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TREATMENT OF BARBITURATE POISONING*

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BARBITURATES vary in their speed of absorption and in their duration and intensity of effect. Their stability in vivo depends upon their chemical structure and there are two ways in which they can be eliminated by the body.

Short-acting compounds, such as quinalbarbitone, are rapidly and almost completely destroyed in the tissues, the liver being the main site of their degradation by a process of side chain oxidation.

The more stable barbiturates, such as barbitone, depend mainly on excretion through the kidneys for their elimination from the body.

The barbiturates in common use may be classified, as follows, according to their duration of action:

Long-acting:	Phenobarbitone Barbitone
Intermediate:	Butobarbitone Amylobarbitone
Short-acting:	Cyclobarbitone Quinalbarbitone Pentobarbitone Tuinal

They are produced in large and increasing quantities for medical use. The output in 1950 was about four times that in 1938 and the quantity prescribed in the general practitioner service has risen to almost fifty tons in a year.

Barbiturates are potentially dangerous drugs, because of their ability to produce habituation and addiction, but there seems little restriction on their extensive use in medical practice. In recent years the vast amounts of these drugs readily available to the public have resulted in a disquieting rise in the number of deaths from taking an overdose of them.

Figure 1 shows the annual deaths due to barbiturate poisoning from 1939 to 1956.

There has been, in the last 10 years especially, a marked rise in the number of suicidal deaths from barbiturate overdose and it must be emphasized that this has occurred without a concomitant rise in the suicide rate as a whole.

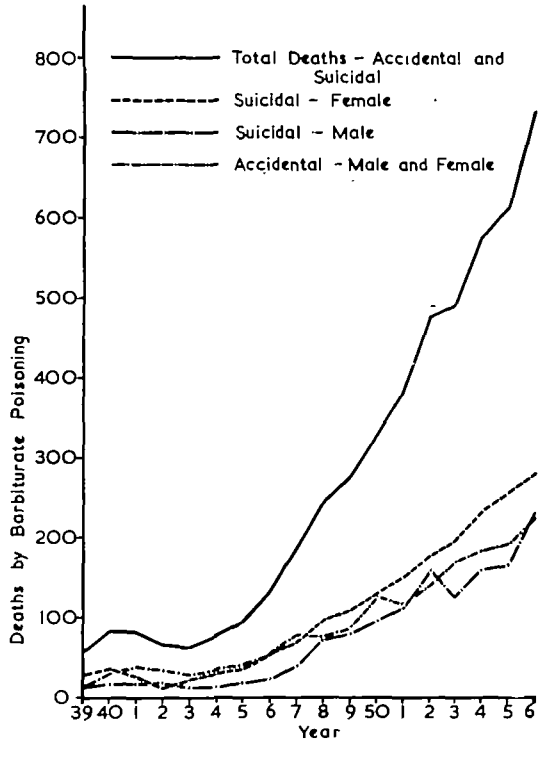

FIG. 1

Accidental, suicidal and total deaths by barbiturate poisoning, 1939–56. (*Registrar-General's Statistical Review of England and Wales.*)

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The fatal dose of barbiturates is dependent upon many factors, but there is a serious risk to life after taking fifteen times the ordinary therapeutic dose.

BLOOD BARBITURATE LEVELS

These have been investigated by Broughton and others (1956), who showed that with the long-acting barbiturates the blood levels were higher and the rates of fall slower than those of the short-acting ones.

They found that the mean levels for the return of consciousness were:

Long-acting	7 mg/100 ml
Intermediate	3 mg/100 ml
Short-acting	1–2 mg/100 ml

As a qualitative test the estimation of blood barbiturate levels helps to elucidate the aetiology of undiagnosed cases of coma and, by serial estimations, it enables the clearance of the barbiturate from the blood to be followed.

Despite the development of this valuable technique, care must be exercised in interpreting the results.

