Similarly, hypertension did not in itself predispose to hyperuricaemia in our series, but it is probable (Breckenridge, 1966) that sustained severe hypertension may be an important factor; this was not, however, apparent in the present study.

It seemed possible that raised uric acid levels might be a transitory phenomenon after a cerebral infarct or haemorrhage, but examination of this hypothesis excluded it as an explanation for the hyperuricaemia (Fig. 5). Further, serial estimations after a stroke showed only occasional and rather wide variation, but no distinctive pattern emerged.

It seems, therefore, that primary hyperuricaemia, in the absence of gout or any other known predisposing cause, is present in a significant proportion of patients with cerebral infarction or haemorrhage. This suggests that hyperuricaemia may be one of many factors predisposing to the genesis of atheroma and its sequelae in the cerebral vasculature. This suggestion correlates with the recent views that the renal lesion in gout is a "vascular nephrosclerosis" (Barlow and Beilin, 1968).

There is no satisfactory explanation at present of the role of uric acid in the causation of atherosclerosis. Traut, Knight, and Szanto (1954) demonstrated the presence of urate crystals in the proliferated intima of coronary arteries and in organized thrombi. Since atheroma is a generalized process, this suggests one possible mechanism by which urate deposits might be the starting-point for progressive atherosclerotic disease. The other explanation was put forward by Gertler *et al.* (1951). They suggested that uric acid, being a powerful cationic surface agent, could perhaps attach itself to the larger cholesterol molecule and bring it into contact with the arterial intima. In this way they envisaged the onset of atheroma. This idea was further elaborated by Schrade, Boehle, and Biegler (1960), who thought that atherosclerosis might be a "complex disturbance of blood lipid and other regulatory mechanisms," and they felt that one of the factors involved was an abnormality in uric acid metabolism.

ism. Apart from these speculations, there is no evidence from experimental pathology to suggest a mechanism which might relate abnormal uric acid levels to atheroma. One possible mechanism might be via abnormalities of plasma lipids, and therefore a further study has been carried out which forms the subject of a separate report (Pearce and Aziz, 1969).

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Iatrogenic Epilepsy due to Antidepressant Drugs

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Summary: An analysis of the case histories of nine patients who developed epileptic fits shortly after starting tricyclic antidepressant drugs showed that all of them had one or more of the following factors: previous or family history of epilepsy, pre-existing brain damage, cerebral arteriosclerosis, alcoholism, withdrawal of barbiturates, and history of previous electric convulsive therapy. Before prescribing antidepressant drugs these factors should be sought for in the history, and if any are present prophylactic anticonvulsant medication is indicated. From a limited experience we do not think that chlordiazepoxide is adequate to counteract the convulsant effect of antidepressant drugs.

Introduction

Although the occurrence of epileptic seizures in patients taking drugs of the phenothiazine group has been known for 15 years,

such attacks appear to be rare in clinical practice. When in 1959 the tricyclic drug imipramine was introduced for endogenous depression it was not at first realized that this drug was also potentially epileptogenic. Kiloh, Davison, and Osseltson (1961) found that imipramine in therapeutic doses increased the frequency of attacks in epileptic patients, and that in large doses it precipitated attacks in non-epileptics, and occasionally therapeutic doses had the same effect. Amitriptyline, introduced in 1960, was found to have anticonvulsant properties in animals (Vernier, 1961), and Winfield and Aivazian (1962) reported that this drug had no effect on the electroencephalogram (E.E.G.). Davison (1965) reported that intravenous amitriptyline had an activating action on paroxysmal activity in the E.E.G.s of 11 out of 20 epileptics, and two patients who had taken overdoses of the drug developed convulsions.

Betts, Kalra, Cooper, and Jeavons (1968) reported seven cases in which it appeared that amitriptyline was the probable cause of epileptic fits in depressed patients. They emphasized that this and other antidepressant drugs should be used with caution, especially in patients whose convulsive threshold might be low, and advised that such patients should be closely supervised,

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TABLE I.—*Clinical Details of Patients Studied*

