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Intracranial Haemorrhage in Patients Treated with Monoamineoxidase Inhibitors

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The monoamineoxidase inhibitor drugs are now widely used in the treatment of depression, and complications occurring in patients so treated have been reported with varying frequency. The drugs most frequently implicated have been tranylcypromine (Parnate), tranylcypromine plus trifluoperazine (Parstelin) and phenelzine (Nardil) in decreasing order of frequency. These complications may be divided into three symptom-complexes which may merge one into the other, as they have the common basis of rapid elevation of systemic blood pressure.

The first and most commonly encountered is paroxysmal headache of great intensity, and has been termed "tranylcypromine cephalalgia" by Mann and Laing (1963). This is an unfortunate name, as the symptom also occurs with other monoamineoxidase inhibitors and should a name be desired, "monoamineoxidase inhibitor cephalalgia" would be more appropriate, though probably too cumbersome. The syndrome consists of excruciating headache associated with a marked elevation in blood pressure. There may be other vascular manifestations, such as pallor, chills, neck stiffness and collapse. Many of these patients are sufferers from headache, but they usually describe this type of headache as something quite different from any that they have previously experienced. It is quite clear that these attacks may simulate an episode of subarachnoid haemorrhage, and when these were first noted, many patients were subjected to lumbar puncture, but with negative findings (Dally, 1962).

This syndrome may merge into the second, in which the cardio-vascular manifestations predominate so that a clinical picture similar to the crises seen in phaeochromocytoma may be produced, as indicated by Dally (1962) and emphasized by Blackwell (1963). There may be a sudden onset of palpitations, chest pain, apprehension, paroxysmal hypertension, sweating, pallor, headache, and collapse. The pulse may be rapid or slow. It is therefore not surprising that patients were investigated for phaeochromocytoma before it was realized that such attacks could also occur as a complication of monoamineoxidase inhibitor administration. (Mann and Laing, 1963; Bass, 1961).

The third syndrome, with which we are really concerned in this communication, is the occurrence of intra-cranial haemorrhage as a complication of treatment with monoamineoxidase inhibitors.

Frequency of Complications

The frequency of complications occurring in patients treated with monoamineoxidase inhibitors varies a great deal in the innumerable reports which have now appeared on this subject. (See Table I).

The variability of the incidence of complications may be an expression of the fact that the reaction to these drugs may be governed by multiple factors. Many of these reports were made from small series and the conclusions are therefore not valid.

Variability in dosage may play a part according to Milligan (1963) who attributed the low incidence of complications in his series to very low dosage. Some studies have been prospective and some retrospective, so that they are not strictly comparable. Blackwell (1963) thought that these drugs were prescribed to a population in which headaches occurred frequently so that another severe headache might well be forgotten, hence the low incidence in complications in retrospective studies. The factors of in-patient or out-patient treatment

TABLE 1

Frequency of Complications in Patients treated with Monoamineoxidase Antidepressants

Author	Year	No. of Patients	Drug	% Complications	Nature of Complications
CLARK	1961	30	Parnate	10	Headache and hypertensive crises
LURIE & SALZER	1961	84	Parnate	2·4	Headache and hypertensive crises
BROWN & WALDRON	1962	150	Parstelin	4	Headache
MACDONALD	1963	600	Parnate	2·3	Headache
MILLIGAN	1963	1200	Parstelin	3	Headache
LEES & BURKE	1963	60	Parnate	18·3	Headache and hypertensive crises
RICHMOND & ROBERTS	1963	38	Parnate	23·6	Headache
BRAM	1963	Several hundred	Parnate	4	Headache
BETHUNE *et al.*	1963	?	Parstelin Nardil	5–10	Headache and hypertensive crises
WATTS	1964	?	Parnate	4	Headache
COOPER *et al.*	1964	174	Parstelin	20	Headache. Hypertensive crises and intracranial haemorrhage

may be important, for Davies (1963) found that patients in bed suffered less than those who were up and about, particularly in situations demanding attention and action. Many of the patients reported have been on other drugs, so that the issue becomes even more clouded. Blackwell (1963) suggested that these reactions are so dramatic and unlike any other drug reaction that their true nature may go unrecognized or be ascribed to the patient's mental instability.

