known that occasionally pethidine, when given to a patient receiving a monoamine oxidase inhibitor, causes rapid collapse with restlessness and signs of cerebral excitement and sometimes death. The reason for this is still doubtful but inhibition of an enzyme, the non-specific oxidase of the microsomes, is probably important. This enzyme is important for the metabolism of pethidine and if it is inhibited metabolites of pethidine accumulate. Now amine oxidase inhibitors vary in the degree to which they inhibit nonspecific oxidase. Iproniazid and phenelzine are strong inhibitors and reactions to pethidine with these drugs are well described. On the other hand isocarboxazid and nialamide are weak inhibitors and reactions are rare; I do not think there has been a single substantiated case with isocarboxazid.

Toxic effects, unlike side-effects, are not common to the group of drugs as a whole. They are not related to the clinical efficiency or antidepressant mechanisms as are many side-effects, and may come on at any time during treatment. Typical examples are the agranulocytosis found with etryptamine and the red-green colour blindness or even amblyopia seen sometimes with pheniprazine. One of the most important toxic effects is the hepatic necrosis found with some monoamine oxidase inhibitors. Iproniazid is recognized as being by far the most liable to cause jaundice, yet the best evidence available gives an incidence of jaundice of only 1 in 5,000 and death for 1 in 20,000 patients treated (Floody 1958, Popper & Schaffner 1959, Griffith & Oblath 1962). The newer hydrazide-type antidepressants rarely give rise to jaundice; in the case of isocarboxazid not a single case of jaundice due to the drug has been reported in the United Kingdom and in the whole of the world literature up to September 1963 only 2 very doubtful and non-fatal cases were reported with this drug.

The antidepressants, like all drugs, should be used with care. I understand that over 250,000,000 tablets of an antidepressant type – and this includes the amphetamines – are prescribed every year in the UK (*The Times* 1964). This is a fantastic amount and obviously it is wrong to use these drugs for minor mood changes. On the other hand it would be wrong to withhold one of these potent drugs from a seriously ill patient just as it would be wrong to withhold ECT if this were thought suitable. Again, the judicious doctor will usually prescribe the safer antidepressants initially and only turn to one with greater risks if the patient fails to respond. It is the doctor's job to assess each patient on his merits and to weigh the risks involved in any treatment he gives, against the morbidity of the condition he is treating. Taking into consideration the morbidity and the risks of the depression itself, or treatment with ECT, the complications of these drugs are a small price to pay for their undoubted value. This is certainly the case when one compares the risks of surgical treatment for a non-killing condition such as a gastric ulcer (Table 2). My own feeling is that when serious mishaps or fatalities are as uncommon as this, it is not so much the danger of the drugs but the skill and conscientious supervision of the doctor, or lack of it, which is important. Certainly an understanding of the pharmacology and mechanism of action of these drugs is essential if the clinician is to minimize their possible complications.

Table 2
Risks of various treatments

	Serious toxic effects	*Death*
Iproniazid	1/5,000	1/20,000
Tranylcypromine	?1/50,000	?1/100,000
Isocarboxazid	Negligible	Negligible
ECT	–	1/2000
Partial gastrectomy	–	1/50
Pyloroplasty and vagotomy	–	1/200

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An Apparently Irreversible Syndrome of Abnormal Movements Following Phenothiazine Medication

Manifest symptoms of extrapyramidal involvement are now known to occur in 10–15% of patients treated with phenothiazine derivatives. They fall broadly into two groups:

(1) A hypokinetic parkinsonian syndrome with akinesia, rigidity, tremor, disturbances of gait and posture, excessive salivation, akathisia and bradykinesia, with slowing and impoverishment of mental processes – the 'pharmacological straitjacket' effect of Cole (1960). It develops insidiously and its severity is related to dose and duration of treatment, although in most cases it reaches its

full development within the first six weeks. Individual susceptibility varies but is increased by the presence of brain disease. For unknown reasons it is twice as common in women. It may be ameliorated by reduction of dose and/or concurrent administration of anti-parkinson drugs. It is assumed to be reversible although doubt has been thrown on this in older patients (McGeer *et al.* 1961).

(2) An acute, dramatic, distressing hyperkinetic syndrome which occurs at the beginning of treatment, characterized by dystonic movements and spasms affecting primarily the head and neck musculature, especially the face, mouth, jaw and tongue; trunk and limbs may also be involved. Because of this distribution it has been called 'facio-bucco-linguo-masticatory' dyskinesia (Delay *et al.* 1959). The picture resembles the 'excito-motor' syndromes described by Marie & Lévy (1920) in the wake of epidemic encephalitis, a similarity first noted by Delay *et al.* (1957). Its occurrence is unrelated to dose and it remits spontaneously when the drug is withdrawn, although emergency treatment may be necessary (Freyhan 1958).

