the frontal or temporal regions and the lapse of petit mal, and here the E.E.G. may be of critical importance in arriving at a correct diagnosis.

You will have observed that I have attached a good deal of importance to the E.E.G. in distinguishing between central and partial seizures and in the localization of the site of discharge in the latter, but, as I have already indicated, the E.E.G. is by no means infallible. A positive E.E.G. depends first upon the chance of an epileptic discharge occurring while the record is being made. This chance may be a very small one, though various methods are now used to precipitate what are called subclinical seizures while the record is in progress. Nevertheless there are a great many cases in which we can be quite sure from the clinical evidence that the patient is suffering from epilepsy yet the E.E.G. is negative. This may be true for partial seizures even though the patient is having clinical attacks at the time the record is made. We recently had in the wards a man who was having partial seizures of precentral origin with tonic and clonic convulsive spasm involving the left side of the face and adversion of head and eyes to the left. These occurred frequently during the period of the E.E.G. record, which showed no abnormality. It is probable in this case that the discharge was arising deeply.

One of the most interesting developments in recent years has been in our knowledge of the pathology of partial seizures, for which it seems possible that there is always an organic cause to be found—that is to say, a demonstrable histological lesion. The importance of scars, due to birth injury, neonatal anoxia, or encephalitis, has been increasingly revealed from the study of brain substance excised by neurosurgeons. Mr. Murray Falconer's lecture has told of what is now being done in the surgical treatment of partial epilepsy.

Conclusion

I will conclude with a brief account of the steps which should be taken in the investigation of a case of epilepsy. First and foremost there is the clinical history, including, of course, the family history, birth, neonatal symptoms, and past history, with special reference to any head injury, or encephalitis complicating one of the exanthemata, leading up to the description of the seizures, by patient and witness. Next comes the neurological and general examination. When this has been completed the distinction between central and partial epilepsy can very often be made on clinical grounds. It is, however, I think essential to have an E.E.G. in every case, for the combination of clinical and electrical data provides the surest basis for diagnosis and treatment. If the clinical and E.E.G. evidence agree in indicating the diagnosis of central epilepsy there is no need for radiographs of the skull, but in every case of partial epilepsy, or whenever there is any doubt, radiographs should be taken. It is true that they will usually reveal nothing, but if this step is not taken the presence of a benign tumour may be missed, at a stage at which there are no symptoms of increased intracranial pressure or any abnormal physical signs—the stage, in fact, at which a benign tumour can be most safely removed. Many benign tumours of the kind which present with epileptic seizures contain areas of calcification ; others may cause a shift of the calcified pineal, or erosion or thickening of bone. It has happened to me twice in the last three years to have encountered a patient in the early teens with seizures taking the form of attacks of unconsciousness, sometimes going on to generalized convulsive spasm, with no certain clue to the site of discharge, and without any other symptoms or signs, in which the radiograph revealed a calcified mass in the left temporal lobe. In each instance this proved to be a benign intraventricular tumour, which was successfully removed.

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A NEW TREATMENT OF BARBITURATE INTOXICATION

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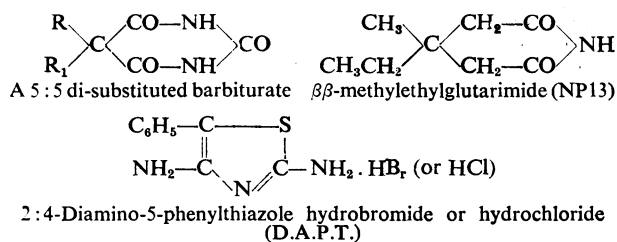
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The increasing popularity of barbiturates as suicidal agents has created a world-wide problem, and over the past decade the amount of barbiturate used on both sides of the Atlantic has more than trebled, while the incidence of barbiturate coma has increased fivefold (Nilsson, 1951 ; Locket and Angus, 1952 ; Clemmesen, 1954 ; Goldstein, 1947 ; Koppanyi and Fazekas, 1950, 1952, 1954 ; Møller, 1954 ; Lancet, 1951, 1953 ; Goodman and Gilman, 1947). Until recently the over-all death rate from barbiturate intoxication treated with central analeptics of different types has remained steady at about 10%, increasing to over 20% in serious cases (defined by Nilsson as " one which has been in coma for 24 hours or in which complications are present "). This figure has now been reduced as a result of improved medical care (Nilsson, 1951 ; Locket and Angus, 1952 ; Clemmesen, 1954) and possibly, although to a much less extent, the more judicious use of the newer central analeptics (Koppanyi and Fazekas, 1950, 1954 ; Eckenhoff et al., 1949). We wish to discuss a new method of treatment incorporating the use of two new substances, $\beta\beta$-methylethylglutarimide (NP13) and 2:4-diamino-5-phenylthiazole hydrobromide or hydrochloride (D.A.P.T.), which we feel should, when used in conjunction with good medical treatment, further reduce the death rate from this condition.

