Hypertension and Depression: interrelated problems in therapy

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In the management of hypertensive patients the question of mental depression has to be borne in mind, not so much because hypertensive subjects are necessarily prone to mental depression but because very real problems arise in connection with drug therapy. Firstly, some antihypertensive drugs can cause depression and must be avoided in patients who seem to have depressive personalities. Secondly, antidepressant therapy can, in the case of the tricyclic drugs, antagonise the effects of the adrenergic neurone-blocking drugs or, in the case of the monoamine oxidase inhibitors, lead to other problems in relation to blood pressure.

The views expressed in this article are based on the literature and on experience gained in the treatment of patients at the Hypertension Clinic, Dunedin Public Hospital. About 900 patients are presently attending; each year about 100 new patients are treated, and 40 to 50 die. Most patients attend once in three months or more often, either for all-day tests or for briefer visits, and are seen on each occasion by a physician. The patients are nearly all Caucasian, with a few Polynesians and Chinese. All social classes and age groups are represented, although the proportion under twenty years of age is very small. The patient population is remarkably static, and physicians and patients get to know each other well.

Many drug trials have been carried out and most of the usual antihypertensive drugs are, or have been, in use. Deliberate trials of antidepressant drugs in patients on adrenergic neurone-blocking agents have not been performed, because the dangers were thought to be too great. However, the widespread use of both antidepressant and antihypertensive therapy in the community has provided a number of examples in which both therapies have been combined.
ASSESSMENT OF DEPRESSION

Assessment of the degree of depression is not an easy matter for the non-psychiatrist and precise figures for the incidence of depression cannot be given at present. However, about 15 of every 100 recently referred patients have had a history of mild depression or were thought to be somewhat depressed at the time of referral; in about one-third of these patients the mild depression could have been due to drugs they had been taking, such as reserpine or methyldopa.

It must be stressed that we have not made use of any standardised means of assessing depression, such as the Beck or Hamilton rating scales (Beck et al., 1961; Hamilton, 1967). Our assessment is a general clinical one, based on the first interview and supplemented by further acquaintance. Occasionally, there is a history of overt depression, treated by electroconvulsive therapy or drugs; more often one has to judge from the symptoms and general demeanour of the patient whether depression is present. It is our impression that tearfulness, feelings of tiredness and inadequacy, and sleep disturbance (early waking) are the most valuable pointers to mild depression; the first two will usually become manifest only after sympathetic questioning. These symptoms are well recognised components of depression (Miller, 1967; Davis et al., 1969; Lader, 1970; Marks, 1970), but some authors (Miller, 1967; Rosenthal, 1968; Marks, 1970) also stress that multiple somatic symptoms are prominent features, e.g. headache, constipation, abdominal pain, loss of appetite and weight, and loss of libido. We have not found these symptoms to be of particular value as indicators of depression in hypertensive patients. Headache is, of course, a common symptom in such patients; it is nearly always relieved by effective antihypertensive treatment, presumably because of the lower blood pressure, although it could perhaps be argued that regular attendance at a clinic for antihypertensive treatment also exposes the patient to some general psychological support. Loss of appetite and weight are features that one sometimes wishes would occur more often: certainly there is no lack of overweight hypertensive patients who show signs of mild depression. Sexual problems, such as failure of ejaculation or impotence, can be side effects of the antihypertensive drug and thus cannot be interpreted as due to depression, although they can contribute to it.

DEPRESSION IN PATIENTS ON ANTIHYPERTENSIVE DRUGS

When depression develops in a patient on antihypertensive therapy, it may be:

(a) due to an antihypertensive drug,
(b) due to a combination of an antihypertensive drug and a bereavement or another disturbing event,
(c) due to another drug given simultaneously, or
(d) purely coincidental.

In this situation, if the patient is taking a drug with a reputation for causing depression, the drug will tend to be blamed. Indeed, the only reasonable line of management is to stop the suspected drug, but clearly there will be a tendency to over-diagnose depression as a side effect of certain drugs: the age group of patients presenting with hypertension is such that a considerable proportion will be liable to menopausal or involutional depression.

