

# RESPONSE TO SOME STIMULANT AND DEPRESSANT DRUGS OF THE CENTRAL NERVOUS SYSTEM

By

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NEARLY one hundred years ago, Anstie (1864) wrote: "Among the too frequent instances which are to be found in medical nomenclature, of confusion and uncertainty in the application of descriptive terms, there is none, perhaps, more striking than is occupied by the words Narcotic and Stimulant." Both classes of substance embrace drugs of antiquity. Thus of the depressants, alcohol dates from the time of the Thracian god, Dionysus, while the earliest use of stimulants such as caffeine and xanthine is lost in the obscurity of the past (Goodman and Gilman, 1955a). Even today, there exists no systematized codification of response to the two classes of drug, although it is implicitly assumed that stimulants and depressants are invariably and mutually antagonistic in their effect on the central nervous system. Advantage was therefore taken of phenomena arising during drug intoxications to categorize abnormal features in the central nervous system common to each of the two classes of intoxicant and to essay a comparison, the one with the other.

## CASE MATERIAL

The material presented is a representative proportion of a considerably larger number of intoxications seen, aspects of which have already been reported (Marley, 1955; Marley and Chambers, 1956). Before conceding a diagnosis of drug intoxication, there are certain criteria to be satisfied. It must be certain (1) that the symptoms (or signs) arise *de novo* following drug ingestion and are not merely grafted on to an antedating illness; (2) the symptoms (or signs) are not due to drug withdrawal; (3) the clinical picture is temporary and reversible, the physical signs disappearing in 1-2 weeks, and the anomalies in the mental state abating ideally within 1 month and at most 2 months, and (4) if possible the diagnosis should be confirmed by blood or urine tests for the intoxicant (e.g. bromides, barbiturates, methylpentynol or its carbamate, and the amphetamine group). It is difficult to abide by all these strictures. Considering each of the desiderata in turn: (1) individuals with affective swings may take to drugs during a depressive phase, and it can then be hard to ascertain which symptoms are due to the intoxicant and which to the underlying illness (Cases 5, 10, 17 are examples); (2) while withdrawal symptoms are elusive with stimulant drugs, definite withdrawal symptoms occurred in only one of the depressant group (Case 4) on the fourth day of reduction of drug dose in hospital. Features ascribed to a drug must therefore be present before reduction of dosage, let alone withdrawal; (3) one to two months may seem excessive

for allowing the disappearance of abnormalities in the mental state. However, Connell (1958a) has emphasized the futility of attaching importance to the continuation of symptoms in amphetamine psychosis unless it is certain that the patient has no access to the drug. This qualification holds for intoxication with other drugs. As amphetamine psychosis may be indistinguishable from schizophrenia (Connell, 1958b) the importance of a follow-up period is obvious. Consideration must also be given to the possibility that amphetamine intoxication may rekindle "quiescent" schizophrenia, or that a brief reversible intoxication resembling schizophrenia may occur in a person previously diagnosed as schizophrenic, and (4) the picture of intoxication may be due to a combination of drugs, one or other predominating. These controversial facets have been given due weight in the selection of the material, the consistent ideal being to include only intoxications with unequivocal diagnoses.

Those intoxications presented are due to inorganic salts (bromides), aliphatic substances such as alcohols (paraldehyde and methylpentynol), substituted alcohols (chloral hydrate), esters (meprobamate, methylpentynol carbamate), aromatic substances such as the salts of barbituric acid (amylbarbitone sodium, phenobarbitone) and the phenyl-alkylamines (amphetamine sulphate, dextro- and methyl-substituted amphetamines, and Preludin). Of the 27 subjects studied, 18 were seen and followed up personally by the author (Cases 1, 4, 6, 7, 10–16, 19, 21, 23–27). To modulate possible observer bias, details of a further nine were taken from the Maudsley Hospital notes. Cases 1–16 are those due to intoxication with central nervous system depressants, and Cases 17–27 subjects suffering from intoxication with central stimulants. (The term central stimulant is used throughout this paper specifically to connote the psychomotor stimulants belonging to the phenyl-alkylamine series and does not include other analeptic or convulsant drugs. Apart from the amphetamines and Preludin, the phenyl-alkyl amines in current use include ephedrine, Meratran, and Ritalin). Details relating to the particular intoxicant are given in Table I. Thus Cases 1 and 2 are paraldehyde intoxications, subjects 3–5 suffered from chloral hydrate poisoning and subjects 6 and 7 from bromism, subjects 8–11 were barbiturate intoxications, subjects 12–15 were cases of intoxication with methylpentynol or its carbamate (Oblivon or Oblivon C) and subject 16 is an instance of meprobamate poisoning (Miltown, 2-methyl-2-n-propyl-1, 3-propanediol dicarbamate). Of the stimulant intoxications, Cases 17–23 and 27 were due to one or other of the amphetamines, while Cases 24–26 were ascribed to Preludin (2-phenyl-3-methyl tetrahydro-1, 4-oxazine hydrochloride). Evidence incriminating the suspected intoxicant often came from finding it in the patient's belongings (Cases 2, 4, 7, 9, 11–13, 16, 18, 19, 23, 24, 26). The majority of the patients suffered from acute or chronic intoxications (Cases 1–9, 17–21, 27) the rest being acute intoxications. The dose of drug and its period of ingestion is that admitted by the patient and must in most instances be regarded as suspect. A large number of the subjects, particularly those with stimulant intoxications had abused other drugs in the past. Fourteen of the subjects were psychopathic personalities (Cases 2, 3, 6, 7, 9, 14, 16, 18–20, 22, 24–27) while six suffered from mood swings or a more serious affective illness (Cases 5, 10, 11, 17, 21, 23). Of the rest, five suffered from neurotic illnesses (Cases 1, 4, 8, 12, 15) and one (Case 13) from paranoid schizophrenia. The age and sex of the patient, together with positive results of tests for intoxicants are also shown in Table I. Unless stipulated, the serum bromide value for all patients was less than 25 mg./100 ml., and the W.R. and Kahn reactions negative. Details of the lapse of time for recovery both of the