In our small series of 41 cases of pure barbiturate intoxication, of which nine were serious, there was one death, which we suggest was not due to the treatment, and we feel that the method has been promising enough to warrant further large-scale clinical trials.

The merit of the method lies in the fact that the more active agent, NP13, unlike the central analeptics in current use, appears to exert, in therapeutic doses at least, a direct antagonism to the offending barbiturate, and will readily restore the patient from a deep coma to a desired state of light anaesthesia—" the safe state "— from which spontaneous recovery to full consciousness usually occurs within eight hours. This removes the need for strict and prolonged medical and nursing care (Nilsson, 1951 ; Locket and Angus, 1952 ; Clemmesen, 1954 ; Møller, 1954) and virtually eliminates the risk of complications. The chemical structure of NP13 indicates a definite resemblance to the barbiturate ring system.

R \\C< CO—NH\ \>CO
R₁/ CO—NH/
A 5 : 5 di-substituted barbiturate

CH₃ \\C< CH₂—CO\ \>NH
CH₃CH₂/ CH₂—CO/
ββ-methylethylglutarimide (NP13)

C₆H₅—C———S
‖ ｜
NH₂—C\ /C—NH₂ . HBr (or HCl)
\N/

2 : 4-Diamino-5-phenylthiazole hydrobromide or hydrochloride (D.A.P.T.)

D.A.P.T., itself a weak barbiturate antagonist, is, however, a good synergist to NP13 as well as an excellent respiratory stimulant. It greatly reduces the risk of toxic manifestations, which sometimes occur when NP13 alone is given rapidly and in high dosage. Both substances in therapeutic doses appear to cause a slight rise in blood pressure, and a large dose (75 mg.) given intravenously to a barbiturized patient has produced a large rise in blood pressure and sweating, suggesting a direct effect on the autonomic ganglia. However, both substances, especially NP13, in high dosage, and particularly if given rapidly, will cause convulsions in both barbiturized and normal animals (Benica and Wilson, 1950 ; Shaw et al., 1954), and we have often deliberately induced convulsions in dogs several times in the course of a single experiment without the loss of an animal. However, full animal investigation (Shaw and Bentley, 1952 ; Shaw et al., 1954) has indicated that these substances possess a high therapeutic index, and no signs of toxicity have been observed with the suggested method of treatment. Investigation of the mode of excretion of NP13 and estimations of the barbiturate content of the cerebrospinal fluid, blood, and urine of our patients were carried out in collaboration with N. E. W. McCallum, Department of Pathology, University of Melbourne. Preliminary work has shown that much of the NP13 is excreted in the urine unchanged.

Method of Treatment

The treatment suggested for cases of barbiturate intoxication consists of: (1) general medical treatment ; and (2) specific treament with NP13 and D.A.P.T.

1. General Medical Treatment

As our patients were returned fairly quickly (two hours) to the " safe state " we have been able to dispense with many of the elaborate procedures employed by Nilsson et al. in their prolonged management of the comatose patient. We have found the following minimal procedures satisfactory. A laryngoscope is passed in the casualty department to assess the pharyngeal and laryngeal reflexes. If these are absent a cuffed tube is inserted, and the stomach contents are carefully aspirated if the patient is treated within 4–5 hours of ingesting the barbiturate. Gastric lavage should not be performed (Møller, 1954 ; Lancet, 1951). An antibiotic " cover " should be employed. The patient is then transferred to the ward if necessary and a clear airway and adequate oxygenation are ensured. Close watch should be kept for complications.

2. Specific Treatment with NP13 and D.A.P.T.

This should preferably be given in the ward, and an emergency tray containing, amongst other things, 2.5% thiopentone sodium should be at hand in case the patient should show any idiosyncrasy to these drugs. The two drugs are administered in physiological saline in the following dilutions: NP13 0.5% (5 mg. per ml.) and D.A.P.T. 1.5% (15 mg. per ml.).

Preparation of Solutions.—NP13 is relatively insoluble in water at neutral pH and room temperature, and 0.5% approaches the maximum degree of solubility obtaining under

these conditions. This low solubility is not a disadvantage, as it minimizes the risk of overdosage. Of the crystalline powder 2.5 g. should be dissolved in 500 ml. of physiological saline at 80°–90° C. The resulting colourless solution is autoclaved and is then ready for use. This solution appears to retain its activity for over three months.

D.A.P.T. decomposes on autoclaving when in solution, but is perfectly stable in the solid state ; consequently 300 mg. of the dry sterilized powder is dissolved in 20 ml. of physiological saline as required. The resulting colourless solution is stable at room temperature for up to 24 hours.

Mode of Administration.—Our experience to date has led us to adopt the following procedures :

Set up a 5% glucose intravenous infusion (dextran if indicated) as a means of affording rapid action of the drugs.