These varying reports on the frequency of complications stimulated a questionnaire to psychiatrists of Great Britain, and this showed that of 21,582 treated with monoamineoxidase inhibitor drugs, 2·08 per cent. had developed headache and 0·27 per cent. had the hypertensive syndrome (Schrire, 1964). Fourteen deaths had been reported in Great Britain, out of an estimated one and a half million patients treated since the introduction of the drugs in 1960. The estimated risk for a patient treated with tranylcypromine is about 2 per cent. for headache, under 0·5 per cent. for hypertensive crises and 0·001 per cent. for death. The frequency of intra-cranial haemorrhage as a complication was not mentioned in this report.

The frequency with which subarachnoid haemorrhage occurs in these patients has not been assessed and it is unlikely that it can be done with any degree of accuracy. Most of the reports of this complication have been concerned with isolated incidents which excited interest by their unexpected and dramatic nature. Blackwell (1963) described hypertensive crises in eleven patients on tranylcypromine and one on phenelzine. In three of these patients neurological symptoms indicated intracranial haemorrhage. Cooper *et al.* (1964) surveyed 174 out-patients under treatment with Parstelin; 20 per cent. of them developed hypertensive crises and three of these suffered intracranial haemorrhage.

Table 2 summarizes the case histories and clinical findings of those patients who have been reported in the literature as having suffered an intracranial haemorrhage during treatment with monoamineoxidase inhibitors. Other patients who developed intracranial haemorrhage while being treated with these drugs have been reported, but not in detail. Sargant (1963) mentions one patient on combined drug therapy who died from "an ordinary severe spontaneous subarachnoid haemorrhage".

Davies (1963b) mentions two cases who took several months to recover. Ayd (1963) noted hemiplegia in several patients after attacks of cephalalgia and hypertension. One case of total hemiplegia is mentioned by Garmany (1964).

One can safely say that the reported incidence of subarachnoid haemorrhage in patients being treated with monoamineoxidase inhibitors will depend on the frequency with which lumbar puncture is performed on the patients with paroxysmal headache. In many patients the diagnosis may be missed because a confident diagnosis of monoamineoxidase cephalalgia is made and so a lumbar puncture is not performed. It is more likely, however, that those patients who develop focal neurological signs associated with the crises will be subjected to lumbar puncture, so that quite naturally a degree of selection will occur. Patients presenting with subarachnoid haemorrhage may not be able to give an adequate history of their drug consumption, so that the cause of their condition may go unrecognized. (Dorrell, 1963b). The fact is that patients are still admitted with subarachnoid haemorrhage in whom the correct diagnosis has not been made, despite the innumerable warnings in the medical press.

Between April, 1962 and April, 1964, sixteen patients were admitted to Atkinson Morley's Hospital for the investigation of subarachnoid haemorrhage which occurred while they were being treated for depression with monoamineoxidase inhibitors. Patients are admitted from a wide area, and as there is special interest in intracranial vascular disease in this Unit there may be naturally some degree of disproportion in the number of patients admitted with such conditions. Table 3 summarizes the clinical features of these patients.

During the period April, 1962 to January, 1964 the total number of patients admitted with subarachnoid haemorrhage was 883. Of these 460 had intracranial aneurysms and 59 had angiomatous malformations. There were 154 patients with intracerebral haemorrhage and 210 with unexplained subarachnoid haemorrhage. Thirteen of our sixteen patients fell within this period. Six of them had an intracerebral haemorrhage, i.e. 3·9 per cent. of intracerebral haemorrhage can be accounted for by this cause. Of these 154 patients with intracerebral haematomas, 44 were normotensive. All six of the patients in our series were normotensive, so that they form 13·6 per cent. of this category. Our six patients with intracerebral haematomas were all females, so that they form an unexpected high percentage (28·5 per cent.) of the total number of normotensive females admitted with intracerebral haematomas.