Case No.	Sex	Age	Diagnosis	Family History of Epilepsy	Previous Medical History of Epilepsy	Attacks	Drugs	Daily Dose (mg.)	Duration of Medication
1	M	58	Mild depression	No	Yes	G.M.	A	50	3 weeks
2	M	55	Manic-depressive psychosis	No	No	G.M. (× 2)	I	150	2 weeks
3	F	39	Chronic neurosis. Anorexia nervosa	No	No	G.M. (2 in 24 hours)	A	50	2 days; total 100 mg.
4	F	23	Post-partum depression	Yes—father	No	G.M. (nocturnal)	A	75	3 months
5	F	53	Compensation neurosis. Depression	Not known	No	G.M. (× 2)	P	30	2 days; total 60 mg.
6	M	54	Depression, with attempted suicide	Not known	No	G.M. (2 in 23 hours)	A	75	1 day; total 75 mg.
7	M	62	Mild depression	No	No	Car accident	T	75	8 weeks
8	F	22	Mild depression (neurotic)	Yes—sister	No	G.M. (× 2 nocturnal)	A	50	1 day; total 50 mg.
9	F	25	Chronic neurosis with hysteria	Yes—sister	No	G.M. (probable)	I	100	2 weeks
							L	30	

G.M. = Grand mal. A = Amitriptyline. I = Imipramine. P = Protriptyline. T = Amitriptyline and perphenazine. L = Chlordiazepoxide.

ideally in hospital, and that all persons on these drugs should not drive a motor-car for the first few weeks of medication. They thought that concurrent use of chlordiazepoxide or diazepam might prevent some fits occurring.

Our purpose is to report seven further cases and two probable cases of iatrogenic epilepsy due to tricyclic antidepressant drugs; all were found in the period of 12 months following the publication of the paper by Betts *et al.* (1968). It would therefore appear that the danger of epileptic attacks in patients on these drugs is greater than it was first thought to be, and in spite of previously published reports is still not well known. It also seems that the advice of Betts *et al.* has not been taken, for all except two of our patients were treated as outpatients, and in none of them had driving been prohibited or anti-convulsants administered.

Cases

As the cases are essentially similar they are reported in table form (see Table I). There were four men and five women. Six were middle-aged, but three women were in their early twenties. The underlying psychiatric disorders were as listed in Table I, all being depressed to a greater or less degree.

Epileptic Attacks

The epilepsy in seven of the patients was observed to be of grand mal type and in another was almost certainly of this type, as her husband heard her fall in the bedroom and found her lying on the floor unconscious. Two patients had nocturnal convulsions. In none of the cases were there any focal features, neither did any have an aura.

Another patient had been taking amitriptyline and perphenazine for a month for a mild depressive illness. While driving his car along a busy high road it was seen to swerve suddenly into oncoming traffic. He sustained a severe head injury and was unconscious for six days; subsequently he had a retrograde amnesia of four hours and a post-traumatic amnesia of seven weeks. It seems likely that the accident was due to an epileptic attack, and later he had several further attacks of loss of consciousness.

Drugs

The drugs given were amitriptyline alone in five, amitriptyline with perphenazine in one, imipramine in two, and protriptyline in one. Two of the patients were also taking chlordiazepoxide. The dose given was the standard for these drugs, and smaller than in the series of Betts *et al.*; but in one patient, a man of 55 who was in a mental hospital, the dose had been doubled from 75 to 150 mg. daily just before he had the fits. This dose is somewhat greater than that recommended for older patients, though not infrequently given.

Fits occurred in three patients after taking only 100, 75, and 50 mg. of amitriptyline (Cases 3, 6, and 8). The other patients

had been taking the drug from periods varying from two weeks to three months. None had been given any anticonvulsants.

Contributory Factors

Only one patient had a history of fits (Case 1)—a man of 58 who 12 years previously had two fits within a week, the second while driving. Although he took anticonvulsant drugs for only a month after that, he remained free from attacks until 14 November 1968, three weeks after starting to take amitriptyline 50 mg. daily for mild depression.

Three women had a family history of epilepsy; in one (Case 4) a parent was affected, and in the other two (Cases 8 and 9) a sister—these three were the youngest patients in the series. One of the patients (Case 4) with a positive family history of epilepsy also suffered from migraine, and she was also taking a contraceptive pill at the time of her attack. One patient (Case 5) had a history of brain damage due to cerebral fat embolism following multiple fractures in a road traffic accident. Two years afterwards she became depressed and was given protriptyline 30 mg. daily; two days afterwards she had two major fits.

Two patients (Cases 1 and 7) had severe retinal and generalized arteriosclerosis, and one of them (Case 7) was also hypertensive and had been treated in the neurological clinic six months previously for symptoms suggestive of vertebrobasilar-artery disease.