Individual variation or the development of tolerance to the drug may influence the degree of depression produced at any given blood barbiturate level, as is demonstrated by figure 2. A chronic alcoholic regularly taking barbiturates was admitted in deep coma, having taken 6 grams of cyclobarbitone 12 hours beforehand, and was found to have a blood level of 10.0 mg/100 ml. In spite of this very high figure for a short-acting barbiturate, adequate ventilation was being maintained and there was no evidence of depression of the cardiovascular system. With the attainment of full consciousness 18 hours after admission the blood level was still 3 mg/100 ml.

In lethal doses the short-acting barbiturates, such as quinalbarbitone and pentobarbitone, produce a profound narcosis and death from respiratory paralysis within 20–30 minutes.

The longer-acting barbiturates result in a lower grade of narcosis, which is liable to terminate in bronchopneumonia.

METHODS OF TREATMENT

Analeptics.

During the 1930s reports were published on the action of nikethamide in antagonizing brome-

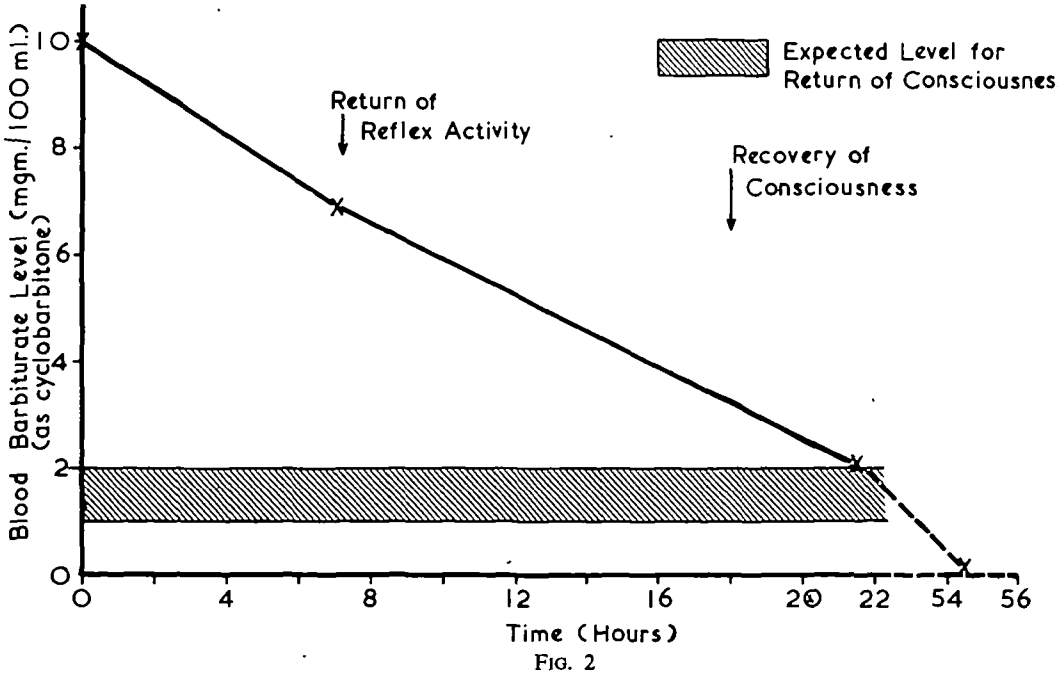

FIG. 2

Fall in blood barbiturate level following overdose of cyclobarbitone (6 grams) 12 hours before admission. (Female—60 years)

thol anaesthesia and the effects of a new convulsant drug, picrotoxin, were described by Maloney and others (1931).

In 1936 Grabfield recommended nikethamide and especially picrotoxin in the treatment of attempted suicide from barbiturate overdose. The repeated injections of large doses of analeptics became established as the most important factor in the treatment of barbiturate poisoning, with supporting measures playing a secondary role. The most commonly used drugs were picrotoxin, leptazol and nikethamide.

In spite of the widespread use of analeptics and the advantages claimed by the protagonists of this form of therapy, the mortality in severe cases remained at about 20 per cent during the period 1930–50. In 1945 Schmidt published the results of experiments performed on monkeys, anaesthetized with barbiturates. After the administration of convulsive doses of analeptics, he demonstrated a marked rise in cerebral blood flow and oxygen consumption, but this was followed by a prolonged period of depressed cerebral activity and oxygen uptake.