If one takes into consideration the age incidence of patients who suffer from intracerebral haemorrhage but who are normotensive, the maximum incidence is found to occur in the age group 50–69 years. Our six patients had an average age of 42·5 years, with only one patient over the age of 50 and three under the age of 40. This shows a much closer correlation with the maximum age incidence of haemorrhage from angiomatous malformations, which lies in the age range 20–49, and significantly in these patients hypertension seems to play no part either. One is left to speculate whether our patients had bled from some pre-existing small vascular malformation, not revealed by angiography.

In conclusion one can therefore say that in our group of patients intracerebral haematoma occurred at an earlier age than natually occurring intracerebral haemorrhage in normotensive individuals.

Out of a total of 210 patients with unexplained subarachnoid haemorrhage, seven were on treatment with monoamineoxidase inhibitor drugs, i.e. 3·3 per cent.

The one feature that all these patients have in common is that they have all suffered from a depressive illness of sufficient severity to merit drug therapy. In this way they have become recognized as a distinctive group when compared with the other patients with subarachnoid haemorrhage admitted to this hospital. Once this association was noted, all patients with a past history of depressive illness were closely questioned as to the drugs they were taking and most of these patients were identified by this method.

Advanced age did not appear to play a part in the predisposition to this complication in our

TABLE 2

Author	Date	Age of Pat.	Sex	Symptoms	Signs	B.P. (Normal B.P. in ())	Lumbar Puncture	Drug	Dosage	Precipitating Factors	Cheese Meal	
ZECK	1961	54	F	Intense headache	Left hemiplegia	170/90 (150/90)	?	Parnate Librium	1 tab. b.d. 1 q.i.d.	Amphetamine 5 mgms.	No	Died in coma 3 days later. No autopsy
MASON	1962	39	M	Severe headache. Left hemiparesis	Left hemiplegia	150/100	Blood stained c.s.f.	Parnate	1 t.d.s.	Methedrine 25 mgm. I.V.	No	Died 36 hours later. Intracerebral haematoma
MCCLURE	1962	27	M	Headache and giddiness.	Coma. Hypotension	140/100 (120/80)	?	Parnate	1 q.i.d.	None	No	Died. Subarachnoid haemorrhage from posterior communicating artery aneurysm
DORRELL*	1963	59	F	Severe headache, and vomiting	Left hemiparesis	185/95	Blood stained c.s.f.	Parnate Chlordiaz epoxide	2 tabs. t.d.s. 10 mgms.	None	No	Intracerebral haematoma aspirated through burrhole.
BLACKWELL	1963	49	F	?	?	Unknown	Blood stained	Parnate	1 tab. b.d.	"Marmite meal"	No	Angiograms normal
		43	F	?	Hemiplegia	170/100 (160/90)	Not known	Parnate	1 tab. b.d.	Not known	No	Hemiplegia for 6 weeks. Normal angiograms
		49	F	?	?	160/100	Not known	Parnate	1 tab. t.d.s.	Not known	No	Died with intracranial haemorrhage. No autopsy
ESPIR & MITCHELL	1963	65	F	Sudden, severe headache	Neck stiffness	130/70	Blood Stained	Parstelin	1 tab. t.d.s.	Not known	Unknown	Negative carotid angiograms. No permanent sequelae
ENOCH	1963	48	F		Hyperpyrexia	170/80 (130/80)	Not done	Parstelin	1 tab. t.d.s.	Unknown	Unknown	Had haemorrhage in the floor of the fourth ventricle and in lateral ventricle at autopsy
GREENE	1963	67	M	Severe headache and vomiting.	Neck stiffness	140/80	Xanthochromic c.s.f.	Parstelin	?	Unknown	Unknown	Complete recovery
COOPER *et al.*	1964	52	M		Frontal syndrome	190/110 (130/90)	Blood stained c.s.f.	Parstelin	2 tabs. b.d.	?	Yes	Left with permanent deficit
		45	M		Grand Mal seizure	180/110 (120/75)	Blood stained c.s.f.	Parstelin	2 tabs. b.d.	? Alcohol	Unknown	Permanent deficit
		46	F		Left hemiparesis	160/100 (125/80)	Blood Stained c.s.f.	Parstelin	2 tabs. b.d.	Unknown	Unknown	?