TABLE I  
Data Relating to 27 Patients with Various Drug Intoxications

Case No.	Age (years)	Sex	Drug	Admitted Duration Drug Ingestion	Admitted Dose/Day	Diagnosis	Special Investigations	Other Drugs Previously Abused
1	42	M	Paraldehyde	3 months	12 drachms or more	"Anxiety hysteria"		Barbiturates.
2	37	F	Paraldehyde	1 year	18-24 drachms	Psychopathic personality		? none.
3	43	M	Chloral hydrate	?	?	Psychopathic personality		Alcohol, Oblivon barbiturates, Carbromal.
4	37	M	Chloral hydrate	3 months	Up to 250 gr.	Neurotic depressive reaction		Alcohol, Sodium Amytal, paraldehyde.
5	55	F	Chloral hydrate	18 months	30 gr.	? Involuntional depression	Serum bromide 300 mg./ml. on admission	None.
6	41	F	"Mist Three Fifteens" (Potassium bromide 15 gr., Chloral hydrate 15 gr., Tinct. opii. 15 minims)	10 years	2-12 x stipulated dose	"Inadequate personality"		Drinamyl.
7	52	F	Mist pot. brom. (10 gr.) and chloral (5 gr.)	3 months	6-10 x stipulated dose	Psychopathic personality	Serum bromide 250 mg./ml. on admission	Alcohol, chloral hydrate paraldehyde.
8	50	M	Sodium Amytal	8 years	18-20 gr.	Anxiety state		None.
9	24	F	Sodium Amytal	15 months	12-36 gr. ?	Psychopathic personality		Other barbiturates.
10	43	F	Sodium Amytal	16 days	?	Manic-depressive psychosis	Serum barbiturates 2.1 mg./100 ml.	None.
11	29	F	Phenobarbitone	2 days	10 gr.	Neurotic depressive reaction		Oblivon.
12	27	F	Methylpentynol	7-14 days	1-2 g.	Hysteria		Barbiturates.
13	46	M	Methylpentynol	2 days	5-0 g.	Paranoid schizophrenic psychosis		None.
14	36	F	Methylpentynol	4 days	1.5 g.	Psychopathic personality	Whole blood methylpentynol 0.05 mg./ml.	Alcohol
15	45	F	Methylpentynol carbamate	5 days	2.0 g.	Neurotic depressive reaction		None.
16	28	F	Meprobamate	3 days	2.8 g.	Psychopathic personality		? none.
17	40	M	M-amphetamine	1 year	?	Recurrent depression		Alcohol, barbiturates, Carbromal, Oblivon.
18	39	M	Amphetamine	2 months	Up to 65 mg. (salt)	Psychopathic personality	Amphetamine-like substances in urine 1.5 mg./100 ml.	Amytal, n-amphetamine
19	55	M	D-amphetamine	8 months	10-30 mg. (salt)	Psychopathic personality		? none.
20	25	F	D-amphetamine	2 years	Recently 100-150 mg. (salt)	Psychopathic personality	Amphetamine-like substances in urine 0.28 mg./100 ml.	Barbiturates, codeine, morphine.
21	48	M	D-amphetamine	3 months	25 mg. (salt)	Manic-depressive psychosis		Alcohol.
22	35	M	Amphetamine	3 months	25-75 mg. (salt) Recently 250 mg. (salt)	Psychopathic personality	Amphetamine-like substances in urine > 1.5 mg./100 ml.	Barbiturates, morphine, pethidine.
23	28	M	Nasotrone by inhalation	3 days	325 mg. base in last 3 days	Recurrent depression	Amphetamine-like substances in urine > 1.2 mg./100 ml.	Amphetamine, Preludin.
24	34	F	Preludin	7 days	0.5 mg. (salt)	Psychopathic personality		Amphetamine, d-amphetamine.
25	32	F	Preludin	9 months	0.25 mg. (salt)	Psychopathic personality		? none.
26	31	F	Preludin	6 months	0.5 mg. (salt)	Psychopathic personality		D-amphetamine, alcohol.
27	44	M	Amphetamine	10 years	Recently 500 mg. (salt)	Psychopathic personality		Alcohol, barbiturates, chloral hydrate.

physical signs and the mental state is depicted in Table II. Uncertainty as to the time of disappearance of the physical signs exists for three patients (Cases 3, 17, 20) and in two for recovery of the mental state (Cases 3, 20). For the rest, all physical signs had gone within 2 weeks of drug withdrawal, resolution of

TABLE II  
*Duration of Abnormal Signs and Symptoms Following Drug Withdrawal*

Case No.	Physical Signs	Mental State
1	.. .. . 4 days	Incomplete recovery by 7 months
2	.. .. . 2 weeks	2 weeks
3	.. .. .	Not Known
4	.. .. . <7 days	<7 days
5	.. .. . 2 weeks	3 months
6	.. .. . 10 days	10 days
7	.. .. . 2 weeks	1 week
8	.. .. . 1 week	1 month
9	.. .. . <6 days	<6 days
10	.. .. . 6 days	Incomplete recovery by 2 months
11	.. .. . 3 days	1 month
12	.. .. . 4 days	4 days
13	.. .. . 1 week	1 week
14	.. .. . 4 days	10 days
15	.. .. . 3 days	3 days
16	.. .. . 3 days	1 week
17	.. .. . Not known	Incomplete recovery by 5 months
18	.. .. . <7 days	<7 days
19	.. .. . 5 days	8 days
20	.. .. .	Not Known
21	.. .. . <7 days	3 weeks
22	.. .. . 2 weeks	2 weeks
23	.. .. . <7 days	1 week
24	.. .. . 1 week	1 week
25	.. .. . 3 days	1 week
26	.. .. . 1 week	2 weeks
27	.. .. . 10 days	10 days

the mental anomalies occurring within the prescribed 2 month period except for Cases 5, 17. The physical and mental abnormalities associated with the intoxications are now considered.