An analogous situation exists in the brain of a patient suffering from barbiturate poisoning, and it would be anticipated that the increased activity and oxygen requirements induced by the use of analeptics would lead to further cerebral depression. Of recent years the weight of opinion has been against their use, especially following the publication of a classic paper by Nilsson (1951). Using a conservative, nonstimulating type of treatment, he obtained a statistically significant improvement in the results of treatment over previously published figures, with a mortality rate of 2.3 per cent in a series of 176 cases.

The complications caused by the excessive use of analeptics include convulsions, vomiting (with an aspiration hazard) and cardiac arrhythmias. A deeply depressed patient can be kept alive only by the delivery of oxygen to his vital organs, especially the brain, and the failure of such cases to respond to analeptics is indicative of the extent to which the central nervous system is depressed.

Succinate.

The use of succinate was introduced following reports that brain tissue in vitro, depressed by barbiturates, could utilize succinate in its metabolism but not glucose, lactate and pyruvate.

The clinical and experimental results, however, have been disappointing, as usually improvement occurs only at light levels of narcosis (Wyke, 1957). Moreover, it has been shown that any effect produced is only indirectly due to the succinate, the immediate cause being changes in the ratio of ionized and un-ionized calcium in the blood, and this method of treatment has fallen largely into disuse.

Bemegride and Amiphenazole.

In 1954 Shulman and Shaw reported on the use of these two new barbiturate antagonists in reversing pentobarbitone narcosis in animals. Shulman and others (1955) subsequently reported on the treatment of barbiturate intoxication with these drugs in 41 cases, with one death.

In the treatment of barbiturate poisoning intravenous injections of bemegride and amiphenazole are made every few minutes until the so-called "safe" state is reached, as shown by the return of muscle tone and reflexes, together with voluntary movement and improvement in the blood pressure and respiration. The toxic signs of these drugs are vomiting, flickering of the fingers and finally convulsions, the e.e.g. showing the characteristic spikes of cerebral irritation.

The authors claim that, using this form of treatment, the immediate risk to life is minimized, complications ensuing from prolonged coma are reduced, and there is economy in the nursing care required in such cases.

Louw and Sonne (1956), in a series of 24 patients treated with bemegride, found it to have a marked effect on both respiration and reflex activity, but it did not influence the rate at which barbiturates were eliminated, the blood barbiturate level on waking, or the duration of coma. They concluded that the actions of bemegride could be explained more readily on the assumption of a central stimulant action, rather than action as a true biochemical antagonist of barbiturates.

Clemmesen (1956) treated 70 cases of barbiturate poisoning, including 7 with complete apnoea, and found that respiration recommenced and was restored to normal during or shortly after a course of bemegride and amiphenazole.

Case Record 1.

Figure 3 represents the course of a woman aged 59, who was admitted to hospital shortly after taking 8 grams of Tuinal. Tidal volume has been charted as a percentage of the optimal value, as calculated from the Radford nomogram (Radford et al., 1954) and a correction has also been made for the reduced dead-space due to the presence of an endotracheal tube.

Shortly after reaching hospital this patient became apnoeic, her pulse impalpable and blood pressure unrecordable. She was intubated with a cuffed endotracheal tube and her circulatory depression was combated effectively with 30 mg of methylamphetamine. Ventilation was maintained by using an intermittent positive pressure respirator adjusted to give her optimal tidal volume, as calculated from the nomogram.

Four hours after admission a course of bemegride 1.1 grams and amiphenazole 330 mg was administered over the course of 3½ hours. This failed to re-establish spontaneous respiration or, indeed, produce any evident response such as a return of reflexes or a rise of blood pressure. Fifteen hours after admission spontaneous respiration recommenced, but it was considered inadequate to prevent carbon dioxide accumulation and artificial respiration was continued until 27 hours after admission, when her tidal volume was 85 per cent of the optimal. A further course of bemegride and amiphenazole was given shortly after this, at a time when the level of narcosis was lightening, as shown by the return of spontaneous respiration and a cough reflex when tracheobronchial toilet was performed.