Inject, by two separate (20-ml.) syringes, into the rubber tubing of the drip every three to five minutes, 1 ml. D.A.P.T. solution, followed immediately by 10 ml. NP13 solution. This probably allows more control than would direct infusion of the two solutions. Decrease these quantities by half if the patient's response should cause concern. The response is assessed by the following, noted after each injection: Pulse, respirations, blood pressure, tone, reflexes (knee, ankle, plantar withdrawal ; the return of laryngeal and pharyngeal reflexes is judged by their effects on the endotracheal tube or, in its absence, by signs of swallowing and coughing) ; eye signs (movement, lacrimation, reaction of pupil to light) ; presence of voluntary movement, reaction to supraorbital pain stimulus (often misleading) ; phonation, state of peripheral circulation, colour and temperature of skin. These afford a good progress report of a patient's recovery.

Continue the injections until the patient is brought to the " safe state," denoted by a return of tone and reflexes (including pharyngeal and laryngeal). This is usually associated with groaning, voluntary movement, and return towards normal of pulse rate, respiratory rate, and blood pressure. The treatment generally takes about two hours in a deeply comatose patient. A total dose of 200 ml. (1.0 g.) NP13 solution and 20 ml. (0.3 g.) D.A.P.T. solution is usually adequate in most cases (see Tables I and II). No attempt should be made to wake the patient.

Once the " safe state " has been reached, remove the endotracheal tube and treat the patient as if recovering from light anaesthesia. Spontaneous recovery to full consciousness usually occurs within eight hours.

Signs of Toxicity

Vomiting or retching is usually the earliest, and may be the only, clinical sign of incipient toxicity. This may rarely be followed by slight flickers of the fingers. In bringing a barbiturized patient to the " safe state " toxic effects are unlikely unless the drugs are given more rapidly or in larger doses than suggested. Should they occur, however, treatment should be temporarily suspended, and, should they be severe, they may be readily reversed by a small intravenous dose of 2.5% thiopentone sodium. A more accurate indication of incipient toxicity is obtainable if the treatment is carried out under electroencephalographic control.

Regression

If after the patient has been brought to the " safe state " his condition regresses, further small treatments may be given as required (Cases 10, 12, 14, 15, 21, 24, 25, 35, 36, 39). Regression is more likely to occur when the coma has lasted a long time before treatment is started, or if the barbiturate concerned is a long-acting one (such as phenobarbitone).

Advantages

The rapid restoration of the comatose patient to the easily manageable " safe state " has three advantages: (1) It obviates the need for prolonged endotracheal intubation ; (2) it minimizes both the immediate risk to the patient's life and the remote risk associated with possible complications

of prolonged barbiturate coma ; and (3) it is valuable from the viewpoint of hospital economy in that it affords relief from prolonged and strict nursing.

Results of Treatment

Details of illustrative cases are presented in Table I, showing (a) the response to treatment with NP13 and D.A.P.T. of a patient suffering from an overdose of a short-acting barbiturate (Case 17) ; (b) the response in a patient with an overdose of a long-acting barbiturate (Case 18) ; (c) the response of a " serious case " (Cases 11 and 24) ; (d) regression (Case 24) ; and (e) the effects of NP13 overdosage (Cases 1 and 26). Table II gives a synopsis of the other cases treated.

The proportion of serious cases in our series (10, 11, 12, 15, 24, 25, 32, 35, 36) was about 25%. Eight patients (Cases 6, 7, 9, 19, 27, 30, 33, 34) presented a picture of light barbiturate coma and would probably have awakened spontaneously without specific therapy, although not nearly so quickly. We found phenobarbitone to be the most frequently ingested barbiturate, with " seconal " (quinalbarbitone), " carbrital " (phenobarbitone+carbromal), and " nembutal " (pentobarbitone) slightly less common. Our oldest patient was 84, the youngest 14. The longest periods of coma preceding treatment were 80 hours (Case 10) and 6 days (Case 32).

Nine patients were treated with NP13 alone (Cases 1–6, 8, 26, 37), and one (Case 33) with D.A.P.T. alone. Signs of overdosage were observed in four of our earliest cases (1, 2, 3, 26), and were due to administration of excessive doses of NP13 in an endeavour to restore complete consciousness immediately. The risk of overdosage was subsequently minimized by using a mixture of NP13 and D.A.P.T. and stopping when the patient had reached the " safe state."

This condition of overdosage, manifested by excessive excitement and restlessness on awaking, was effectively reversed by sedation with paraldehyde or a barbiturate such as quinalbarbitone, amylobarbitone, or diallylbarbitone. No residual effects were encountered.

Thirty patients given a mixture of NP13 and D.A.P.T. (Cases 7, 9–25, 27, 30–32, 34–41) were readily brought to the " safe state," from which they awoke spontaneously, usually within eight hours. No toxic manifestations, either acute or chronic, followed.

Ten patients (Cases 10, 12, 14, 15, 21, 24, 25, 35, 36, 39) regressed and received more than one treatment. This generally followed (a) the ingestion of a large dose of barbiturate, usually of the long-acting variety, or (b) a long delay before specific treatment was started. In Case 14 the second treatment was purely diagnostic to assess the degree of regression.