*Physical Signs.* The physical anomalies referable to the central nervous system are depicted in Figure 1a. For the depressant drugs there is an emphasis

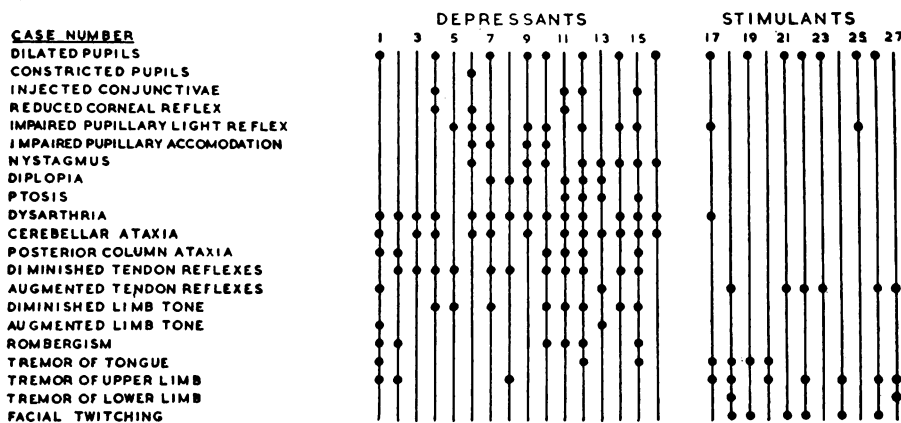


FIG. 1a.—Abnormal physical signs referable to the central nervous system found in 27 persons suffering from drug intoxications.

upon ataxic phenomena, cerebellar ataxia being found in 12 patients (Cases 1, 3, 4, 6, 7, 9, 11–16) and posterior column ataxia in six (Cases 1, 2, 10–12, 15). Typical of the specific cerebellar features were those seen in Case 12 in whom rapidly alternating movements were made clumsily, and on the finger-nose and heel-shin tests there was ataxia not compensated for by vision. Ataxic accompaniments included sustained horizontal nystagmus on conjugate lateral deviation of the eyes (Cases 6, 9, 10, 12–16), dysarthria (Cases 1–4, 6–12, 14–16) and Rombergism (Cases 1, 2, 9–11, 15). Other phenomena implying loss of muscle tone were ptosis, which might be accompanied by over-action of the frontalis muscle (Cases 11–13, 15), reduced corneal reflexes which were considered significant only if there was loss of facial muscle tone (Cases 4, 6, 11) and reduced tendon reflexes (Cases 2–5, 7, 8, 10–12, 14, 15). Increased limb tone, together with augmented tendon reflexes might be found in association with ataxic phenomena (Cases 1, 13). Thus the picture in Case 13 comprised rhythmic nystagmus on conjugate lateral deviation of the eyes, with diplopia in all directions of gaze, and right-sided ptosis. The gait was ataxic with a negative Romberg sign. Muscular tone was increased with positive Hoffman and Wartenberg signs and augmented tendon reflexes.

Equal bilateral dilatation of the pupils was noted in eight instances (Cases 1, 4, 7, 9, 10, 12, 14, 16) with sluggish direct and consensual responses to light (Cases 5–7, 9, 10, 12, 14, 15) and an impaired accommodation-convergence reflex (Cases 6, 7, 9, 10). In spite of the absence of paralytic strabismus or of any apparent disturbance of reflex conjugate lateral or vertical gaze, erroneous projection of the visual field was noted in six patients (Cases 7–9, 11–13).

The anomalies encountered with the central stimulants were of a different order. Thus, although equal bilateral dilatation of the pupils of 8–10 mm. diameter were found in 7 of the 10 subjects, an impaired direct or consensual response to light was found in only two (Cases 17, 25) while there was no alteration of the accommodation-convergence response. Perhaps the most striking difference from the depressant intoxications was the absence of ataxic features. Instead, there was increase of limb tone and augmented tendon reflexes (Cases 18, 21–23, 26) together with tremor of the tongue and/or upper limb (Cases 17, 18, 20, 22, 24, 26). Facial twitching (Cases 18, 19, 21, 22, 24, 26) was also noted. This seemed part myoclonic, i.e. brief shock-like contractions confined to the facial muscles, and part tic, i.e. repetitive movements involving the face and upper limb, particularly “hand-face” touching and plucking.

Many intoxications occur in subjects taking large quantities of either a medley of depressant and stimulant drugs (e.g. alcohol, barbiturates and amphetamine) or of a compound substance such as Drinamyl (amylorbarbitone and d-amphetamine). The signs usually present are those of the depressant drug intoxications. To quote two examples (not shown in Fig. 1a), the first (an individual taking amphetamine, barbiturates, methylpentynol) exhibited tremor of the out-stretched tongue and upper limb, and was dysarthric and ataxic: the other (ingesting Drinamyl), had nystagmus, dysarthria, and cerebellar ataxia with diminished tendon jerks.

*Mental State.* A synoptic version of the abnormalities in the mental state are shown in Figure 1b. The predominating behavioural anomalies were drowsiness with the depressant drugs (Cases 1, 4, 6, 7, 10–16) and excessive activity both at rest or in motion with the stimulants (Cases 17–19, 22–24, 26, 27). Typical descriptions for the depressants are (Case 12) “Drowsy on admission. The patient spent the first day asleep in bed, but is restless and wakeful at night.

