THE USES AND DANGERS OF HYPNOTIC DRUGS OTHER THAN ALKALOIDS

BY

SIR WILLIAM WILLCOX, K.C.I.E., C.B., C.M.G., M.D., F.R.C.P.

PHYSICIAN TO ST. MARY'S HOSPITAL

In July, 1913, I had the privilege of opening a discussion at the Annual Meeting of the British Medical Association at Brighton, in the Section of Pharmacology and Therapeutics, on "The Use and Abuse of Hypnotics." Sir Maurice Craig participated with me on that occasion, dealing with the subject from the aspect of psychiatry. It is appropriate that on the present occasion the same subject should be discussed by the Royal Society of Medicine by the Section of Therapeutics and Pharmacology and the Section of Psychiatry at a joint discussion.

Since 1913 the chief advances in our knowledge of hypnotic drugs have been: (1) the discovery and addition to the list of hypnotic drugs of very many new derivatives of the barbituric acid series; (2) the introduction of a number of drugs other than alkaloids for purposes of basal anaesthesia.

A hypnotic drug may be defined as a drug or combination of drugs which produce sleep resembling natural sleep. Insomnia is due to many causes, such as pain; nervous causes, such as psychical disturbances and organic diseases of the nervous system; toxic causes, such as microbic infections, auto-intoxication, drug addiction, and chemical poisons; disorders or diseases of the various systems, such as gastro-intestinal, cardiovascular, respiratory, genito-urinary, or endocrine systems.

In the treatment of insomnia the first step is to elucidate its cause, and it will be generally agreed that the use of hypnotic drugs should be resorted to only when other general methods of treatment have failed to bring about a satisfactory result or are likely to be of inadequate effect. The choice of the hypnotic for a particular case will largely depend on the cause of the insomnia—for example, after a severe abdominal operation one would probably select a drug not belonging to this series at all (such as a hypodermic injection of morphine) in order to induce sleep on the night after the operation. Drugs of vegetable origin will be excluded from consideration.

CLASSIFICATION OF HYPNOTICS

The classification of hypnotic drugs on a purely chemical or pharmacological basis is difficult and unsatisfactory, so that an attempt will be made to classify them on chemical and clinical lines.

Hypnotic drugs of low toxicity are: the inorganic bromides (for example, potassium, sodium, ammonium, calcium, and strontium)—they are mild hypnotics suitable for certain nervous cases, and may be given in full doses up to 30 grains at night; alcohol in certain cases in prescribed amount; phenazone and its derivatives, such as pyramidon; aceto-salicylic acid, and salicylate derivatives; phenacetin, etc. Combinations of these with other hypnotics, such as opium preparations or codeine, are often effective.

A number of hypnotic drugs of varying degree of toxicity belong to the alcohol-chloral group.

THE ALCOHOL-CHLORAL GROUP

Chloral (dose 10 to 20 grains) is an effective, rapidly acting, and safe hypnotic. In full doses it is depressant to the heart and respiratory functions. If used continuously it may have a toxic action on the liver and

cause toxic jaundice; also it may give rise to addiction. This hypnotic has undeservedly fallen into disuse.

Chloralamide (chloral formidum, *B.P.*—dose 15 to 45 grains) is a safe and mild hypnotic. Like chloral, it is incompatible with alkalis, which cause decomposition. When used on successive nights the hypnotic effect is apt to diminish, so that this drug is used much less than formerly.

Other chloral derivatives not commonly used at the present time are: Butyl chloral (dose 5 to 20 grains), useful in the insomnia of neuralgia. Chloralose (dose 3 to 10 grains), a compound of chloral and glucose; it is not free from toxic effects such as excitement, tremors, and cardiac depression, and is rarely used. Chlorbutol, also known as "chloretone" (dose 5 to 20 grains); more toxic and less effective as a hypnotic than chloral. Hypnal, a compound of chloral and antipyrine (dose 5 to 15 grains), is rarely used. Dormiol, a compound of chloral and amylene hydrate (dose 5 to 40 minims), is rarely used. Ural, a compound of chloral and urethane (dose 15 to 45 grains), a dangerous and uncertain hypnotic. Isopral is trichlor-isopropyl alcohol (dose 10 to 30 grains); it has fallen into disuse owing to its toxic effects in causing cardiac depression and gastric disturbance. Bromal (dose 2 to 5 grains) is more toxic and less certain in hypnotic action than chloral.

Paraldehyde (dose 1/2 to 2 drachms) is a useful and safe hypnotic, with an unpleasant taste; soluble in water 1 in 9; it is contraindicated in gastric and respiratory diseases; its repeated use may cause toxic liver effects and give rise to addiction. Amylene hydrate (dose 30 to 60 minims) acts like paraldehyde, but is less certain and more toxic. Aponal, a compound of amylene hydrate and urea (dose 10 to 20 grains), is said to be a safe hypnotic and less unpleasant to take than amylene hydrate; it is rarely used. Hedonal is isomeric with aponal (dose 10 to 20 grains); it is an uncertain hypnotic. Neuronal, diethyl bromide acetamide (dose 5 to 20 grains), is a powerful hypnotic, but has toxic effects on the heart and alimentary system, and causes skin rashes; it has fallen into disuse.