Last year we described a syndrome of abnormal movements of a type similar to those of the hyperkinetic syndrome of acute phenothiazine intoxication but which developed after some years of phenothiazine medication and which persisted after withdrawal of the drug for a period of observation of up to two years and may therefore be considered irreversible (Earl & Hunter 1963). Our first 3 patients had all been leucotomized for mental illness six to twelve years before, and had subsequently been treated with phenothiazines for periods of two to six years. All were more or less severely demented and this, in the setting of abnormal movements which in the limbs appeared choreiform, led us first to suspect Huntington's chorea. This was excluded not only because of the grotesque facial involvement, but also because in none was a family history of similar disorder found depite extensive enquiry. Next we considered a lesion of the caudate nucleus, which is recognized to play an important role in the genesis of abnormal movements (Denny-Brown 1962), either due to surgical damage at the time of leucotomy, or as a consequence of the progressive neuronal and transneuronal degeneration which the operation is known to initiate (Meyer & Beck 1954). Indeed, pneumoencephalography in one patient revealed the characteristic frontal horn enlargement with atrophy of the head of the caudate seen in Huntington's chorea.

At this time we saw reports from France of Sigwald and his associates (Sigwald, Bouttier & Courvoisier 1959, Sigwald, Bouttier, Raymondeaud & Piot 1959) who described a hyperkinetic syndrome affecting face, mouth, tongue and jaw which developed insidiously, as in our cases, after phenothiazines had been administered for from eight to eighteen months. In their 4 patients – who, like ours, were women in the older age groups – the abnormal movements persisted after the drug had been withdrawn for up to twenty-seven months at the time of their report. A further group of apparently irreversible dyskinesias following phenothiazine medication was reported from Denmark by Uhrbrand & Faurbye (1960) who stressed the role of ECT in its development. Their patients showed essentially involuntary grimacing, masticatory movements of the jaw, propulsion of the tongue, akathisia and tasikinesia. The syndrome persisted unchanged during an observation period of up to twenty-two months in seven of fifteen patients who developed it while receiving perphenazine, in 3 of 10 receiving chlorpromazine, and in one of 3 on a combination of both with thioridazine. Their conclusion coincided with ours (Hunter *et al.* 1964) that prolonged administration of psychotropic drugs which cause neurological side-effects, carries the risk of structural damage to the nervous system signalized by irreversible dyskinesia. This risk is increased by the presence of brain damage or disease whether due to ECT, leucotomy, or senile degenerative changes with or without cerebrovascular disease.

Material

We have since surveyed a chronic population of approximately 450 patients in a mental hospital where physical treatments – ECT, leucotomy, drugs – were formerly widely used, and where we had observed our first patients. None was seen among the men, who number 200. This may be due to chance, may reflect their easier management without the need for restraint by physical treatments, or illustrate their readier tolerance of the drug. Among the 250 women, most of whom had been given phenothiazines at one time or another, 13 showed this syndrome, an incidence of 5%. Patients with only fidgety movements which could have been interpreted as the mannerisms of ageing, institutionalized patients were omitted.

Patients ages ranged from 56 to 84. All were brain damaged as shown by the presence of dementia. Six had been leucotomized between 1947 and 1956; 9 had had ECT from 14 to 212 times; 2 had had insulin coma treatment.

They had been on phenothiazine derivatives for periods varying from eighteen months to five years before abnormal movements were first recorded, but these may have started earlier and had been either overlooked or not entered in the case notes, perhaps because they were at first

mistaken for psychotic mannerisms and stereotypies.

The derivatives of phenothiazine and the doses given were: chlorpromazine, 13 patients, 100–600 mg/day with an average of 300 mg/day; trifluoperazine, 9 patients, 10–45 mg/day; promazine, 3 patients, 75–200 mg/day; prochlorperazine, 3 patients, 75–200 mg/day; perphenazine, 1 patient, 12 mg/day; thioridazine, 1 patient 200 mg/day. In addition 3 patients had received reserpine for periods of months.

Nine patients had developed transitory parkinsonism from phenothiazine intoxication, for which 7 were concurrently given anti-parkinson agents: benzhexol, benzol hydrochloride, orphenadrine hydrochloride, or benztropine methanesulphonate.

Where abnormal movements were recorded, they seem to have developed insidiously twelve to thirty months after drug-induced parkinsonism was first noticed. Four patients who were still receiving phenothiazines when seen in this survey had, in addition to abnormal movements, mild features of parkinsonism such as rigidity, tremor, abnormal stance and gait, salivation and disturbances of balance, but these gradually receded when the drug was withdrawn. Akathisia and tasikinesia, where recorded as a feature of parkinsonism, have persisted unchanged.