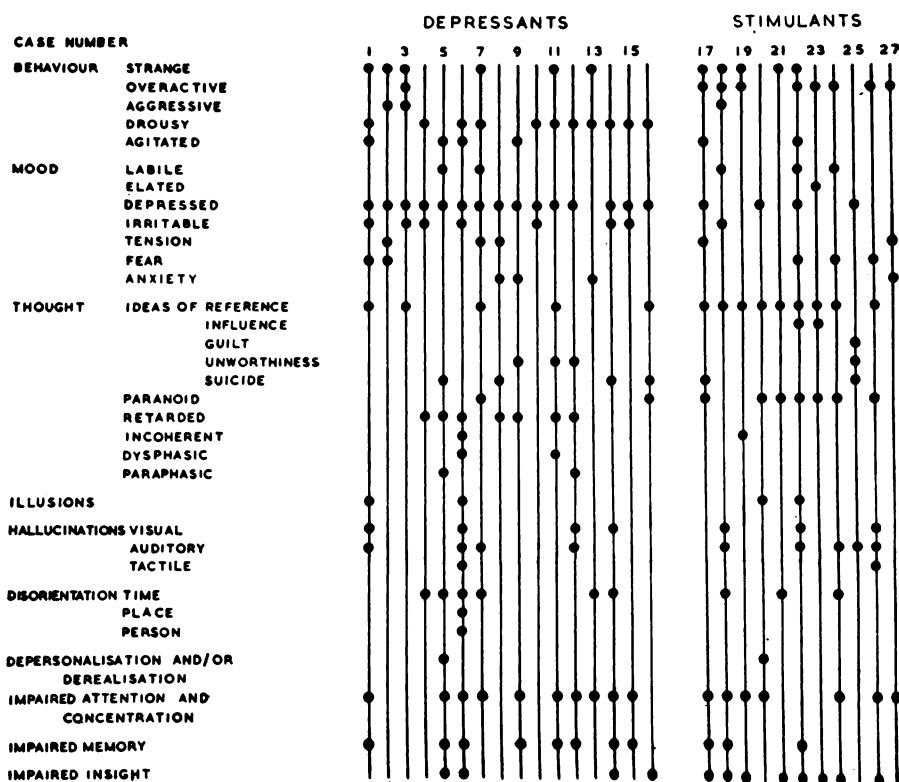


FIG. 1b.—Alterations in the mental state for 27 persons suffering from drug intoxications.

She may be talking to you one moment and then suddenly falls asleep”, or in an extreme instance (Case 6) “stuporose on admission with slight response to painful stimuli. A few hours later, there were movements and muffled answers to questions. The speech was slurred”. Typical for the stimulant drugs is subject 22. He was “fidgety, moving and changing his position frequently. He played with his hand on the table or passed his hand over his face, rubbing his eyes and pulling at his spectacles”.

Mood changes with the depressants were mostly depression combined with irritability. The depressive component may be quite marked. Thus one subject stated (Case 8), “I just feel depressed—that life is not worth living. I have thought of committing suicide by an overdose of drugs. No treatment has done me any good. I have no interest in anything.” Another patient (Case 9) remarked “I wish I was dead. I’ve had enough of it. I can’t stand it any longer. Oh, my head. What is wrong with it? Am I insane? Oh my children, my children” (weeps). There was a broader spectrum of mood change with the stimulants although depressive features might be found (Cases 17, 20, 22, 25) reaching even psychotic dimensions (Case 25). Fear was conspicuous in three subjects (Cases 22, 24, 26); rather surprisingly elation was found in only one stimulant intoxication (Case 23).

Thought, and its consort conversation, are particularly swayed by the affective state. As noted above there were ideas of suicide in those individuals who became depressed. Thus four subjects intoxicated with depressant drugs

(Cases 5, 8, 14, 16) and two with the stimulants (Cases 17, 26) expressed suicidal ideas. Ideas of unworthiness were found in three depressant intoxications (Cases 9, 11, 12) and one of the stimulants (Case 25). Slowness of thinking was marked in patients who were drowsy. In contrast, subjects with stimulant intoxications were often over-talkative, evincing ideas of reference (Cases 17–24, 26) and paranoid material (Cases 17, 20–24, 26). Thus (Case 26) the patient believed that her man friend was outside the house waiting with a gun to shoot her. She became frightened to go out and even afraid of the people in the house. "She would hear footsteps and then see the doorhandle turn. Someone was going to shoot her. There were women's voices calling her a prostitute". Another (Case 21) believed he was wanted by M.I.5. "They were getting at him through the telephone system". Ideas of reference, although present, were less common with the depressant intoxications (Cases 1, 3, 7, 11, 16). One patient (Case 7) "heard people on the ward planning to go and raid her house. They were going to steal her pictures and books. The nurses were communists and this was part of a communist plot." Ideas of influence were also found with the stimulants (Cases 22, 23). Only one subject was grandiose (Case 23). He insisted that he was brother of the Queen. This patient also showed disconnection of thought. The following is an abstract from one of his letters. "Made me altar hand. Righting boat and encore. Remember seing insect. Could it be a baby elefant, but had never seen an elephant. Word ending in G Rug, Bug, Tug." Dysphasic and paraphasic disorders were found only with the depressants, but although not elicited it would be unrealistic to suppose that they do not occur with stimulant intoxications.

Illusions were noted in four instances (Cases 1, 6, 20, 22). One (Case 1) thought that there was a man crouching down where actually there was just a chair. Visual and auditory hallucinations occurred in both groups (Cases 1, 6, 7, 12, 14, 18, 22, 24–26) there being a predominance of auditory hallucinations with the stimulants. Whereas those found with the stimulant intoxications occurred both during the day and night, there was a definite nocturnal emphasis for those with the depressant intoxications. Even if the patient had previously experienced auditory hallucinations under the influence of the drug, on subsequent occurrence they still bore the stamp of authenticity. One subject commented (Case 22) that "before taking the drug (amphetamine) he says to himself that he is going to hear the voices". Yet when they occur, "they are absolutely real". Visual hallucinations were complex rather than simple.

Disorientation for time was noted in six of the depressant group (Cases 4–7, 14, 15) and disorientation for all modalities in one (Case 6). Temporal disorientation was elicited in three of the stimulant intoxications (Cases 18, 21, 24).