*Case 1 reported by Dorrell in 1963a is Case 1 on Table 3 and the case reported by him in 1963b is Case 4 in Table 3. They are therefore not summarized here.

TABLE 3

Case No.	Age	Sex	Symptoms	Signs	Blood in Lumbar C.S.F.	B.P.	Carotid Arteriography	Vertebral Arterio-graphy	Drug	Dosage	Precipitating Factors	Previous History of Headache	Comments
1	47	M	Sudden severe headache with neck stiffness	No abnormal signs	Yes	120/70	Normal	Failed	Parst-elin	10 mgms. t.d.s.	Unknown	Unknown	No permanent deficit
2	62	F	Sudden severe occipital headache	Neck stiffness	Yes	140/80	Normal	Normal	..	10 mgms. t.d.s.	Cheese meal	No	No permanent deficit
3	52	F	Severe occipital headache. Left limb weakness	Left hemiplegia	Yes	120/80	Normal	Not done	..	10 mgs. t.d.s.	No cheese	No	Left hemiparesis. Focal Epilepsy
4	38	M	Sudden headache. Weakness of left arm and leg	Slurred speech. Left hemiparesis	? Traumatic tap	130/80	Normal	Not done	..	10 mgms. t.d.s.	Unknown	No	No permanent deficit
5	43	M	Severe headaches with loss of consciousness	Neck stiffness. Minimal left arm weakness	Yes	130/80	Normal	Normal	..	10 mgms. b.d.	Unknown	No	No permanent deficit
6	42	M	Sudden severe headache with neck stiffness	Neck stiffness. Haemorrhage in right fundus	Yes	160/100	Normal	Normal	..	20 mgms. b.d.	Unknown	No	No permanent deficit
7	46	F	Sudden severe headache with diplopia. Right limb weakness	Spastic right hemiplegia	Yes	130/70	Left parietal intracerebral haematoma	Not done	..	10 mgms. t.d.s.	Cheese meal	No	Right hemianopia. Right hemiparesis with athetosis
8	45	F	Sudden severe headache with weakness of right limbs	Right hemiplegia Aphasia	Yes	180/90	Left intracerebral haematoma	Not done		10 mgms. t.d.s.	Unknown	No	Hemiparetic and dysphasic
9	35	F	Sudden severe headache. Generalized convulsion	Right ptosis and left facial weakness	Yes	160/90	Normal	Normal	..	10 mgms. b.d.	Cheese meal	Migraine	Gross abnormal movements
10	45	F	Sudden severe headache	Neck stiffness	Yes	140/80	Normal	Normal	..	10 mgms. b.d.	Cheese meal	No	No permanent deficit
11	58	F	Sudden severe headache and neck stiffness	Neck stiffness	Yes	120/70	Normal	Normal	..	1 mgm. b.d.	Cheese meal	No	No permanent deficit
12	35	M	Sudden headache	Neck stiffness	Yes	155/80	Normal	Normal	..	70–80 mgms. per day	Cheese meal	No	No permanent deficit
13	33	F	Confusion, dysphasia. Right hemiparesis	Right homonymous hemianopia and right hemiplegia	Yes	125/90	Left intracerebral haematoma	Not done	..	?	Probably cheese meal	No	Right hemiplegia and dysphasia
14	58	F	Sudden headache and dysphasia.	Right hemianopia	Yes	120/80	Probable left temporal haematoma	Normal	..	10 mgms. t.d.s.	Alcohol	No	No permanent deficit
15	38	F	Sudden severe headache	No abnormal signs	Yes	120/70	Normal	Normal	Nardil	15 mg. t.d.s.	Probably cheese meal	No	No permanent deficit
16	39	F	Severe headache with right limb weakness	Right hemiplegia	Not done	120/70	Left intracerebral haematoma	Not done	..	?	Cheese meal	No	Right hemiplegia and dysphasia