The largest effective single dose of NP13 used in one treatment was 2.0 g. (Case 8), and of D.A.P.T. 0.62 g. (Case 12). The largest effective over-all dose of NP13 used in one patient was 5.49 g., and of D.A.P.T. 1.70 g. (Case 24).

The most reliable single sign of a favourable response was the plantar withdrawal reflex, its increased activity usually paralleling the patient's progressive recovery. The fact that NP13 has some analgesic properties of its own made the response to supraorbital pressure an unreliable index of recovery.

Our experience to date indicates that treatment with NP13 and D.A.P.T. is quickly effective in reversing the most severe respiratory and circulatory depression accompanying barbiturate intoxication. Indeed, on restoring the patient to the " safe state " the blood pressure, pulse rate, and respiratory rate usually return towards normal. The respirations, previously shallow, irregular, and sometimes stridulous, assume a deep, regular, and more even character. We have had no occasion to give vasopressor agents once the specific treatment has been instituted, and we feel that these should be

TABLE I.—Reports of Selected Cases of Barbiturate Intoxication

Case No.	Age and Sex	Agent and Quantity Taken	Duration of Coma before Treatment (Hours)	State before Specific Treatment	Total Specific Treatment (Dose in Grammes)	Dose (in Grammes) Required to Produce " Safe State "	State after Treatment	Comments
17	F 40	Quinal-barbitone 2 g.	5	P. 120, R. 22, B.P. 140/90. Atonia, areflexia, no response to supraorbital pressure. Pupils sluggish to light. Moist crepitations in chest	NP13 D.A.P.T. 0·45 0·2 in 1 hour	NP13 D.A.P.T. 0·45 0·2 in 1 hour	P. 80, R. 18, B.P. 170/110. Brisk reflexes, good tone, marked reaction to painful stimulus, voluntary movement of whole body. Responds to orders; asked for a drink of water	No regression. Following morning: Feels well; rational; wants to go home; no signs of toxicity. 3rd day: Tried to walk out of hospital; restrained. 4th day: Signed herself out. Routine tests: Only abnormality low serum potassium (3·6 mEq/l.). E.E.G.: Return to normal pattern, no signs of drug toxicity
18	M 34	Pheno-barbitone 3·3 g. +alcohol	7	P. 120, R. 26, B.P. 120/80. Knee reflexes slightly active only. Ankle clonus. Atonia, pupils fixed and unreactive. No response to supraorbital pressure. Peripheral return poor, rectal temp. 95° F. (35° C.)	1·8 0·57 in 3 hours	1·8 0·57 in 3 hours	P. 132, R. 24, B.P. 125/80. Reflexes brisk, good tone, swallowing, coughing, groaning, trying to get up, obeying orders. Pupils react briskly to light. Colour and peripheral return good	No regression. Quite conscious and trying to get up. Following morning: Talking rationally though a little dull; eating. 3rd day: Well, wants to go home, asks about wife; uneventful recovery. Routine tests: No abnormality detected. E.E.G.: Within normal limits
11	F 36	Butobar-bitone 8·3 g.	17	P. 120, R. 6, B.P. 85/60. Cold and cyanosed. Atonia, areflexia, incontinent. Pupils irregular and fixed. No response to supraorbital pressure. Peripheral circulatory failure	3 doses of 9 mg. picrotoxin given ½-hourly produced transient return of reflexes 1·2 0·44 in 1¼ hours	1·2 0·44 in 1½ hours	P. 110, R. 18, B.P. 110/80. Reflexes brisk, groaning, voluntary movement of head and body, good tone, brisk pupillary light reflex	No regression. 6 hours later: Co operative, speaking, obeying orders. 2nd day: Tried to walk out of hospital; restrained. 3rd day: Discharged for psychiatric treatment. Routine tests: Only abnormality low serum potassium (3·3 mEq/l.). E.E.G.: Normal tracing on day of discharge
24	F 47	Phenobar-bitone 7 g.	30	P. 80 (weak), R. 10, B.P. 50 ?. Areflexia, atonia, fixed pupils. No response to supraorbital pressure. Cyanosed, peripheral circulatory failure, chemotic conjunctivae	(1) 0·9 0·15 in 2 hours	0·9 0·15 in 2 hours —	P. 90, R. 32, B.P. 95/60. Some reflexes present. Patient spastic. Respirations good depth and regular, full pulse	Patient returned from critical toward safe state. Regressed. Given further treatment on 2nd day (2)