This course was accompanied by a rapid return of reflexes and a marked improvement in respiratory activity, the minute volume rising from 2.3 litres to 4.2 litres. The improvement shown in figure 3 is only 20 per cent, for a correction has been made for the hypothermia which existed before commencing the course of treatment. The temperature rose from 91° to 98°F over a period of 5½ hours, coinciding with the course of bemegride and amiphenazole and probably due to increased metabolism and a return of muscle tone.

The actual improvement in respiration accompanying such a rise in temperature obviously will not be as great as clinical observation or measurement of tidal volume would lead one to suppose, because of the increased metabolism which must be sustained at the higher temperature.

This sequence of events has been observed on several occasions when bemegride has been used in the presence of hypothermia and it may account in part for its reputation for improving respiration.

Case Record 2.

Figure 4 is a record of the progress of a man aged 35, admitted about 5 hours after taking 25 tablets of butobarbitone.

Gastric lavage was performed and he was intubated with a cuffed endotracheal tube, but the depth of coma increased and 4 hours later his tidal volume was only 50 per cent of the optimal, with evidence of carbon dioxide accumulation. Artificial respiration was com-

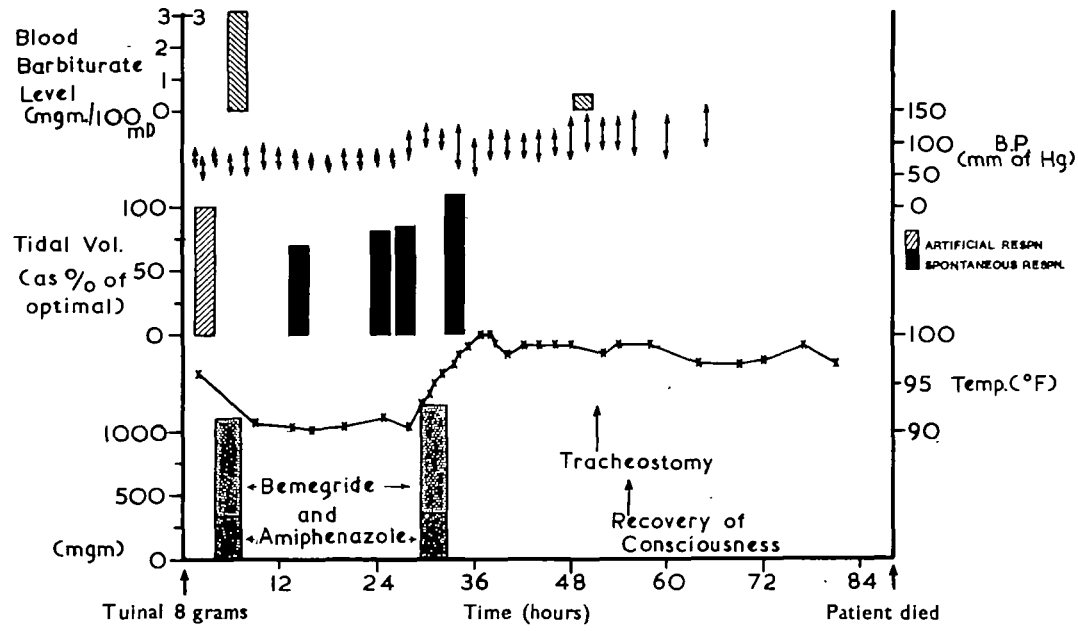

FIG. 3

Woman, aged 59, following overdose of Tuinal.