Depersonalization and/or derealization were found in two subjects (Cases 5, 20). This probably underestimates the true incidence, their presence escaping the patient possibly because of impaired attention, concentration, or recent memory. The antithesis may also occur. One subject (Case 27) remarked, "Things are more real. Everything looks more alive and coloured." Another subject commented (Case 22) that after the drug "sounds outside the room appear magnified and louder. They are related to me". Body-image disturbances were also complained of. One of the more interesting was that of Case 22. He stated that within 10–15 minutes of ingesting a large quantity of drug, "his whole body would feel swollen". This was associated with a sensation of flushing.

Impaired attention and concentration were elicited regularly in both

groups of intoxications (Cases 1, 5-7, 9, 11-15, 17-20, 24, 26, 27) as was impairment of memory for recent events (Cases 1, 5, 6, 9, 11, 12, 14, 18, 22). Diminished insight was much more common with the stimulant intoxications. One patient (Case 19) ascribed his admission to hospital to "My whole trouble started by being 10 minutes late. There was nobody at the reception office and I was there until quarter-to-twelve."

#### DISCUSSION

The material presented above was selected because of the presence of physical signs referable to the central nervous system together with abnormal mental phenomena. It is not intended to suggest that they are the exclusive prototype of all intoxications with central stimulants or depressants, for these may manifest with none, or a minima of signs and symptoms.

It is hoped that the divergent character of the spectra of signs produced by central depressants or stimulants is apparent. It seems that abnormal signs are more likely to follow intoxication with the depressant drugs. Washburne (1934) describes double vision, sluggish pupillary reactions, ataxia of gait and speech, tremors and abolition or diminution of corneal, abdominal, knee and ankle reflexes in association with bromism. Isbell (1950) noted ataxia of gait and station, dysarthria, dysnergia, adiadochokinesis, hypotonia, tremor, depressed abdominal reflexes, and occasionally transient clonus and Babinski signs with chronic barbiturate intoxications. Nystagmus also occurs, being reproducible by the intravenous injection of quick-acting barbiturates (Bender and Brown, 1948). Bender and O'Brien (1946) attribute barbiturate nystagmus to the drug interfering both with control of eye movements and ocular fixation, an effect demonstrable in animals (Spiegel and Collins, 1940). Nystagmus was never found with intoxication by central stimulants, and contrasts with the fact that opticokinetic nystagmus or that induced by labyrinthine stimulation is elicited with greater difficulty after central depressants but facilitated by central stimulants (Cogan, 1948). Curran (1938) feels that nystagmus is infrequent in bromism, but Copas *et al.* (1959) refer to it with "carbromal poisoning". Alcohol intoxication may present with mydriasis, impaired pupillary responses, suffused conjunctivae, nystagmus, and ataxia with a positive Romberg sign (Howells, 1952). Drowsiness is one of the principal side-effects of meprobamate (Hinton, 1958) although coma and neurological signs have been encountered (Heberden and Cooper, 1957; Bedson, 1959). With methylpentynol intoxications the abnormalities include pupillary reflex anomalies, nystagmus, dysarthria, tremor of the protruded tongue, and cerebellar ataxy in the limbs or admixtures of this with posterior column ataxia. Muscular tone was usually diminished as were the tendon reflexes (Marley and Chambers, 1958). Similar signs were found with methylpentynol carbamate intoxications (Bartholomew *et al.*, 1958; Marley, 1958). Hypotonia with normal or exaggerated tendon reflexes was occasionally seen with the depressant intoxications. Kremer (1958) discusses this anachronism in the light of work by Hammond *et al.*, (1958) on the function of the  $\alpha$  and  $\gamma$  efferent nerve fibres to the muscle and muscle spindles. That the effect of paraldehyde, chloral hydrate and the barbiturates in reducing muscle tone is a central action and not on the muscle itself or the neuromuscular junction was confirmed by Quilliam (1955) the same being true for methylpentynol and its carbamate (Marley, 1959a).

The nervous system signs with stimulant intoxications are less dramatic. Connell (1958c) feels that there are no specific signs of amphetamine intoxication,



and indeed alludes to the few references to the physical state in amphetamine poisoning (Connell, 1958d). In the cases mentioned here, a coterie of signs, not all invariably present, stand out. These are mydriasis with occasionally impaired pupillary response to light and accommodation, tremor of the tongue and limbs, augmented tendon jerks with increased limb tone, and facial tics and twitching.

Dilatation of the pupils or "spastic mydriasis" occurs with either central depressants (Duke-Elder, 1949a) or stimulants (Duke-Elder, 1949b). There may be diminished or absent reflex pupillary changes to light and convergence, although an "incomplete light rigidity" (Duke-Elder, 1949c) is more likely, the pupillary reflex to light being impaired before that to convergence (Duke-Elder, 1949d). The phenyl-alkylamines have been used as mydriatics (Myerson and Thau, 1938; Mayer, 1939) and Goodman and Gilman (1955b) comment that the light reflex is not affected except after repeated local instillation of amphetamine into the conjunctival sac, an effect which is rarely seen after its systemic administration in man. Nevertheless, mydriasis with amphetamine (or other phenyl-alkylamine) intoxications have been reported in man (Shorvon, 1945; Herman and Nagler, 1954; Martimor *et al.*, 1955; Patuck, 1956; Shanson, 1956) and in animals (Stern, 1889; Dale and Laidlaw, 1912; Udenfriend *et al.*, 1957). Of Connell's 42 cases, 12 had dilated pupils and 3 an impaired light response (Connell, 1958c).