TABLE I.—continued

Case No.	Age and Sex	Agent and Quantity Taken	Duration of Coma before Treatment (Hours)	State before Specific Treatment	Total Specific Treatment (Dose in Grammes) NP13 D.A.P.T.	Dose (in Grammes) Required to Produce "Safe State" NP13 D.A.P.T.	State after Treatment	Comments
24	(continued)			P. 108, R. 16, B.P. 75/50. Areflexia, atonia, fixed pupils. Slight cyanosis and poor peripheral return. No response to supra-orbital pressure	(2) 1·35 0·57 in 2½ hours	1·35 0·57 in 2½ hours	P. 108, R. 24, B.P. 90/55, T. 99° F. (37·2° C.). Reflexes present, fair tone, good plantar response. Good peripheral return. No cyanosis. Swallowing. No response to supraorbital pressure. Brisk pupillary light reflex	5 hours later: Some regression; "intra-dex" substituted for 5% glucose. 10 hours later: Developing R. basal pneumonia; T. 101·5° F. (38·6° C.). Has allergic penicillin rash. Given aureomycin. Regressed. Given further treatment (3)
				P. 128, R. 26, B.P. 80/60. Atonia, areflexia, slight pupillary reflex. No response to supra-orbital pressure. Peripheral return adequate	(3) 0·5 0·15 in 45 minutes	0·5 0·15 in 45 minutes	P. 132, R. 28, B.P. 90/60. As in (2) above. Conjunctivae still chemotic. Response to supraorbital pressure	3rd day: Again some regression. Forced cough occasionally present. Oral therapy by Ryle's tube. Right chest consolidated. Regressed again on 4th day. Given further treatment (4)
				P. 92, R. 18, B.P. 60/35. Atonia, areflexia, mildly cyanosed. Poor peripheral return. Right lung consolidated, some dullness left base	(4) 0·95 0·29 in 1½ hours	0·95 0·29 in 1½ hours	P. 96, R. 16, B.P. 110/65. Active reflexes, good tone. Swallowing, moving jaw. Colour peripheral return good. No response to supraorbital pressure	6 hours later: Slight regression, but B.P. 125/70. Regression on 5th day. Given further treatment (5)
				P. 108, R. 18, B.P. 110/65. Sluggish reflexes slight tone; pupillary reflex good. Right chest still consolidated. No response to supraorbital pressure	(5) 0·3 0·1 in 40 minutes	0·3 0·1 in 40 minutes	P. 100, R. 15, B.P. 120/75. Brisk reflexes, good tone. Definite response to supraorbital pressure, swallowing and chewing. Raising eyelids. Colour and peripheral return good	6 hours later (6th day): Some regression, but condition satisfactory; good urinary output. Given further treatment (6)
				P. 100, R. 18, B.P. 115/75. Decreased reflex response, slight tone. No response to supra-orbital pressure. Colour and peripheral return good	(6) 0·45 0·14 in 45 minutes	0·45 0·14 in 45 minutes	P. 84, R. 18, B.P. 125/65. Brisk reflexes and good tone; yawning, coughing, swallowing, moving jaw and eyelids. Groaning. Marked response to supraorbital pressure	14 hours later (7th day): Some regression, but condition satisfactory. Given further treatment (7)
				P. 108, R. 25, B.P. 115/65. Decreased tone and reflexes. No response to supraorbital pressure. Colour and peripheral return good. Right lung still fully consolidated	(7) 0·65 0·19 in 55 minutes	0·65 0·19 in 55 minutes	P. 108, R. 22, B.P. 135/75. Brisk reflexes, good tone; swallowing, coughing, moving jaw, and opening eyes. Groaning	Large quantities of barbiturate still present in urine. 15 hours later: Some regression. Given further treatment (8). Patient started menstruating. Serum electrolytes: Sodium 139 mEq/l.; potassium, 3·4 mEq/l.; proteins, 6 g. %; pH of serum —7·4. Given 8 g. KCl per day
				P. 84, R. 22, B.P. 120/65. Decreased tone and reflexes. Some response to supraorbital pressure. Colour and peripheral return good	(8) 0·25 0·08 in 30 minutes	0·25 0·08 in 30 minutes	P. 104, R. 20, B.P. 135/75. Brisk reflexes, good tone, coughing more strongly. Opening eyes and rejecting oral airway. Groans on supraorbital pressure	Pneumonia resolving; slow progress over next 2 days. Still much barbiturate in urine. Further treatment next day (9)
				P. 108, R. 16, B.P. 105/60. Decreased tone and reflexes. Groaning on supraorbital pressure	(9) 0·15 0·04 in 15 minutes	0·15 0·04 in 15 minutes	P. 112, R. 16, B.P. 120/65. Brisk reflexes, good tone. Obeying orders and trying to talk in a slurred voice; moving head and biting airway	No regression; patient talking rationally on 12th day. Very weak. Eating. No apparent residual cortical damage. Good insight into domestic problems. Chest almost clear. Slow progress and uneventful recovery
1	F 26	Cyclobarbitone 3·6 g.	2	P. 88, R. 18, B.P. 105/90. Atonia, areflexia, pupils sluggish to light, no reaction to supraorbital pressure	1·75 — in 95 minutes	0·25 0·35 in 20–30 minutes	P. 92, R. 18, B.P. 115/80. Restless, moaning, retching; brisk reflexes	Patient overdosed, required paraldehyde after 8 hours. 2nd day: Still restless and confused. 3rd day: Quieter. 4th day: Normal, no after-effects
26		Voluntary patient given 0·75 g. sodium pentobarbitone under E.E.G. control	½	P. 84, R. 12. Decreased tone, depressed reflexes, some intercostal paralysis. Slight response to supraorbital pressure	1·0 — in 30 minutes	0·3 —	Reflexes exaggerated, groaning, moving whole body and opening eyes. Flushed, vomiting. Did not wake completely	3 hours later: Flushed, irritable, dizzy, confused; rambling speech. Reflexes exaggerated, tossing in bed, slight muscular twitches of fingers, arms, and isolated facial muscles. P. 92, R. 14, B.P. 100/70. Patient presented with picture of cerebral irritation due to NP13 overdosage. Sedated with paraldehyde, "sodium amytal," and "luminal." Took 2 days to return to normal. There were no residual after-effects, but there was amnesia for the event. E.E.G.: The "spikes" indicative of incipient NP13 toxicity were initially hidden by muscle spikes and appeared only later, whereupon NP13 was stopped