patients; on the contrary it is noteworthy that only four patients were over the age of 50. The average age was 44 years. This may indicate nothing more than selection in the patients who have been treated with these drugs. Some authors have warned against the use of the drugs in the elderly athero-sclerotic individual. (Cooper *et al.*, 1964). No statistical conclusions can be drawn from a group of patients as small as this, but there appears to be a preponderance of females over males (2:1) as has been described in monoamineoxidase inhibitor cephalalgia by Mann and Laing. The symptomatology displayed by our patients does not distinguish them from those patients reported in the literature who merely had severe paroxysmal headache unassociated with subarachnoid haemorrhage. It is important to realize that in many of our patients the diagnosis would not have been made had lumbar puncture not been performed. Only in those who developed focal neurological signs, such as unilateral weakness or sensory disturbance or convulsions was the suspicion of intracerebral haemorrhage aroused.

Most of our patients were admitted some considerable time, usually not less than twenty-four hours, after the subarachnoid haemorrhage had occurred. The pre-ictal blood pressure was unknown in all of them except Case 6, where it was known to be 190/100. In only one (Case 9) was the ictal blood pressure noted; in this case the patient was admitted to the Casualty Department immediately after the haemorrhage had occurred and the blood pressure was found to be 190/115, whereas her normal pressure was 160/90.

Carotid arteriography was performed on all our patients and vertebral arteriography if the carotid angiograms were normal or inconclusive. The presence of a vascular anomaly such as an aneurysm or angiomatous malformation was not demonstrated in any of our patients. In five patients the arteriogram revealed the features of an intracerebral haematoma, and in three more the clinical features left no doubt as to the diagnosis. It is interesting to note that the presence of a vascular anomaly has only been noticed once in the cases reported in the literature who developed subarachnoid haemorrhage after treatment with monoamineoxidase inhibitors. This was the case of McClure (1962) where the patient had a ruptured posterior communicating artery aneurysm demonstrated at post mortem.

Fourteen of the patients were taking tranylcypromine in the form of Parstelin, which is a combination of tranylcypromine and trifluoperazine, and two of the patients were taking phenelzine (Nardil). There was nothing noteworthy about the dosage schemes of these patients, except in Case 12. This patient, who had been a known Drinamyl addict in the past, was taking seven to eight tablets of Parstelin a day in order to improve his feeling of well-being. It is also known that he was using an ephedrine inhaler for his asthma. Prior to the subarachnoid haemorrhage, he had also taken a cheese meal. The patients had been taking these drugs for periods varying from one day to several weeks.

Ingestion of cheese as a precipitating factor is definitely known to have been present in seven cases and likely in two further cases. One patient was quite sure that she had not eaten any cheese. In the remaining four patients the dietary history was not known. Bram (1963) has suggested that patients subject to migraine or other forms of headache are more likely to develop the paroxysmal headache when treated with monoamineoxidase inhibitors. Only one of our patients was a known migrainous subject, the others did not give a past history of headache of any significance.

Ten of our patients who developed subarachnoid haemorrhage did not have any permanent neurological disabilities. Six of them were, however, left with neurological lesions of considerable magnitude. (Cases 3, 7, 8, 9, 13 and 16). In this group of six patients, there were no features to distinguish them from the rest of the patients in relation to age, blood presure or drug dosage. They were all healthy, normotensive adult females, who were perfectly well before this incident. They all remain with severe permanent neurological disability. Three patients (Cases 7, 8 and 16) underwent surgical evacuation of the intracerebral haematoma.