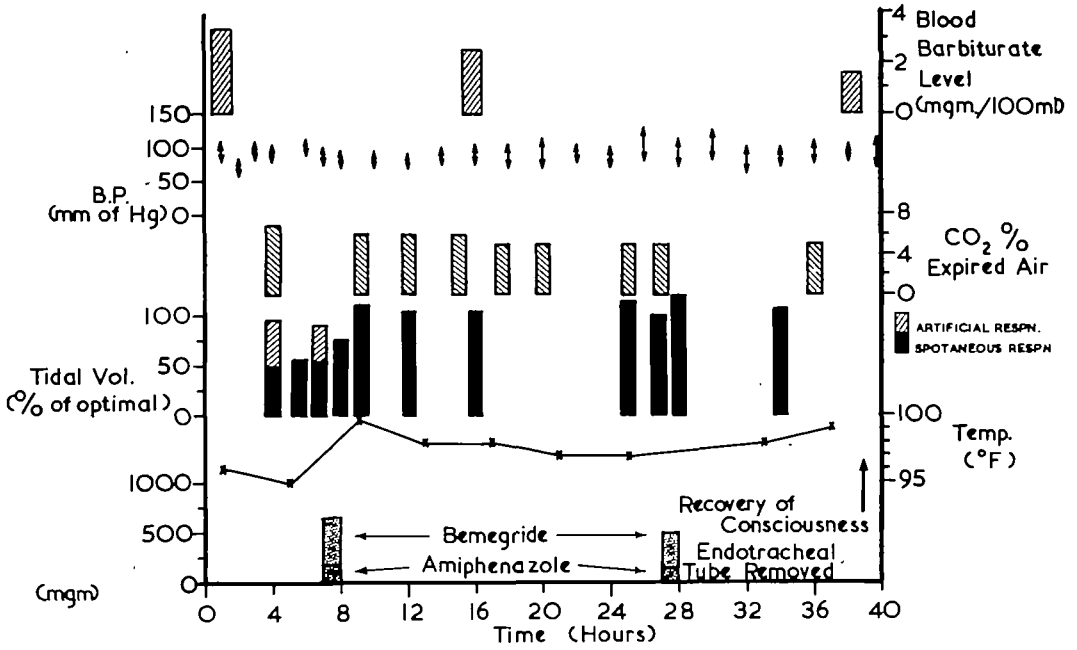

FIG. 4
Male, aged 35, following overdose of 25 tablets of butobarbitone.

menced with an intermittent positive pressure respirator adjusted to give his optimal tidal volume.

Following a course of bemegride 650 mg, and amiphenazole 195 mg, which had to be stopped because of the onset of generalized twitchings and tremors, the tidal volume rose by 50 per cent over a period of 2½ hours.

This case also demonstrated a rise in temperature from 95° to 100°F during the course of treatment. Reflexes became hyperactive and he coughed when the endotracheal tube was disturbed.

Subsequently respiration remained adequate and the carbon dioxide percentage fell to normal limits.

A second course of bemegride and amiphenazole did not produce any alteration in his condition, and he recovered consciousness 39 hours after admission with a blood barbiturate level of 1.6 mg/100 ml.

It is difficult to assess the true position of bemegride in therapy, but from these reports it can be concluded that it is not the complete answer to the problem of barbiturate poisoning.

It does not appear to act as a true antagonist, but rather by a central stimulant action.

Little improvement can be anticipated when it is used in the presence of deep coma, for the results achieved seem to be inversely proportional to the degree of depression present.

It is a useful adjunct to other methods of treatment, especially for its stimulant action on respiration, but in severe barbiturate poisoning it can play only a subordinate role to the maintenance of an adequate blood pressure and respiratory exchange.

Physiological Methods.

General measures. The following scheme of treatment is based mainly on the methods of Plum and Swanson (1957), who have published the results of a series of 243 cases, with a mortality of 1.6 per cent.

Gastric lavage is performed on those patients who have taken the drug within the previous 6 hours. A cuffed endotracheal tube will guard against flooding of the tracheobronchial tree during this measure.

The patients are nursed on their side, with a head-down tilt, and are turned from side to side every 2 hours.

All patients in coma are placed on prophylactic penicillin therapy and the bladder is emptied periodically through an indwelling catheter.

Regular records are made of respiration, blood pressure, pulse, temperature, the reflexes present and urinary output

Patients in prolonged coma require parenteral fluid therapy and fluid balance is controlled by serial estimation of serum electrolytes.