The association of mydriasis with or without an impaired light reaction was found with both amphetamine and Preludin intoxications. In an attempt to elucidate the mechanism of this effect, cats were given various phenyl-alkylamines intravenously. Considerably greater doses were required to produce impairment of reflex response to light than for mydriasis. The pupillary dilatation could be elicited after immediate removal of both superior cervical ganglia, both suprarenal glands and unilateral resection of the ciliary ganglion. If the post-ganglionic cervical sympathetic trunk was allowed to degenerate after removal of the superior cervical ganglion, then homolateral pupillary dilatation was either absent or minimal with these drugs (Marley, 1959, unpublished data). The production of mydriasis with amphetamine or Preludin must therefore depend partly on the integrity of post-ganglionic sympathetic nerve endings in the iris.

Mydriasis, tremor, and restlessness occur after overdoses of ephedrine (Goodman and Gilman, 1955c) and the drug may produce a picture not at all unlike amphetamine intoxication (Locket, 1957a). Tremor in humans after amphetamine was mentioned by Monroe and Drell (1947) and Knapp (1952) and may occur in animals after central stimulants (Alles, 1927; Chen and Bohner 1958). It is also seen in poisoning with the caffeine-xanthine group of stimulants (Locket, 1957b). Deniker (1957) describes mydriasis and tremor after mescaline which is a central stimulant (Stockings, 1940; Speck, 1957). Tremor and augmented tendon jerks were noted with the amphetamine and Preludin intoxications and one may speculate whether it is due to the drugs increasing the servo instability in the stretch reflex arc, a mechanism proposed by Halliday and Redfearn (1956). Tremor of the tongue and upper limb may be found with the central depressants, particularly the barbiturates (Maurer and Vogel, 1954), although it is more dramatic as a feature of drug withdrawal.

Facial twitching was also noted. Small tic-like movements of the hands, feet, eyes, ears, and especially of the lips and mouth with frequent touching of the naso-labial region have been produced in monkeys with amphetamine or Ritalin (Cole and Glees, 1957). Klüver (1958) describes an identical syn-

drome in these animals elicited by mescaline and other phenethylamine compounds. The facial twitching with the amphetamine and Preludin intoxications seemed part tic and part myoclonic in nature. The two interpretations are not irreconcilable, for Pfeiffer (1957) refers to photic-stimulation induced seizures in normal subjects receiving mescaline, and convulsions have followed an overdose of amphetamine (Apfelberg, 1938). In animals, fatal doses of amphetamine provoke tremors and clonic convulsions (Leake, 1958a).

Restlessness was also marked with the stimulant intoxications, and Fullerton (1956) found increased abnormal activity in humans after Meratran. Dews (1953) observed with mice that psychomotor stimulants such as cocaine or methamphetamine greatly increase co-ordinated activity, while central stimulants such as picrotoxin have no effect or depress activity. Central depressants usually decrease activity. Thus Laverty and Franks (1958) were impressed by the significant diminution of spontaneous movement following a non-hypnotic dose of barbiturate, and it can be shown quantitatively that pentobarbitone sodium or meprobamate significantly reduce movement during sleep (Hinton and Marley, 1959).

An explanation of the difference in response to the two classes of drugs may lie in their effect on the postural and righting reflexes. Analogies have mainly to be drawn from animal work, and impairment of postural mechanisms have been demonstrated to occur with alcohol (Versteegh, 1922; Alexandroff and Talpis, 1928) and with barbiturates (Hondelink, 1932; Beecher *et al.*, 1939). In contrast, righting and other postural activity returns in decerebrate cats after d-amphetamine (Maling and Acheson, 1946; Macht, 1950), after Meratran (Brown and Werner, 1954) and in decapitate dogs after ephedrine (Hinsey *et al.*, 1931). Factors such as these may account for the comparative absence of ataxic phenomena with stimulant intoxications and their abundance with the depressant drugs. Nevertheless, ataxy and cerebellar signs may occur in humans with amphetamine intoxication (Mathias, 1951) and cerebellar inco-ordination has been encountered with Preludin intoxications (Bartholomew and Marley, 1959). The presence of ataxic signs with stimulant drug intoxications could lead one to suspect the patient had also been taking depressant substances (alcohol, barbiturates, etc.). Certainly subjects given large doses of pentobarbitone sodium and leptazol have ataxy of gait and station, nystagmus and involuntary clonic jerks (Fazekas *et al.*, 1956) as they do after barbiturate and Bemigrade (Gershon and Shaw, 1957).

It would be only reasonable to expect a wide range of behavioural responses with these drugs. This was so, with an emphasis on drowsiness for the depressants and overactivity and restlessness with the stimulants. Restlessness and aggressive incidents may occur during depressant drug intoxications being possibly a catastrophic response to disorientation or impaired consciousness. Curran (1944) noted restlessness and hypomanic episodes with barbiturate poisoning, while Connell (1958f) in his superb monograph on amphetamine psychosis, mentions a plethora of behavioural anomalies, including "found wandering, suicidal attempt, violent behaviour, assaulting police" etc.

As behaviour and thought are affectively determined, the effect of drugs on mood is of cardinal importance. Depression with irritability was a salient feature of the depressant drug intoxications whereas there was a greater spectrum of mood pattern with the stimulant drugs, elation rather surprisingly being uncommon. Dissimilar effects on mood may be associated with the same drug. Thus of 54 patients prescribed methylpentynol, 14 became euphoric or elated and 23 depressed or irritable (Marley and Bartholomew, 1958). With both

depressants and stimulants, the mood response may initially be elation ultimately transforming to depression. It is for such reasons that affective changes following drug administration have been categorized as non-specific (Cleghorn, 1952). Elevation of mood is conventionally associated with the administration of amphetamine (Peoples and Guttman, 1936; Guttman and Sargent, 1937) and Preludin (Randell, 1957). However, depressive mood changes followed the ingestion of amphetamine or Preludin and this paradoxical affective response has not passed unheeded (O'Flanagan and Taylor, 1950; Leake, 1958b). Elation and depression may occur as complications of barbiturate therapy (Curran, 1944). In synopsis then "it would appear that the terms stimulant and depressant outside the isolated organ context are not specific enough to be rigidly adhered to. In the human frame of reference such drugs may produce antipodal mood effects even in the same person" (Marley, 1959b).

