulfiram is probably the most common drug used in managing alcoholism. If alcohol is consumed after the drug some alarming effects may result. These include severe nausea, vomiting, headache, sweating, and increase in pulse rate, and these symptoms, which clearly serve as strong deterrents to drinking alcohol, are attributable to increased acetaldehyde concentrations. Alcohol is metabolised to acetaldehyde by the enzyme alcohol dehydrogenase and this enzyme is particularly active in the liver. Disulfiram prevents the metabolic removal of acetaldehyde by inhibiting aldehyde dehydrogenase and so the concentration of acetaldehyde in blood and tissues rises and in the brain this gives rise to the extremely unpleasant effects. A point which may be overlooked is that disulfiram can inhibit enzymes other than aldehyde dehydrogenase and it may increase the sensitivity of the patient not only to subsequently ingested alcohol but also to drugs such as the oral anticoagulants.

Insomnia

Many clinical conditions can cause insomnia and the drug of choice to induce sleep depends on the diagnosis of the condition underlying the problem. Hypnotics like the barbiturates are still prescribed, but these have given way to minor tranquillisers (nitrazepam, diazepam) and to antidepressants in some cases. The pharmacological bases for the actions of the last two general groups have been discussed already but the use of barbiturates requires comment.

Barbiturates cause several biochemical and electrophysiological changes in brain tissue and it has been difficult to ascribe the hypnotic action to any one of these.

For many years it was thought that the hypnotic effect resulted from a general depressant effect and this was manifested, in experiments both in vivo and in vitro, as a decreased oxygen consumption of brain tissue. Evidence now suggests that at concentrations lower than those depressing tissue respiration barbiturates depress arousal mechanisms in the reticular formation of the brain stem in a relatively specific manner. This effect can be detected in electrophysiological experiments where the spontaneous activity of neurons in the reticular formation is reduced by applying barbiturates iontophoretically. At the molecular level this effect, which is not restricted to the barbiturates used clinically as hypnotics (butobarbitone, quinalbarbitone, amylobarbitone), may be due to inhibition of ion movements at the cell-membrane.

Tolerance to these hypnotics is common and dependence also occurs. They may also be potent inducers of enzymes in the liver which are responsible for metabolising other drugs so that dose regimens of drugs may have to be adjusted in the light of barbiturate treatment. Non-barbiturate hypnotics, which also depress the CNS include antihistamines (promethazine, triprolidine) glutethimide, chloral hydrate and its derivatives, and other drugs. Their mechanisms of action are not clear.

Is it wise for a 50-year-old man who sustained a spiral fracture of his tibia playing hockey to resume the game?

Firstly, I do not see why a man of 50 should not play hockey, and, secondly, a well-plated spiral fracture of his tibia is no contraindication—but it must always be remembered that every screw hole is a point of weakness in the bone and a potential fracture line.