Circulatory depression, with a fall in blood pressure to 80 mm Hg or less, is treated by injecting vasopressor agents such as ephedrine and methylamphetamine, while the more intractable cases may require phenylephrine, noradrenaline or even blood or dextran. Maintenance of the blood pressure at this level helps to sustain urinary secretion and also acts as a prophylaxis against cardiac arrhythmias.

Management of respiration. In the presence of respiratory obstruction which does not disappear with an oral airway, or in deep coma with absent laryngeal and pharyngeal reflexes, the patient is intubated with a cuffed endotracheal tube.

The mouth and pharynx are kept clear of mucus and saliva by frequent suction, while those cases with an endotracheal tube in situ must have tracheobronchial toilet performed when necessary, for secretions readily collect in the lower respiratory passages. Collapse of a lobe by a plug of mucus may necessitate bronchoscopy.

The value of artificial respiration has become increasingly recognized in the treatment of barbiturate poisoning for, in addition to complete apnoea, it may be required for shallow respiration. The assessment of its need, however, is made difficult by the reduced metabolism in the presence of hypothermia.

Measurement of the oxygen and carbon dioxide tensions in arterial blood would provide the answer, but is impracticable for general clinical use. A simpler way is to find the carbon dioxide tension of alveolar air, which ordinarily is the same as that of arterial blood. Samples of end expired air have a carbon dioxide tension close to that of alveolar air, but difficulty is experienced with this technique when respirations are shallow. Reventilation of expired air by the technique originally described by Plesch (1909) and more recently by Scurr (1956) gives consistent sampling values for carbon dioxide, which are of use in the assessment of ventilation.

Care is required in the use of oxygen therapy, for it does not aid the elimination of carbon dioxide and with a deeply depressed respiratory centre removal of the stimulus of hypoxia may result in complete apnoea.

Artificial respiration with intermittent positive pressure respirators and the indications for tracheostomy. In recent years tracheostomy has been performed on an increasing scale to provide a route through which artificial respiration can be provided for certain types of cases, including barbiturate poisoning, over a varying and often prolonged period (Nelson et al., 1957).

It is necessary to provide a clear airway and at the same time ready access to the tracheobronchial tree, so that accumulated secretions can be removed. Provision must also be made to guard against the ingress of salivary secretions and vomitus.

Initially these criteria can be met by a cuffed endotracheal tube, but the duration for which this can be left in situ is governed by the development of laryngeal oedema and ulceration of the cords and mucosa. The maximum safe period is thought to be about 48 hours. After this interval there is danger of complete respiratory obstruction from laryngeal oedema when the tube is removed.

Therefore, if the patient is still incapable of guarding his own airway after 48 hours, tracheostomy should be performed, although most cases will have attained adequate spontaneous respiration.

Briggs (1950), however, has reported a case in which an endotracheal tube was left in place for 42 days in a case of acute infectious polyneuritis. It must be emphasized that the percentage of barbiturate poisonings of such severity as to require tracheostomy and artificial respiration is very small.

The usual practice in America is to nurse the patient in a tank respirator. In this country, however, the use of an intermittent positive pressure respirator with a specially designed cuffed rubber tracheostomy tube has found more favour, the advantages being that the patient is readily accessible for nursing care, physiotherapy and frequent turning. The cuffed tube, moreover, provides an absolute barrier against the inhalation of material from the pharynx.

In order to ensure correct ventilation, more attention is being paid to the measurement of tidal volume with a spirometer or dry gas meter, and a nomogram (fig. 5) has been devised by Radford and others (1954) for estimating the expected optimal tidal volume for patients of different ages and weights, with correction for fever and the presence of a tracheostomy.

To assess spontaneous breathing, while artificial respiration is being employed, a period of apnoea must be permitted at regular intervals to allow sufficient carbon dioxide to accumulate to restart respiration. Use of the respirator is discontinued only when the tidal volume reaches the optimal level for the patient.

Positive pressure respirators, together with cabinet respirators, have the disadvantage that venous return is impaired during the inspiratory phase, resulting in a rise in central venous pressure and a fall in cardiac output. To counteract this undesirable tendency, inflation pressures should not be allowed to exceed 15–20 cm H_2O and the pressure curve should fall rapidly to that of the atmosphere at the end of each inflation of the lungs. The effect can be lessened by arranging a negative phase for part of the respiratory cycle, but in practice little advantage seems to accrue from having this additional refinement in the respirator.