The drugs that in our experience have caused trouble in this regard are reserpine, methyldopa, clonidine, propranolol and, very occasionally, guanethidine and bethanidine. All these drugs, except guanethidine and bethanidine, have a CNS depressant or central hypotensive action. The pattern of development of depression seems to vary to some extent with the different drugs, and they will be considered in turn. Precise data for the incidence of depression will not be given, as this is difficult to assess accurately. It must be clearly understood that the occurrence of depression as a side effect of these drugs is not to be taken as a contra-indication to their use. They are all effective and useful drugs. However, the first four drugs mentioned should preferably not be used in patients with a history of depression, and a watch should always be kept for the development of mild depressive symptoms in patients being treated with them.

**Rauwolfia Alkaloids**

Rauwolfia alkaloids cause depletion of catecholamines and serotonin in the brain (e.g. Schlittler and Bein, 1967) and reserpine is the archetype of the depression-producing antihypertensive drug. When it was used in large doses, severe depression quite often resulted (Doyle and Smirk, 1964; Freis, 1954; Locket, 1955) and there were some cases of suicide. It has been roundly condemned (Turner, 1962) but many clinics are prepared to use it with caution (e.g. Freis, 1962; Finnerty et al., 1965; Brest and Moyer, 1962; Smirk, 1964; Hollander and Wilkins, 1966; Simpson and Hodge, 1967; *British Medical Journal*, 1969a). With the doses now used (usually 0.25 mg of reserpine daily, or less), depression, when it occurs, generally develops slowly and insidiously. It may not become apparent for several years and may be precipitated by a bereavement or other difficult life situation. If the Rauwolfia drug is stopped, the patient often comments that he feels much better and has more energy.

The possibility of suicide must still be borne in mind, even with the low doses of Rauwolfia used now. However, there is no doubt that Rauwolfia drugs
are useful in the management of hypertension and we believe that they can be given with safety provided that the following rules are observed:

(a) They must not be used in patients who have a previous history of depression or who appear to be depressed.
(b) They should not be prescribed in a person who has had a recent bereavement.
(c) When they are started, the patient should be warned of the possibility of depression and should be told that if he becomes depressed he must stop taking the tablets and see his doctor; this advice can quite easily be given without frightening the patient.
(d) The dose should preferably be restricted to the equivalent of 0.25 mg reserpine daily.
(e) A watch must be kept for warning signs and symptoms, and the relationship between doctor and patient must be such that the patient will confide his problems.
(f) The drugs must be stopped if there is any suspicion of depression.

The question of whether other Rauwolfia alkaloids have less of a tendency to cause depression than reserpine has not really been resolved by any full-scale long-term double-blind trials. There is some evidence that alkaloids such as deserpidine (recanescine) (Simpson, 1961) and methoserpidine (Harris Jones et al., 1961) have less depressive effects, but they tend also to have a weaker antihypertensive action. The large amounts of mixtures of Rauwolfia alkaloids used in general practice may perhaps be taken as evidence that depression is not too troublesome an adverse effect with these preparations. We have for many years made use of deserpidine and have had little trouble with depression at a dosage of 0.25 mg twice daily.

**Methyldopa**

Methyldopa has a number of pharmacological actions on the CNS and causes depletion of brain noradrenaline, serotonin and dopamine in the experimental animal (Sourkes, 1965). The antihypertensive effect may well be in part due to its central action (Henning and van Zwieten, 1967). Drowsiness is a common side effect in man (Gillespie et al., 1962; Smirk, 1963; Lauwers et al., 1963; Johnson et al., 1966; Horwitz et al., 1967), but it usually occurs early and tends to pass off with continued use of the drug: it can be partially avoided by the use of small doses initially. Drowsiness and tiredness, not necessarily related to hypotension, may become very marked and the patient may become tearful and depressed or have other psychic disturbances.
Occasionally, insomnia may occur (Smirk, 1963; Horwitz et al., 1967), sometimes on withdrawal of the drug (Horwitz et al., 1967). Nightmares and hallucinations have been reported by our patients (Smirk, 1963) and some have developed nightmares or depression when a small dose of Rauwolfia was added to a regimen of methyldopa. Other drugs that have been reported to cause psychiatric problems when given in combination with methyldopa include pargyline (hallucinations: Paykel, 1966), amitriptyline (agitation: White, 1965) and phenothiazines (puerperal depression: Fullerton and Morton-Jenkins, 1963).