Factors known to precipitate complications

When these complications of monoamineoxi-

dase inhibitor drugs were first described, quite naturally such factors as drug dosage, duration of treatment and drug combinations were considered. It seems quite certain that drug dosage and duration of treatment play no part at all (Brown and Waldron, 1962).

The simultaneous administration of other drugs may precipitate a hypertensive crisis, and particularly potent in this respect are the sympathomimetic drugs, such as ephedrine and amphetamine. This is not surprising in view of the pharmacological structure and similarity between tranylcypromine, amphetamine and ephedrine. Mason (1962) reported a patient being treated with Parnate who developed severe headache and an intracerebral haemorrhage shortly after the intravenous administration of 25 mgs. of methedrine. Zeck's (1961) patient was receiving chlordiazepoxide (Librium) as well as tranylcypromine, and on taking one 5 mgm. tablet of amphetamine sulphate suffered a fatal intracerebral haemorrhage. Low-Beer and Tidmarsh's (1963) patient was taking Parstelin and received ephedrine shortly before death. It is remarkable, however, that some patients can take monoamineoxidase inhibitors in combination with the amphetamines without adverse affects, (Davies, 1963b; Sargant, 1963). This indicates that individual idiosyncrasies may play a part in the reactions to these drugs.

During 1963 it became evident that the ingestion of cheese might figure in the production of hypertensive crises. Blackwell (1963b) first drew attention to this when he found it in eight out of ten of his patients who gave an adequate dietary history. The complication actually developed in two patients while in hospital. His report was soon followed by several others substantiating this observation (Foster, 1963). Davies (1963a) stated that he had observed this complication after nialamine in 1958. Since then he had also noticed it in patients being treated with phenelzine, iproniazid and tranylcypromine. He also noted that it occurred conspicuously more often following the evening meal. Womack (1963) reported a young boy who died after a cheese meal and a similar fatal reaction was reported by Cuthill *et al.* (1964). Thomas (1963) described the hypertensive syndrome after a cheese meal in a patient being treated with phenelzine. Arenillas (1963), however, could not confirm this relationship in a retrospective study of his patients who had developed hypertensive crises.

Other articles of diet which have also been implicated as probable precipitating factors are Marmite (Blackwell, 1963), broad beans (Hodge and Nye, 1964) and salad dressing (Richardson, 1964). Alcohol has also been incriminated, and support for this comes from the observation of one of our own patients (Case 14) and the work of Horwitz *et al.* (1964).

Mechanism of Hypertensive Attacks

Monoamineoxidase participates in the metabolic breakdown of the biologically active amines like noradrenaline, adrenaline, serotonin, tyramine and dopamine (Resnick, 1959). The precise action of the monoamineoxidase inhibitor drugs is not clear as yet, and the mechanism of the acute hypertensive crises remains uncertain, as these drugs usually tend to cause a fall in blood pressure. As already stated, the attacks may be precipitated by the administration of sympathomimetic drugs. Monoamineoxidase is essential for the inactivation of pressor amines, and if this is inhibited both naturally occurring and pressor amine ingested in articles of diet may reach dangerously high levels in the body.

Cheese is thought to produce these crises by virtue of its high tyramine content (Asatoor *et al.*, 1963; Blackwell and Marley, 1964; Natoff, 1964; Horwitz *et al.*, 1964). Tyramine is present in greatest concentration in the "stronger" types of cheese, but normally has no effect because of its rapid inactivation by monoamineoxidase. If, however, this enzyme should be inhibited tyramine will be present in the body fluids for a considerable time and exert its pressor effect (Asatoor *et al.*, 1963). This reaction to cheese has also been described in patients treated with the monoamineoxidase inhibitor Pargyline used in the treatment of hypertension (Glazener *et al.*, 1964). All the factors are certainly not known, as some patients on these drugs may eat cheese with impunity and others suffer hypertensive attacks without having eaten cheese. There is still a great individual variability which has not been fully

explained. The tyramine content of the cheese, the quantity of the cheese taken, the level of amineoxidase inhibitors in the gut, liver and vascular system determine to some extent the individual reaction of the patient.