TABLE II.—*Summary of Other Cases Treated*

Case No.	Age (Years) and Sex	Agent and Quantity Taken	Duration of Coma before Treatment Started (Hours)	Complications Present	Regression Present	No. of Treatments Given	Total Dose (grammes) NP13	D.A.P.T.	Comments
2	F 38	Quinalbarbitone ? dose	6	Nil	—	1	1·8 in 90 minutes	—	One of our earliest cases. Patient overdosed. At safe state with 0·5 g. Restless 3 days
3	M 54	"Sedormid" ? dose	14	,,	—	1	0·75 in 45 minutes	—	Overdosed. Safe state with 0·4 g. Restless 3 days
4	F 21	Phenobarbitone ? dose	13	,,	—	1	0·45 in 2¼ hours	—	Some regression 6 hours later, but uneventful recovery
5	F 14	Phenobarbitone ? dose (? also small amount of bromide or paraldehyde)	11	,,	—	1	0·6 in 2 hours	—	No regression or signs of toxicity. Uneventful recovery
6	F 27	"Carbrital" ? dose	9	,,	—	1	·1·7 in 1½ hours	—	Awake 1 hour later. Uneventful recovery
7	F 44	Quinalbarbitone 1·6 g.	7	,,	—	1	0·43 in 2 hours	0·1	No signs of toxicity. E.E.G. 3 days later, normal rhythm
8	M 28	Phenobarbitone ? dose	?	,,	—	1	2·0 in 50 minutes	—	Completely conscious after 2 days. Uneventful recovery. Some signs of toxicity due to rapid administration
9	F 32	"Carbrital" (pentobarbitone sodium 1 g., carbromal 2·7 g.)	4	,,	—	1	0·3 in 25 minutes	0·18	Well next day. No signs of toxicity
10	F 49	"Carbrital" and phenobarbitone ? dose	80	Bronchopneumonia and peripheral circulatory failure	Yes	2	0·9	0·5	2nd day co-operative; 5 days later approaching normal
12	M 84	?	?	Bronchopneumonia	,,	2	2·1	0·77	Conscious 2nd day, talking 3rd day, normal 5th day
13	F 28	Bromvaletonum 20 g.	12	Nil	—	1	0·7 in 1½ hours	0·3	Uneventful recovery next day
14	M 42	"Carbrital" (pentobarbitone sodium 3 g., carbromal 8 g.). Phenobarbitone ? dose	12	,,	Yes	2	0·4	0·57	Uneventful recovery
15	F 49	Phenobarbitone 5 g.	12	Peripheral circulatory failure	,,	4	1·55	0·63	Patient took 5 days to return to normal. No after-effects
16	F 23	Quinalbarbitone 2·5 g. Amylobarbitone 2·5 g.	?	Nil	—	1	0·8 in 2 hours	0·3	Well next day. Uneventful recovery
19	M 25	"Carbrital" (pentobarbitone sodium 3 g., carbromal 8 g.)	13	,,	—	1	0·4 in 40 minutes	0·12	,, ,, ,, ,, ,,
20	F 46	Butobarbitone 2–4 g.	14	,,	—	1	0·25 in 30 minutes	0·1	,, ,, ,, ,, ,,
21	F 50	Phenobarbitone 6·5 g.	3	,,	Yes	3	0·85	0·45	Patient took 5 days to return to normal. No after-effects
22	F 22	"Carbrital" (pentobarbitone sodium 1 g., carbromal 3 g.)	8	,,	—	1	0·6 in 1½ hours	0·18	Well next day. Uneventful recovery
23	F 28	"Carbrital" (pentobarbitone sodium 2 g., carbromal 5·6 g.)	3	,,	—	1	0·5 in 1½ hours	0·17	,, ,, ,, ,, ,,
25	M 57	Phenobarbitone 3 g.	30	Peripheral circulatory failure. On noradrenaline drip	Yes	4	1·85	0·63	Conscious after 5 days. Slow subsequent uneventful recovery
27	M 50	Given phenobarbitone sodium 1·4 g. in an attempt to control hiccup over 5 days	—	—	—	1	0·13 in 20 minutes	0·1	Patient initially drowsy, quickly recovered. Subsequent regression, return of hiccups
30	M 53	Pentobarbitone sodium 2·5 g.	7	Nil	—	1	0·3 in 45 minutes	0·1	Uneventful quick recovery
31	F 54	"Carbrital" (pentobarbitone sodium 2 g., carbromal 5·5 g.)	10	,,	—	1	0·5 in 1½ hours	0·15	Quick response, uneventful recovery
32	F 64	Phenobarbitone ? dose	6 days	Early pneumonia	—	1	0·2 in 20 minutes	0·08	Patient not very deep; quick response. Took 3–4 days for full recovery
33	F 38	Quinalbarbitone sodium 3 g. Amylobarbitone sodium ? dose	12	Nil	—	1	— over 30 minutes	0·18	Patient in light coma at start of treatment. Quick response; no regression; uneventful recovery
34	M 36	Pentobarbitone sodium ? dose	14	,,	—	1	0·15 over 15 minutes	0·05	Patient bright when treatment started. Quick response, uneventful recovery
35	M 65	Phenobarbitone 6 g.	Over 24	Early bronchopneumonia and peripheral circulatory failure	Yes	2	0·95	0·3	Very ill. Good response to safe state with 1st treatment. Regressed. Not fully recovered for 5 days
36	M 57	Phenobarbitone 3 g.	30	Peripheral circulatory failure. Put on noradrenaline drip before specific treatment started	,,	4	0·9	0·33	Very ill. Initial response good, but regressed. Not fully recovered for 5 days
37	F 45	"Carbrital" (pentobarbitone sodium 1·5 g., carbromal 3·5 g.)	6	Nil	—	1	0·25 in 30 minutes	—	In deep coma on admission. Recovered suddenly; sat up and talked. No regression; uneventful recovery
38	M 33	Pentobarbitone sodium ? dose	About 12	,,	—	1	0·23 in 35 minutes	0·24	Quick response, uneventful recovery
39	F 66	Phenobarbitone ? dose	12–18	,,	Yes	3	3·0	0·69	Patient in deep coma on admission. Regressed. Not fully recovered for 7 days
40	M 56	"Sedormid" ? dose	About 6	,,	—	1	0·65 in 40 minutes	0·15	Suddenly recovered. Confused and restless. Uneventful recovery
41	F 46	Pentobarbitone sodium 5 g.	17	Peripheral circulatory failure	—	1	0·2 (given ammonium ββ-methylethylglutaric acid 0·7 g. over 3 hours initially)	0·3	The ammonium salt afforded some lightening of the coma, but gave rise to symptoms of cerebral irritation. Subsequent NP13 gave rapid, uneventful recovery
29	F 61	"Carbrital" (pentobarbitone sodium 5 g., carbromal 12 g.)	12	Nil	Yes	2	1·0 Over 3 hours	0·3	The only fatality in the series. See text for case report