The incidence of really troublesome depression is not very high, about 4 per cent, according to some authors (Johnson et al., 1966; Hamilton, 1968). This may be partly because tiredness and drowsiness are a fairly prominent part of the symptomatology, so that the patient has a fairly concrete warning sign to mention to his doctor. The depression can certainly be quite severe (McKinney and Kane, 1967), but the onset of depression with methyldopa usually seems to be less insidious and treacherous than it is with reserpine.

**Clonidine**

Clonidine is another drug with mixed central and peripheral action. It causes bradycardia and lowering of blood pressure, partly at least by a central inhibition of sympathetic activity (Magus and Long, 1968; Hughes, 1968; Nayler et al., 1969). In our hands (Ng et al., 1967) it caused some problems with depression, usually occurring after several weeks of therapy. Four patients out of 39 who took clonidine for an average of four months had symptoms of depression. Cases of depression have been reported only occasionally from other clinics (Raftos, 1969; Kellett and Hamilton, 1970) but a high incidence of drowsiness and fatigue has been reported (Iisalo and Laurila, 1967; Onesti et al., 1969; Raftos, 1969; Seedat et al., 1970; Trinker and Barnett, 1970; Ebringer et al., 1970; Kellett and Hamilton, 1970). The drowsiness and fatigue tend in many patients to improve with time but other psychiatric manifestations may occur, such as nightmares (Iisalo and Laurila, 1967; Ng et al., 1967; Trinker and Barnett, 1970) disturbed sleep and early waking (Iisalo and Laurila, 1967), and fear (Kellett and Hamilton, 1970). Clonidine should be avoided in any patient who has a psychiatric history or who appears to be depressed or unstable.

**Propranolol**

Propranolol has, in our hands (Waal, 1967), appeared to be responsible for depressive symptoms. It is known to have CNS depressant properties in animals (Leszkovszky and Tardos, 1965; Murmann et al., 1966) and to have
some central hypotensive activity (Kelliher and Buckley, 1970). Two of our patients actually committed suicide while taking the drug, but there were other factors present. One patient had also been treated with reserpine until about two months before her death, and she had had a stressful and unstable domestic life. The other patient had had numerous hospital admissions for various disorders, including anxiety state and depression, and had previously threatened suicide; she had a history of depression also when taking methyldopa. Both these deaths occurred more than five years ago.

Tiredness is in our experience a fairly common symptom, and insomnia and nightmares can occur as well as depression. This type of symptom has been reported also by Prichard and Gillam (1969) who in their series of 109 patients had one case of depression, one of insomnia, four of vivid dreams and four of tiredness. We believe it is important to avoid the use of propranolol in patients with psychiatric histories; other beta-blockers seem to be much less prone to cause these symptoms.

The adrenergic neurone-blocking agents such as guanethidine, bethanidine and debrisoquine do not cause depletion of cerebral amines (Maxwell et al., 1960; Boura and Green, 1963; Moe et al., 1964) and in our experience seem to cause depressive symptoms only very occasionally. Most reports of series of patients treated with guanethidine either do not mention depression as a side effect (Lowther and Turner, 1963; Leishman and Sandler, 1967) or mention occasional cases (Dollery et al., 1960; Galskov et al., 1961). However, Prichard et al. (1968) in their comparative study report a 21 per cent incidence of mild depression on guanethidine, compared with 7 per cent on bethanidine (and 13 per cent on methyldopa); tiredness was a prominent symptom in their patients on both drugs. Therefore, while serious depression is not a common side effect of the adrenergic neurone-blockers, the possibility of their causing depression must not be overlooked.