Some patients can remain on large doses of these drugs for prolonged periods without adverse effects, some can even take combinations of the drugs without suffering ill effects. There may still be such factors as individual idiosyncrasies and inherent vascular instability or a constitutional abnormal amine metabolism. This is illustrated by the patient of Warner (1964) who developed a hypertensive crisis after a meal of ripe cheese although he was not taking any monoamineoxidase inhibitors at the time.

Precautions to be taken by patients on these drugs

The manufacturers have repeatedly stressed the various precautions that should be taken by patients on these drugs. They should avoid both alcohol and cheese. Sympathomimetic drugs should not be prescribed in association with monoamineoxidase inhibitors; it should be remembered that ephedrine is a constituent of certain common cold cures which may be bought without prescription, so patients should be warned against these. Pethidine, which is inactivated by monoamineoxidase should not be given, owing to its dangerously prolonged action (Taylor, 1962). Reserpine and guanethidine should be avoided on account of the potentation of their hypotensive effects. Moreover, in the treatment of depression, drugs of the iminodibenzyl group, such as imipramine, should not be given at the same time as monamineoxidase inhibitors, since, according to the work of Luby and Domino on rats (1961), they seem to have a synergistic effect; and as the monoamineoxidase inhibitors are excreted slowly there should be an adequate interval between treatment by drugs of the two groups—an interval of between 7 and 14 days has been recommended (Schrire, 1963). Burke (1963) goes further and advises that in the present state of our knowledge monoamineoxidase inhibitors should not be given in combination with any other drugs whatever.

We are not in a position to assess the value of these drugs, and it is not within our province to judge whether they should be used or not. Some psychiatrists (Garmany, 1964) have advised against their use on account of the risks involved. Sargant (1963) has pointed out that depression is a disease with a definite mortality rate and therefore justifies the use of drugs with a slight risk attached to their use in its treatment. He thinks that it would be a pity if these drugs, which have revolutionized the simple treatment of depression and recent anxiety states, had their value minimized on account of over-attention to rare complications.

The treatment of intracerebral haemorrhage is very unsatisfactory and the best we can strive for is to prevent its occurrence. When, therefore, one finds that a drug causes this condition albeit infrequently, one is left with the choice of eliminating the drug, or using it with great caution, and allowing the patient to take the risk of permanent disability, if not death. Mendels (1964) only administers the drug to patients who sign a consent form allowing its use.

In conclusion, I should like to quote an extract from an Editorial of "The Canadian Medical Journal".

"Whenever a new and serious side effect has been attributed to a pharmacological agent, it should oblige the physician to re-examine in respect of that drug the indications for its usage, the proper dosage, the kinds of side effects and their incidence, the contra-indications to its use and the general precautions to be observed when it is administered. He must weigh the benefits and the risks as they pertain to each item in his therapeutic armamentarium and in the light of his knowledge of the natural history of the disease under consideration decide whether therapy with a particular drug or the witholding of it carries the greater risk."

Summary

The complications occurring in patients treated with monoamineoxidase inhibitors are reviewed under the headings of paroxysmal headache, cardiovascular and cerebrovascular syndromes.

Sixteen patients are described who developed intracranial haemorrhage.

Fourteen were being treated with Parstelin, and of these five were left with severe permanent neurological disability.

Two were being treated with phenelzine, and one had a permanent hemiplegia.

The importance of precipitating factors, such as a cheese meal and sympathicomimetic drugs, is discussed.

The syndrome of intracranial haemorrhage occurring in an individual who is being treated for his depression with monoamineoxidase inhibitor drugs is one which will probably decrease in frequency.

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