used only as supportive measures during the initial acute phase of the coma pending the start of treatment.

NP13 has been used to advantage as an aid in the differential diagnosis of cerebrovascular accident and barbiturate intoxication in a patient whose condition was rapidly deteriorating and in whom no localizing signs were present (Case 28).

Control electroencephalograms (E.E.G.s) were taken in three patients (Cases 11, 15, 22) and one volunteer (Case 26). In ten other cases (7, 10, 16–23) recordings were made at the end of treatment. The volunteer was given an overdose of NP13 in an endeavour to effect immediate and complete awakening, and the E.E.G. showed the characteristic spikes of cerebral irritation. The remaining patients all received a mixture of NP13 and D.A.P.T. In the cases under E.E.G. control treatment was stopped either before, or as soon as, there was any suggestion of sharp wave activity. All records taken after termination of therapy showed varying degrees of abnormality indicated by slow or increased low-voltage fast activity. Serial records revealed a gradual disappearance of these abnormalities. Complete clinical recovery was usually apparent for some time before the E.E.G. pattern became normal, especially in patients who had taken long-acting barbiturates.

Routine investigations were carried out in 14 cases (10, 11, 12, 14–23, 25) during the week following recovery. These included tests of renal and liver function, full blood count, naked-eye and microscopical examination of cerebrospinal fluid, electrocardiography, and estimation of serum electrolyte balance. The only abnormality detected in seven cases (11, 15–17, 20–22) was a low serum potassium value of the order of 3.5 mEq per litre. This was occasionally accompanied by a concomitant imbalance of the other ions.

Case 24 deserves special mention. This patient (probably the most seriously ill patient in our series) was comatose for ten days, and during this period was given nine consecutive treatments with NP13 and D.A.P.T., with eventual restoration to full consciousness. Her subsequent rehabilitation was slow and uneventful. We followed this procedure as we felt that the patient's severe and prolonged coma was in part due to a secondary cerebral hypoxia of hypotensive origin superimposed on the primary barbiturate hypoxia. We were therefore disinclined to give more than minimally adequate doses of NP13 and D.A.P.T. (to maintain the "safe state"), to avoid the risk of excessively stimulating an already overburdened nervous apparatus and mechanism. An adequate blood pressure and high renal output were maintained throughout. Large quantities of barbiturate were still being excreted in the urine seven or eight days after the coma began.