On examination the striking feature of these patients was the continuing grimacing with mouth, jaw and tongue movements which varied from writhing movements of the tongue with opening and closing or lateral chewing movements of the jaw, sucking movements of lips, and bulging of cheeks, to continuous rapid protrusion and withdrawal of the tongue – the so-called fly-catcher tongue of epidemic encephalitis. In patients in whom tongue movements were gross they greatly interfered with eating and drinking; in 5, real muscular hypertrophy of the tongue was evident, the tip extending down to or even beyond the point of the chin. Two patients suffered from spasms in which their mouth opened widely, their tongue writhed and their face became suffused giving a weird impression of sardonic laughter. Speech was usually hoarse, came in expiratory bursts and was accompanied by marked contortions of the face; in the 3 worst cases it was unintelligible. Two patients had periodic disturbances of respiratory rate, rhythm and amplitude with pauses in mid-inspiration and absence of pause between in- and expiration even during sleep. Attacks of respiratory distress occurred in mid-inspiration, when they clenched their mouth, grimaced and appeared to make a respiratory effort against a closed glottis. At such times their eyes bulged, they became cyanosed and grabbed at any object within reach to aid their attempts to overcome the obstruction, while their tongue and jaw kept working – a most pitiful and distressing sight (Fig 1).

All showed associated smaller abnormal movements of the choreiform type of all four limbs. The leucotomized patients walked in a peculiar stiff-legged manner with abducted arms; others bunched their shoulders and made paddling movements with elbows flexed and rocking from side to side as they walked. Some made similar lateral or antero-posterior rocking movements at rest. Akathisia was present in all in varying degree; when severe, patients could not remain seated for longer than a few minutes at a time.

All patients were demented, the leucotomized ones most severely. So far as could be ascertained patients were extremely distressed by their continual movements. In all, these were aggravated and distress increased when they were noticed or approached. Some were continually agitated and accosted appealingly anyone entering the ward.

Six patients had fits in the course of phenothiazine medication, but 3 had had them before, following leucotomy. Six patients were deaf. Three patients with normal blood pressures had hypertension in the second and third year of phenothiazine medication.

Laboratory findings were such as are common in long-term patients in this hospital judging from a recent survey: ESR was raised in 8; 7 had an iron deficiency anæmia, 2 had non-specifically abnormal serum electrophoretic patterns and one an abnormal pyruvate tolerance curve. To what extent these reflect malnutrition or cross-infection or are the effect of long-term medication is not clear.

All have now been off phenothiazine medication for between eight months and three years but in all abnormal movements and other manifestations persist unchanged.

Discussion

This syndrome is of considerable practical and theoretical interest and concern. It suggests that the neurotoxic effects of phenothiazines may be more far reaching than has been thought, and that they may cause not only transitory and functional but in time permanent and so presumably structural changes, although proof of this must await neuro-pathological study.

That this syndrome was discovered in a mental hospital population is no coincidence, since not only are patients under observation for many years, but there is an unfortunate tendency to give drugs freely and, once prescribed, to continue them indefinitely. Further, the agitation and restlessness of these patients and their obvious distress may be mistaken for manifestations of the illness for which they were originally