It was noted with methylpentynol intoxications that ideational content was congruous with the prevailing mood change (Marley and Bartholomew, 1958). Similarly, for the stimulant intoxications, appropriate thought content may be found with dissimilar affective changes. In this series, one patient on Preludin became severely depressed with typical depressive ideas and hallucinations. Ideas of reference occurred in both groups, but more so with the stimulants. Fully matured paranoid ideas were also commoner with the stimulant intoxications, although they may occur with the depressants and Isbell *et al.*, 1950 refer to patients with barbiturate intoxication who became euphoric or paranoid. The difference between thought content for the two groups of intoxications could be that with the depressants the drowsiness and difficulty in thinking vitiate the development of paranoid material, while with the stimulant intoxications the subject, if anything, registers a larger number of impressions, and this with perhaps misinterpretation of sensory cues due to impaired consciousness, commits him to delusional elaborations. Connell (1958g) describes the amphetamine psychosis (to whom its separate categorization is due) as a paranoid psychosis with ideas of reference and persecution, auditory and visual hallucinations, in a setting of clear consciousness. Paranoid reactions with the amphetamines were noted also by Freyhan (1949); Norman and Shea (1945); Knapp (1952); and Tolentino (1957); with cocaine intoxication (Bleuler, 1951) and with the phenyl-alkylamines Preludin (Bethell, 1957; Glatt, 1957) or Meratran (Begg and Reid, 1956). Transitory schizophrenic and paranoid states with clear consciousness may occur with depressant drugs (Levin, 1947).

Illusions and hallucinations are found with both central depressants (Curran, 1944) and with central stimulants such as the amphetamines (Wallis *et al.*, 1949; Carr, 1954). They tend to be mood determined and to relate to events in the patient's life. They might therefore be regarded as epi-phenomena. Noyes (1948a) remarks that not only are illusions likely to be determined by the prevailing trend of the patient's preoccupation, but that the mental material which is externalized in the form of hallucinations is of a most intimate, subjective and personal nature (Noyes, 1948b). In this series they were relatively commoner with the stimulants than the depressants, with a slight predominance (in the case of the stimulants) of the auditory over the visual. The phenomena occurred both during the day and at night with the stimulant intoxications, but were primarily nocturnal with the depressant drugs, a point emphasized by Wolff and Curran (1935).

Levin (1956) distinguishes between delirious and paranoid disorientation

and that found with organic brain disease. He considers the disorientation of toxic delirium the easiest to understand, being in Hughlings Jackson's words a "reduction to a more automatic condition" (Levin, 1936). Levin (1951) formulated the entity of "partial delirium", which depends on the fact that orientation for time, being an abstract concept, is more vulnerable and consequently more likely to be upset than orientation for place or person. This "partial delirium" was found in six of the depressant and three of the stimulant intoxications. Thus the majority of the patients were not delirious in the strict sense, and belong to what Cameron (1947) has termed the syndrome of progressive cerebral incompetence. A subacute delirious state with Preludin intoxication has in fact been reported (Silverman, 1959). Connell (1958g) noted the absence of disorientation as a symptom of amphetamine intoxication. Connell (1958h) also points out that the term toxic confusion is sometimes used to imply confusion with disorientation, at others to mean cognitive disturbance without disorientation. Impaired attention and concentration were found with ten of the depressant intoxications, and with six of the stimulants. That clouding of consciousness existed is evident from the incidence of impaired memory for recent events in both groups of intoxications. Impaired cognitive function with the depressant drugs is well known. Hoch (1906) and Kornetsky (1951) found declines in digit retention with either intoxications or prolonged drug administration. Weinstein and Kahn (1955) regard disorientation, re-duplication and paraphasia as manifestations of denial of illness rather than being specific deficits.

More piquant anomalies such as depersonalization, derealization and body-image disturbance did occur but were less frequent than might have been anticipated. Body-image disturbances were classifiable into Bonnier's (1905) category of paraschemata, the best examples of which are usually seen in drug intoxications (Critchley, 1950). The final striking feature with the stimulant drugs was the frequent loss of, or impairment of, insight during intoxication, an aspect nothing like so conspicuous with the depressant intoxications. This may be linked with the differing mental content with the two classes of drug response.

What generalizations emerge from this appraisal? Perhaps first the uniformity of response within each of the two groups of intoxicants. For the group of depressants, ataxic features dependent upon loss of muscle tone predominated, whereas enhancement of postural function seemed typical of the stimulant intoxications. The distinction between the mental anomalies produced by the two classes of intoxicant was not so forthright. Nevertheless, some categorization can be made, with an emphasis for the depressants on drowsiness, depression and irritability, slowness of thinking, impaired attention, concentration and memory for recent events. With the stimulants there was overactivity, garrulity, ideas of reference and paranoid features, impaired attention, concentration and memory for recent events, together with diminished insight. Allusion might also be made to the greater incidence of temporal disorientation with the depressants and auditory hallucinations with the stimulant intoxications. These distinguishing criteria are set out in Table III (p. 88).

The central depressant drugs considered here fall into the group of "hypno-sedatives and tranquillo-sedatives" designated by Jacobsen (1958). Other groups suggested by him are (1) the "major tranquillizers" (reserpine, chlorpromazine), (2) the "minor tranquillizers" (antihistamines) and (3) the "central acting anti-acetylcholines" (atropine, benactyzine). Ataxic phenomena may

TABLE III

*Distinguishing Criteria between "Depressant" and "Stimulant" Drug Intoxications*