Another complication arising from the use of a

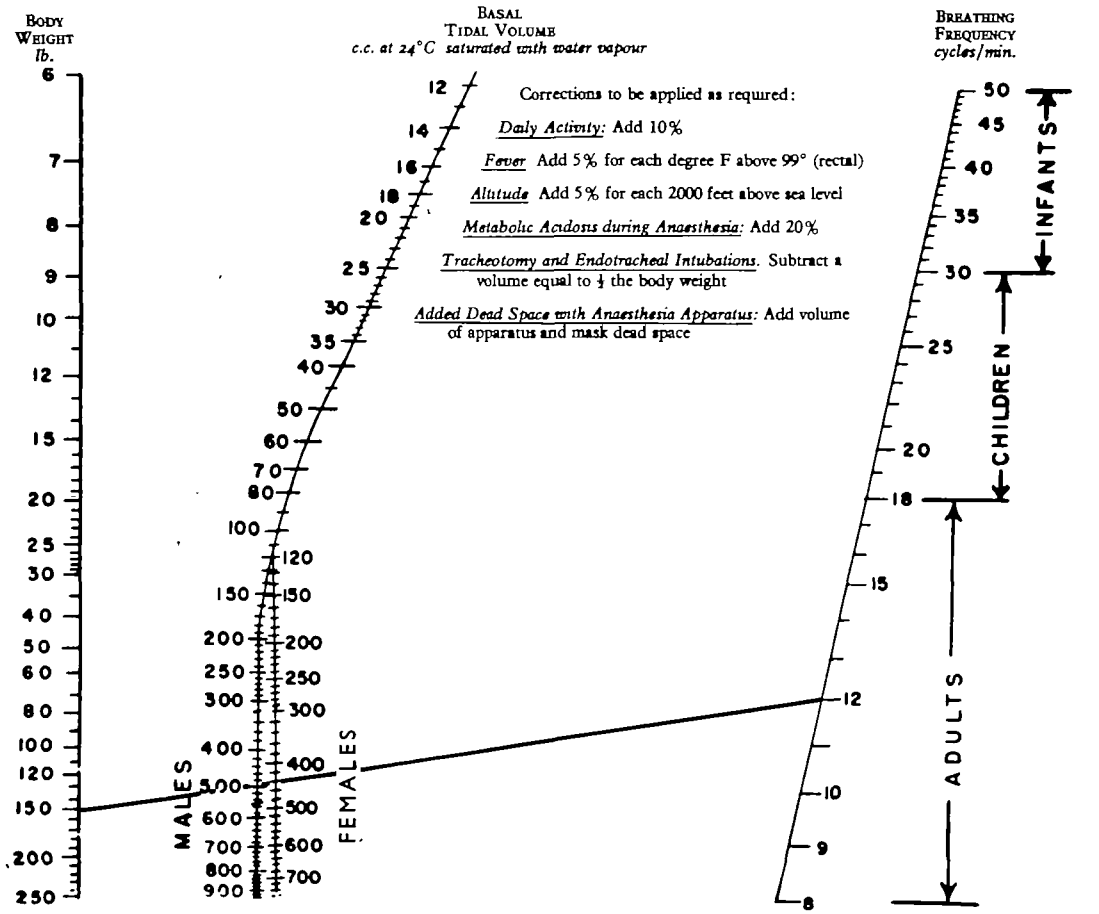

FIG. 5
Nomogram for predicting the optimum tidal volume from the breathing frequency, body weight and sex of the patient.
(Reproduced by kind permission of the Authors and the Editor of the *New England Journal of Medicine*.)

positive pressure respirator is the occurrence of extreme drying and crusting of bronchial secretions, but this may be prevented by adequately humidifying the inspired air. Special emphasis must be placed on preventing blockage of the tracheostomy tube from encrustation or a plug of mucus. The patient previously mentioned (fig. 3), who had been brought from deep barbiturate coma to consciousness, died from this cause 60 hours after the cessation of intermittent positive pressure respiration.