One patient (Case 29) died, but death was not thought to be due to the specific treatment. Details of this case follow.

Report of a Fatal Case

A woman aged 61 took 50 "carbrital" capsules (containing 5 g. pentobarbitone sodium and 12 g. carbromal) about 12 hours before treatment was instituted. On admission: pulse rate 72 per minute; shallow, irregular respirations (rate 32 per minute); blood pressure 120/70 mm. Hg. No reflexes could be elicited. She was atonic, hypothermic (temperature 95° F.—35° C.), and unresponsive to painful stimuli, with unreactive pupils and a poor peripheral return. She was given 1 g. NP13 and 0.3 g. D.A.P.T. in two treatments over three hours. There was a rapid return of reflexes and some response to painful stimuli, but facial twitches suddenly developed and there were signs of respiratory depression. The twitching was quickly controlled with thiopentone sodium; the patient was intubated and artificial respiration started. Owing to a fault in the circuit the patient rebreathed air with a high CO_2 content for several hours before it was discovered. When, eight hours later, in an attempt to promote normal respiration, a small dose of D.A.P.T. (60 mg.) was given in divided doses over 12 minutes, the patient had a unilateral left-sided epileptiform convulsion which 0.4 g. thiopentone sodium failed to

control. Lumbar puncture gave a blood-stained cerebrospinal fluid with a protein content of 1,600 mg. per 100 ml. and showing xanthochromia on sedimentation of the red cells. There were no localizing signs of a cerebro-vascular episode.

In spite of prolonged artificial respiration following tracheotomy and the administration of a continuous noradrenaline drip, the blood pressure progressively fell and the patient died.

Significant Post-mortem Findings.—The skull was normal. The arteries to the brain were well preserved and showed minimal atheroma. In the middle cranial fossa there was a little brownish-yellow staining of the dura. Over the parietal surface of the left cerebral hemisphere there was a very small localized area of subarachnoid bleeding, not sufficiently marked to lift the membrane off the brain; there was also a very small amount of subdural bleeding in this area. The brain did not show evidence of compression; it was symmetrical and the convolutions appeared normal. On routine serial section of the substance of the brain no naked-eye abnormality was detected. There was no bruising or evidence of injury on the scalp. The coronary vessels showed marked thickening and calcification. The heart was a little enlarged. No infarction or scarring was visible in the heart wall. There was patchy atheroma of the aorta. Both lungs showed extensive consolidation and waterlogging. The liver and kidney contained ¼ gr. of carbromal and 1/10 gr. of pentobarbitone per lb. (124 and 14 mg. per kg.).

Discussion

There are at present two schools of thought as to the treatment of acute barbiturate intoxication. Both agree that the basis of good management is thorough and intelligent medical care. They are, however, at variance regarding the concomitant use of central analeptics, of which only picrotoxin, leptazol, "geastimol," and occasionally amphetamine and nikethamide are in present-day use.

The conservative school is led by Nilsson, who regards acute barbiturate intoxication as "an anaesthesia which is drawn out to last for days instead of lasting, like a common so-called surgical anaesthesia, for at most a few hours," and who therefore treats the condition "in accordance with anaesthesiological principles." Nilsson (mortality rate 2–3%), Locket and Angus (mortality rate 3–4%), and Clemmesen (mortality rate 1.6%) relied solely on a carefully planned medical regimen. None used central analeptics, and indeed all stressed the dangers involved in their use. Their excellent results afford strong support for their expectant routine of treatment.

This mode of management has been criticized by the protagonists of the analeptic school of treatment led by Koppanyi and Fazekas (1952), who insist that there is still a definite place for central analeptics, especially in cases of severe barbiturate·intoxication.

In the absence of adequate information concerning the mode of action of central analeptics (Eckenhoff *et al.,* 1949), and in the presence of many animal experiments (Maloney, 1935, 1936; Mousel and Essex, 1941; Schmidt, 1945; Davis *et al.,* 1944) and clinical data (Nilsson, 1951; Locket and Angus, 1952; Clemmesen, 1954) indicating the dangers involved in their use, we find ourselves drawn more closely to the conservative school of treatment led by Nilsson. There appear to be, however, two disadvantages to this conservative management. (1) One can never be sure, with a patient in deep barbiturate coma, if and when he will regain consciousness, and if and when complications which could alter the whole outlook of the case will develop. Naturally, the more prolonged the coma the greater would be the risk of this occurring, despite the most scrupulous medical care. (2) The management of a case of prolonged barbiturate coma presents a serious problem in a busy overcrowded hospital. Our new method of treatment helps by bringing such a patient in two hours to a desired state of light anaesthesia—the "safe state"—from which