Two other patients (Cases 3 and 6) consumed excessive quantities of alcohol, and one (Case 6) had also been taking a barbiturate hypnotic regularly. He was admitted to hospital unconscious, having taken an overdose of sodium pentobarbitone. After recovery he was found to be depressed, so amitriptyline was started. He took the drug for only one day (dose of 75 mg. daily), when he had two fits. It seems likely that coincidental withdrawal of the barbiturate contributed to these attacks.

The only patient (Case 2) in whom none of these factors was present had had electric convulsion therapy (E.C.T.) two months before being started on a large dose of imipramine, and it seems that this may also have contributed to the aetiology of the attacks.

Electroencephalography

E.E.G.s were done on all the patients (see Table II), and none of them were still taking their antidepressant drugs at the time of recording. In two patients (Cases 1 and 5) the E.E.G. was done within a few days, in six between 9 and 18 days after the attacks, but in one patient (Case 3) the E.E.G. was delayed for three months. In six cases the E.E.G.s were reported as normal, but in two (Cases 4 and 8) the findings were suggestive of subclinical epilepsy, and these also had a family history of epilepsy. In Case 2 mild abnormalities, maximal in the left temporal leads, were present on two occasions. Repeat E.E.G.

on one other patient still showed a normal record, but in another a minimal left temporal abnormality was found on the second E.E.G.

TABLE II.—E.E.G. Results

Case No.	Interval after Fits	Result	Repeat E.E.G. Interval	Result
1	6 days	Normal	—	—
2	16 days	Mildly abnormal theta activity, maximal in left temporal leads	3 months later	No change
3	3 months	Normal	—	—
4	18 days	Sharp waves and diffuse theta favours idiopathic epilepsy	—	—
5	5 days	Normal	2 weeks	Normal
6	16 days	Normal	—	—
7	12 days	Normal	2 months later	Minimal left temporal abnormalities
8	9 days	Paroxysmal discharges on overbreathing "suggestive of epilepsy"	—	—
9	14 days	Normal	—	—

Follow-up

Patients have been followed for a minimal period of six months, and two (Cases 6 and 7) have had further epileptic attacks. In one the depression has also recurred and has necessitated admission to a mental hospital.

Discussion

Our experience over a period of 16 months shows that epileptic fits are by no means uncommon in patients on anti-depressant drugs. In none of them had these drugs been thought responsible for the fits, and a diagnosis of hysteria had been made in three cases. It is noteworthy that in all the cases

predisposing factors for epilepsy were present. Although E.C.T. had not previously been reported as predisposing to fits, most neurologists have seen epilepsy following this mode of treatment. In three cases only a few tablets of amitriptyline had been taken, suggesting a drug idiosyncrasy.

Our experience confirms that of Betts *et al.* (1968), and in our view if any of the factors we regard as predisposing to epilepsy are present in the patient's history—namely, previous or family history of attacks, previous brain damage or E.C.T., cerebral arteriosclerosis, alcoholism or barbiturate withdrawal—we suggest that an anticonvulsant drug should be simultaneously administered. The most suitable in our opinion is phenytoin.

As two of our cases were already taking chlorthalidopoxide it is clear that the anticonvulsant action of this drug is insufficient. The road accident that occurred in Case 7 draws attention to the inadvisability of allowing patients to drive a car while on the drug, unless they are also taking an anticonvulsant.

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Plasma Factor IX Levels in Patients Given Hexoestrol or Stilboestrol to Suppress Lactation

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Summary: A single injection of hexoestrol, 45 mg., is effective in suppressing lactation. Given in this way hexoestrol causes a small rise in plasma factor IX levels, of shorter duration than that produced by a customary and equally effective oral course of stilboestrol. With hexoestrol the plasma factor IX levels reverted to normal by the sixth day of the puerperium.

Introduction

Oral administration of stilboestrol for the suppression of lactation has been reported to be associated with an increased

incidence of thromboembolic episodes in the puerperium (Daniel *et al.*, 1967). Stilboestrol administration is also known to cause an increase in the level of plasma factor IX in puerperal women (Daniel *et al.*, 1968).

The present work consists of a study of factor IX levels in the plasma of three groups of puerperal women—some in whom lactation was suppressed with intramuscular hexoestrol or oral stilboestrol and others in whom lactation proceeded.

Methods

The patients investigated were primigravidae under 30 years of age. All had a normal labour, delivery, and puerperium. There was no history of liver disease or of thromboembolic episodes. No such episodes were encountered during this study. Patients who were lactating acted as a control group.

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