It has to be remembered that other drugs, given coincidentally, may play a part in causing symptoms of depression. Oral contraceptives are probably the most troublesome of these (British Medical Journal, 1969b; Huffer et al., 1970), and they may also play a part in the pathogenesis of the hypertension. Diazepam has been reported to cause an increase in suicidal thoughts (Ryan et al., 1968) and fenfluramine has been reported as increasing the depression in five out of eleven obese depressed patients (Gaind, 1969). We have seen occasional patients in whom diazepam could have contributed to the depression, and others in whom fenfluramine caused troublesome drowsiness, but not a definite depression. Clearly, all aspects of therapy must be reviewed when a patient on antihypertensive therapy shows signs of depression.

When an antihypertensive drug is thought to be responsible for the onset of
depressive symptoms, there is usually no need to do anything other than stop the offending drug. In most cases some other drug will have to be substituted and it may be appropriate to admit the patient to hospital for the change-over, particularly if there are any misgivings over the depth of the depression. As already mentioned, not all cases of depression occurring in patients on anti-hypertensive treatment are drug-induced: more active treatment of the depression may be needed if it is really of endogenous origin.

ANTAGONISM BETWEEN TRICYCLIC ANTIDEPRESSANTS AND ADRENERGIC NEURONE-BLOCKERS

When a patient has hypertension requiring treatment, and when he is also depressed, problems arise if the decision is made to treat the depression with drugs. Electroconvulsive therapy causes no particular problem, although some patients are apprehensive of it, and there may be transient rises of blood pressure after the shock, especially if atropine has been given (Bodley and Fenwick, 1966). The main difficulties occur with the tricyclic antidepressants such as imipramine and amitriptyline which prevent the uptake into sympathetic nerve endings of noradrenaline (Klerman and Cole, 1965) and also of drugs such as guanethidine (Gilette, 1965; Gokhale et al., 1966), bethanidine and debrisoquine (Mitchell et al., 1970). The action of these antihypertensive drugs is thereby blocked.

This antagonism between the tricyclic antidepressants and the adrenergic neurone-blocking drugs was first noted clinically by Leishman et al. (1963). Our experience of it was briefly described in 1967 in a general review of the use of antihypertensive drugs in combinations (Simpson and Hodge, 1967): it was clear to us that patients on tricyclic antidepressants could not be successfully treated with drugs such as guanethidine or bethanidine. Puzzling cases of resistance to antihypertensive drugs were in a few instances solved by the discovery that the patients were taking an antidepressant drug. Once the antidepressant drug was stopped, the blood pressure fell markedly, requiring radical changes in the antihypertensive therapy.

Similar cases have been reported from elsewhere (Mitchell et al., 1967; Skinner et al., 1969). Mitchell et al. (1970) have proved the occurrence of the antagonism by deliberately administering tricyclic antidepressants to patients taking adrenergic neurone-blocking drugs. They found antagonism to the guanidine drugs (guanethidine, bethanidine and debrisoquine) but not to methyldopa. They concluded that the antagonism was due to blockade of the uptake 'pump' whereby noradrenaline and the guanidine drugs are taken up into the neurone and not to a supersensitivity to noradrenaline, because:
(a) methyldopa was not affected,
(b) the administration of guanethidine to mildly hypertensive patients on desipramine did not lead to a rise in pressure,
(c) the raised blood pressure in patients on a guanidine drug plus an antidepressant could not be lowered by phentolamine, and
(d) the sensitivity to pressor doses of noradrenaline was no higher with desipramine and guanethidine than with desipramine alone.

These conclusions seem eminently reasonable, but it is possible that individual patients may react differently in this situation or that different mechanisms may come into play when treatment takes place over a longer period of time. We have seen cases where the combination of antidepressant and antihypertensive drugs appeared to result in a far higher blood pressure than was explicable simply on the basis of a nullification of the effect of the antihypertensive drug. We have also seen cases where antagonism to methyldopa appeared to have occurred, although this was less dramatic than in the case of the guanidine compounds. White (1965) described a case of tachycardia and confusion when amitriptyline was added to a regimen of methyldopa. Although the uptake of methyldopa into the sympathetic nerves is not blocked by the antidepressants, presumably the re-uptake of alpha-methylnoradrenaline will be blocked and this could give rise to symptoms.