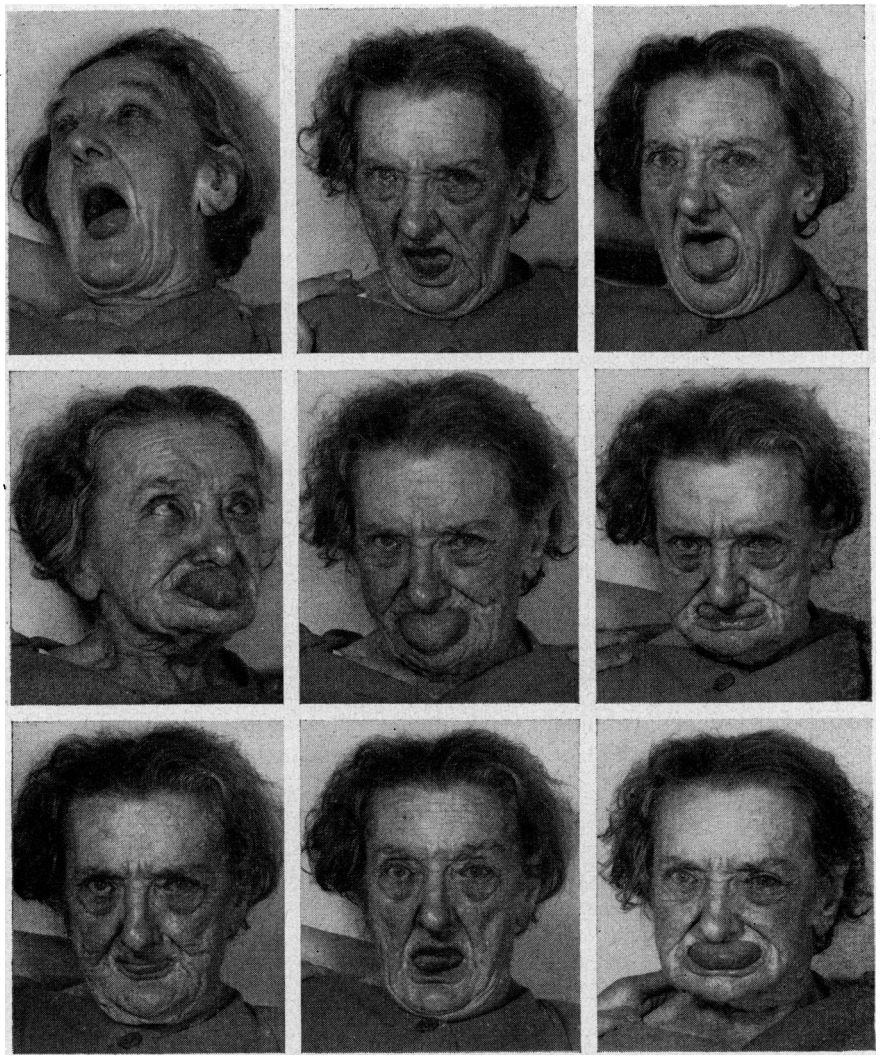

Fig 1 *Views of the persistent, continuous dyskinetic syndrome of face, mouth, tongue and jaw following prolonged phenothiazine medication*

prescribed, if it is not realized that they may in fact be due to phenothiazine intoxication. Indeed a number of ward sisters expressed concern about their patients being taken off their 'tranquillizing' regime.

It is not surprising that a brain already damaged either by physical treatments, in particular ECT and leucotomy, by cerebrovascular disease, or by the changes of senescence is more sensitive and either shows drug damage earlier or in more obvious form. This is in keeping with common experience that acute dystonic reactions, parkinsonism and fits are all more liable to occur when phenothiazines are given to patients with brain disease.

The question arises to what extent anti-parkinson drugs given concurrently with phenothiazines contributed to the development of this syndrome either by potentiation or summation of action, or by masking the severity and persistence of the phenothiazine-induced parkinsonism. In fact anti-parkinson drugs were given to our patients to try to reduce their movements; they not only had no effect but if anything tended to make them worse.

Although these cases at first sight may resemble Huntington's chorea, senile chorea, or even the grosser mannerisms and stereotypies of institutionalized patients, the major incidence of movements in the head and neck and the peculiar

affection of the mouth, tongue and jaw and the associated respiratory disturbances, make distinction obvious once the occurrence of this syndrome in the wake of prolonged phenothiazine medication is appreciated. Most closely they resemble the hyperkinetic encephalitic syndromes seen in the 1920s, as Dr Macdonald Critchley pointed out to us (*cf.* Wilson 1940), although paradoxically in cases of encephalitis abnormal movements of the kind exhibited by our patients occurred early in the illness and parkinsonism was a late complication, whereas in our patients this order was reversed and drug-induced parkinsonism was established before abnormal movements appeared. However, the analogy is sufficiently striking to suggest that our patients suffer from a chemically induced as opposed to a viral encephalitic process.

Once this syndrome is generally recognized we suspect a spate of cases will come to light, especially since ten years have now elapsed since phenothiazines were introduced into psychiatry and many patients will have received the drug long enough to manifest these effects. It seems to us therefore an urgent matter to draw attention to this unfortunate, distressing and seemingly irreversible complication of these widely used drugs, the more so since the advice that they should, and safely may, be continued indefinitely is still given in the literature and not only in that issuing from pharmaceutical firms.

Summary

A syndrome of persistent abnormal movements of a grotesque and distressing kind affecting particularly the face, mouth, tongue and jaw musculature is described in 13 chronic mental hospital patients. All were brain-damaged women in the older age groups, and all had received prolonged treatment with phenothiazine derivatives in the course of which the majority had developed parkinsonism which was treated with anti-parkinson drugs. Since this distressing and disabling syndrome, once established, appears to be permanent, much greater caution seems indicated in the prolonged use of phenothiazines.

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Dr E Marley also took part in the discussion.

Meeting March 10 1964

The following papers were read:

Chromosome Abnormalities
Professor L S Penrose
(*University College, London*)

Research in Clinical Genetics
Dr J A Fraser Roberts
(*Institute of Child Health, London*)