	"Depressants"	"Stimulants"
Pupils .. ..	May be dilated; may be impaired reaction to light and accommodation.	May be dilated; may be impaired reaction to light and accommodation.
Nystagmus ..	Often present on conjugate deviation of the eyes.	Absent
Diplopia ..	May be present.	Absent
Ptosis .. ..	May be present.	Absent.
Facial twitching/tic	Facial twitching may be present during intoxication. Also a withdrawal sign.	Facial twitching often present during intoxication. "Hand-face" touching common.
Dysarthria ..	Often present.	Infrequently present.
Tremor .. ..	Exaggeration of physiological tremor, cerebellar or posterior column varieties. Marked during drug withdrawal.	Exaggeration of physiological tremor. Not a withdrawal sign.
Muscle tone ..	Usually decreased but can be augmented.	Usually augmented.
Tendon reflexes	Usually diminished.	Exaggerated.
Ataxia .. ..	Often present. Cerebellar or posterior column varieties.	Rare.
Spontaneous movements	Reduced in quantity and amplitude.	Frequent fidgeting. May be tics and grimacing.
Behaviour ..	Usually underactive, drowsy. May be excited. Restless at night.	Overactive, restless.
Mood .. ..	Any mood change. Usually, depressed and irritable.	Any mood change. Often anxiety, fear. Rarely elated.
Thought .. ..	Slow with poverty of thought. May be paranoid ideas.	May be disconnection of thought. Often paranoid ideas.
Illusions and hallucinations	Visual, predominantly nocturnal.	Auditory, and occur both day and night.
Orientation ..	Often temporal disorientation.	May be temporal disorientation.
Attention and concentration	Usually impaired.	Usually impaired.
Insight .. ..	Usually adequate.	Frequently impaired.
Withdrawal symptoms	May be marked.	Minimal.

occur with overdose of any of these groups but particularly (2) and (3) (White *et al.*, 1956; May, 1958; Baker and Farley, 1958), the righting reflexes usually being preserved even after large doses of (1) (Jacobsen, 1958). Other central depressants eluding the above classification include the analgesics morphine, pethidine, etc. Harris (1951a) envisaged a standard sequence of response to volatile or non-volatile anaesthetic drugs, implying thereby an orderly descending depression of central nervous function from the cerebrum via the midbrain to the medulla. Depressant drugs with an oil/water partition coefficient between unity and eight (amylobarbitone sodium, phenobarbitone, paraldehyde, methylpentynol and its carbamate) produce the standard sequence of response. In contrast, substances such as ethanol or chloral hydrate with an oil/water partition coefficient less than unity, depart from the sequence, the medulla being depressed coincidentally or soon after the cerebrum (Harris, 1951b). It is surprising then to encounter such uniformity of reaction to the cadre of depressant drugs, although this may devolve from some pharmaco-

logical action common to all. Apropos this, Nicholls and Quilliam (1956) suggested that paraldehyde and methylpentynol reduce the amount of acetylcholine (ACh) released at the neuromuscular junction, and it is known that the barbiturates (Exley, 1954) and methylpentynol as well as the carbamate (Marley and Paton, 1959) depress the release of ACh from the cat's superior cervical ganglion. This is not the simple answer to their mechanism for the morphine analogues also reduce the ACh output (Paton, 1957) but only infrequently produce ataxia in the human.

The central stimulants embrace not only convulsants such as picrotoxin, but also the psychomotor stimulants of which the phenyl-alkylamines have been taken here as the paradigm for study. Various pharmacological classifications of these substances have been proposed (Fleckenstein and Burn, 1953; Fleckenstein and Bass, 1955). Recently it has been suggested (Vane, 1958, personal communication) that the phenyl-alkylamines should be subdivided into (a) those mimicking (5HT) 5-hydroxytryptamine (amphetamine, mescaline, etc.), (b) those behaving like a mixture of 5HT and adrenaline (ephedrine, Preludin, etc.) and (c) those acting like adrenaline (dopamine, etc.). In this series, uniformity of response was found with drugs falling into the categories (a) and (b). The central action of amphetamine may be on receptors in the brain stem area (Bradley and Elkes, 1957) as has also been suggested for ephedrine, Meratran, and Ritalin (Himwich, 1959); certainly many of the side-effects with both the stimulant and depressant group of drugs indicate a brain stem locus of effect. Finally, while there is a great deal of overlap in response to the two groups of drugs, the dichotomy between them may be examples of what Davis (1950) considered failure of normal homeostasis, the one representing a too high level, the other a too low level at which regulation of the nervous system is being maintained.

#### SUMMARY

Twenty-seven instances of drug intoxication are presented, sixteen due to "central depressant substances" (bromides, paraldehyde, chloral hydrate, barbiturates, methylpentynol and its carbamate, meprobamate) and eleven due to "central stimulants" as specifically exemplified by the phenyl-alkylamines (amphetamine, d- and m- amphetamine, Preludin).

The nervous system physical signs found during intoxication with the "depressant" drugs consisted mainly of ataxic features (nystagmus, dysarthria, cerebellar and/or posterior column ataxia) and those dependent upon loss of muscle tone (ptosis, loss of limb tone and diminished tendon reflexes). In contrast, enhancement of postural function seemed typical of the "stimulant" intoxications, there being augmented limb tone and tendon reflexes. Other signs included mydriasis with impaired pupillary response to light, tremor of the tongue and limbs, and facial twitching and tics.

In the mental state, the emphasis with the "depressants" was on drowsiness, depression and irritability, slowness of thinking, impaired attention, concentration and memory for recent events. With the "stimulants" there was overactivity, garrulity, disconnection of thought, ideas of reference and paranoid features with diminished insight, impaired attention, concentration and memory for recent events. In addition, there was a greater incidence of temporal disorientation with the "depressant" drugs, and auditory hallucinations with the "stimulant" intoxications.

The internal uniformity of response (both for the physical signs and the

mental state) within each of the two cadres of intoxicants is discussed and, contrasted with the dissimilarity of response of the two groups as a whole, each to the other.

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## ADDENDUM

*Methods for estimating drugs in body fluids.* The serum bromides were determined by the gold chloride method (Harrison, 1947), the serum barbiturates by the calorimetric method described by Varley (1954), methylpentynol by the technique of Marley and Vane (1958), and the amphetamines by the method of Connell (1958i).

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