Whatever the mechanism may be, it is evident that the adrenergic neurone-blocking drugs cannot be relied on to reduce blood pressure in patients taking antidepressants. Skinner et al. (1969) mention two patients in whom blood pressure control with bethanidine was successful in spite of antidepressant therapy, and they suggest that these patients may have been so susceptible to bethanidine that the dose was sufficient to overcome the antagonism. Our experience suggests that, at least in some instances, the antagonism cannot be overcome by increasing the dose of antihypertensive agent, and that the blood pressure may rise rather than fall with increasing dosage. However, we do have a few patients with mild hypertension who take a small dose of an adrenergic neurone-blocking drug along with an antidepressant and whose blood pressure control is satisfactory; they have been allowed to continue on this regimen because it seems to suit them and, in individual cases, stopping adrenergic blockade led to a small increase in blood pressure. So far as is known there is no antagonism by the adrenergic neurone-blocking drugs of the antidepressant action of the tricyclic drugs.

MANAGEMENT OF A PATIENT WITH HYPERTENSION AND DEPRESSION

The patient who is both depressed and severely hypertensive remains a
problem and the relative urgencies of the two conditions have to be assessed. Clearly, a patient with malignant hypertension or left ventricular failure requires urgent reduction of his blood pressure and this must take precedence over treatment of mild depressive symptoms. On the other hand, antihypertensive therapy in a severely depressed person with mild or even moderate hypertension can well be postponed until the depression is dealt with.

When drug treatment of the depression is decided on, this can be either by means of a monoamine oxidase (MAO) inhibitor or a tricyclic antidepressant. In a small number of cases we have made use of the MAO inhibitor, pargyline, in an attempt to treat both the depression and the hypertension with a single drug, and we have the impression that this has been successful. However, cases of depression have been reported in patients on pargyline (Oates et al., 1965) and the problems associated with the MAO inhibitors are such that we do not recommend their use except in special cases.

A tricyclic drug, given alone, can reduce blood pressure a little and a thiazide diuretic can be given at the same time. If the blood pressure is still unsatisfactory, we prefer at present to add a beta-blocking drug (other than propranolol). The antihypertensive action of the beta-blockers does not appear to be antagonised by the tricyclic antidepressants. Some patients do not respond to beta-blockers, however, and at this point one is starting to run out of alternatives. Rauwolfia alkaloids should not be given in this situation, nor should methyldopa or (in our opinion) clonidine. There is a small place here for ganglionic-blockers, there is the possibility of using pargyline, and, finally, there is the possibility of using ECT followed by an adrenergic neurone-blocking drug such as bethanidine or debrisoquine.

**Summary**

Hypertension and mental depression have a curious relationship to each other: drug treatment of one tends to lead to problems with the other. Certain antihypertensive drugs with a central action (reserpine, methyldopa, propranolol, clonidine) are capable of causing depression and are best avoided in patients who have been depressed. Patients on these drugs should be watched for evidence of developing depression.

The tricyclic antidepressant drugs are given for their central action. However, they also act peripherally, blocking the uptake of adrenergic neurone-blocking drugs into the nerve endings, thus interfering with their antihypertensive action.

**Acknowledgements**

The work of the Dunedin Hypertension Clinic is supported by the Otago Hospital Board, the University of Otago and the Medical Research Council of New Zealand.
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To Travel is to Arrive

In our own day an equipage of some sort is considered so necessary an appendage to a medical practitioner, that a physician without a carriage (or a fly that can pass muster for one) is looked upon with suspicion. He is marked down mauvais sujet in the same list with clergymen without duty, barristers without chambers, and gentlemen whose Irish tenantry obstinately refuse to keep them supplied with money. If the early struggles of many fashionable physicians were fully and courageously written, we should have some heartrending stories of the screwing and scraping and shifts by which their first equipages were maintained. There was one noted case of a young physician who provided himself with the means of figuring in a brougham during the Mayfair morning, by condescending to the garb and duties of a flyman during the hours of darkness. He used the same carriage at both periods of the four-and-twenty hours, lolling in it by daylight, and sitting on it by gaslight. The poor fellow forgetting himself on one occasion, so far as to jump in when he ought to have jumped on, or jump on when he ought to have jumped in, he published his delicate secret to the unkind world.

Abridged from A Book about Doctors by J. C. Jeaffreson (1861)