Figure 6 is a photograph of an endotracheal tube which was left in position for about 24 hours

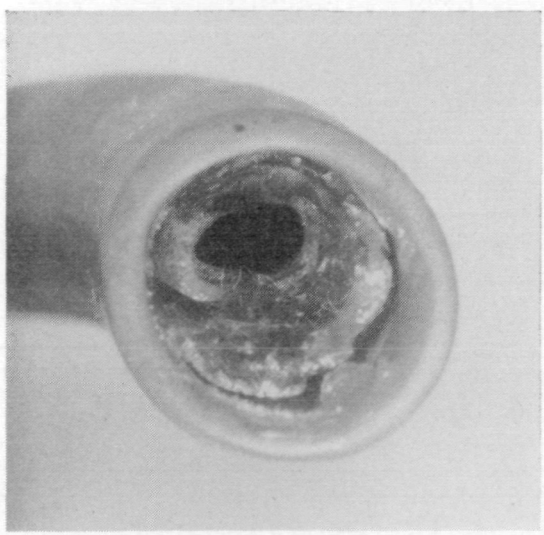

FIG. 6
Partial occlusion of the lumen of an endotracheal tube by dried, inspissated secretions.

postoperatively in a patient with a scabbard trachea and demonstrates the occlusion of its lumen by dried inspissated secretions. As can be seen, the occlusion was almost complete and the secretions had become so hard that they could not be removed by suction. An identical sequence of events and end result can occur when an endotracheal tube, or cuffed rubber tracheostomy tube, is used in cases of barbiturate poisoning.

Tracheobronchial toilet must be performed regularly and with the utmost thoroughness, especially after artificial respiration has been stopped and the air is no longer being humidified.

The replacement of the cuffed rubber tube by the more usual metal type, with a removal inner tube, is the most effective prophylaxis against excessive crust formation, but a certain interval must elapse before it can be certain that there is unlikely to be need for further artificial respiration.

During this period the inspired air may be humidified intermittently with Alevaire or even water by using a nebulizer. The vapour is delivered to the tracheostomy tube through a catheter.

Haemodialysis.

None of the methods so far described increases the rate of elimination of barbiturate from the body, yet this would appear to be the most rational approach to the treatment of this condition.

Using haemodialysis, 40 per cent of a dose of phenobarbitone in dogs can be recovered.

Berman and his colleagues (1956) have treated 8 cases of barbiturate poisoning by haemodialysis with an artificial kidney and have recovered up to 37 per cent of the dose of drug taken.

The rate of removal is dependent on the concentration gradient of barbiturate between the blood and the bath fluid. The greatest recovery is obtained, therefore, in deeply comatose patients with high blood barbiturate levels.

This procedure involves considerable technical difficulties and cannot be set up quickly. It cannot replace maintenance of respiration and the circulation, but it does pave the way for future developments in treatment, especially for prolonged coma due to long-acting barbiturates.

Electrical Stimulation.

Nonconvulsive electrical stimulation has been used since 1950 in cases of barbiturate poisoning to stimulate respiration and the circulation. Deeply comatose patients fail to respond to this measure and it is no substitute for the physiological methods previously advocated.

CONCLUSION

The results obtained in the treatment of cases of severe barbiturate poisoning depend in the ultimate analysis on the experience of the medical and nursing staff treating them. The principles of treatment are becoming more clearly defined, but

the number of cases seen annually in even a large hospital is limited.

The hour-to-hour medical supervision required is made difficult often by the calls of routine work and great reliance must be placed on the nursing staff, who need to have special experience of managing this type of case.

The physician, ear-nose-and-throat surgeon, and anaesthetist must work in close collaboration. The anaesthetist, by virtue of his special experience in the care of the air passages and maintenance of the failing circulation, has a very important part to play in therapy, but the ultimate responsibility for treatment rests with the physician.

In large centres of population the setting up of special units for treating cases of barbiturate poisoning, as has been done in Scandinavia, would help in reducing the mortality to the unavoidable minimum.

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