Avertin is tribromomethyl alcohol. It has been used extensively as a basal anaesthetic and is administered rectally. The dose recommended by the introducers is 1 1/4 to 1 1/2 grains (0.1 gram) per kilogram body weight of the patient, but there are many conditions which would demand a considerably smaller dose than this. Care and experience are required to decide on the suitable dosage for basal anaesthesia. It may cause prolonged coma, or toxic liver effects such as jaundice in susceptible patients.

THE UREA GROUP

Urethane (ethyl carbamate—dose 15 to 30 grains) is a mild and safe hypnotic, suitable for children. Alendrin (dichlor-isopropyl carbamate—dose 10 to 30 grains) is little used. Uradal, or adalin, is brom-diethyl-acetyl urea (dose 5 to 15 grains), a sedative as well as a hypnotic; it is a useful and safe hypnotic; I have met with no cases of addiction or toxic effects from its use. Uvaleral or bromural or dormigene is a monobrom-isovaleryl urea (dose 5 to 10 grains); it is a useful and safe hypnotic. Somnosal is a proprietary preparation composed of a mixture of bromural and dimethyl-amido-phenyl-methyl-iso-pyrazolon (dose 5 to 10 grains); it is a mild and safe hypnotic.

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SULPHONE GROUP

Sulphonal is dimethyl-methane-diethyl-sulphone (dose 10 to 30 grains). Trional is methyl-sulphonal (dose 10 to 20 grains). Tetronal is ethyl-sulphonal (dose 10 to 20 grains). These three hypnotics are only slightly soluble in water. They are very slowly absorbed, and their action thereby may be much delayed. They are powerful hypnotics, but owing to their delayed and uncertain action are less used than formerly. They have been much used in asylum practice.

Dangers from this group are a cumulative effect, owing to delayed absorption if the drug has been taken in repeated daily dose, when coma may develop unexpectedly. There are many recorded cases of drug addiction. Repeated use of the drugs may lead to troublesome skin rashes of urticarial or erythematous type, often associated with marked prurigo. Vesicular and bullous eruptions and purpura have been observed. Haemato-porphyrinuria is a common but not constant symptom. Mental depression leading to suicidal tendency and the taking of an overdose may occur. Subjective and objective toxic effects on the nervous system have been observed, such as hallucinations, slurred and thick speech, diplopia, squint, ataxy, drowsiness, and stupor. Overdosage may be followed by deep coma lasting over a prolonged period (several days), and during this period there is danger of the development of basal bronchopneumonia, which is usually fatal. In these cases the drug has been found in the cerebro-spinal fluid. An extensive plantar reflex is common during the stage of coma.

Death has occurred after one dose of 30 grains in a neurasthenic woman. Probably an average minimum fatal dose for an adult is about 75 grains, but recovery has occurred after very much larger doses. Several deaths have followed the daily use of from 10 to 20 grains over periods of from two to twelve months.

THE BARBITURIC ACID GROUP

Barbitone or veronal is diethyl barbituric acid. Sodium barbitone or medinal is the sodium salt of barbitone. Propenyl is dipropyl barbituric acid, and neonal or soneryl is *n*-butyl-ethyl barbituric acid. Dial is diallyl barbituric acid. Phenobarbitone, or luminal, is diphenyl barbituric acid, and sodium luminal is its sodium salt. Phanodorm is cyclo-hexenyl-ethyl barbituric acid, evipan is *n*-methyl-C-cyclo-hexenyl-methyl barbituric acid, and sodium evipan is its sodium salt. Pentobarbitone is ethyl-methyl-butyl barbituric acid, and its sodium salt is nembutal. Ipral is calcium ethyl-isopropyl barbituric acid.

Allonal is a combination of allyl-isopropyl barbituric acid with amidopyrine (it gives a reddish-brown colour to the urine from the amidopyrine present). Veramon is a combination of veronal with amidopyrine (it gives a reddish-brown colour to urine). Gardenal is phenyl-ethyl barbituric acid. Cibalgine is a combination of dial and amidopyrine (it gives a reddish-brown colour to urine). Somnifaine is a combination of allyl-isopropyl barbituric acid and veronal. Beatol is a proprietary preparation, said to be a mixture of veronal with extracts of valerian and jusquimane. Quadronox is a proprietary preparation said to contain 80 per cent. veronal, with phenacetin, phenazone, etc. (urine may be coloured reddish brown from the phenazone present).

Sandoptal is isobutyl-allyl barbituric acid. Amytal is isoamyl-ethyl barbituric acid; the sodium salt is used for intravenous purposes. Pernocton is 2-butyl-bromethyl barbituric acid; the sodium salt is used intravenously.

Hebaral sodium is the sodium salt of hexyl-ethyl barbituric acid, and is given by the mouth for insomnia. A considerable number of other preparations containing barbituric acid derivatives are on the market. The addition of

alkyl or aryl radicals of higher molecular weight than ethyl adds to the toxicity of the substance; thus luminal, dial, propenal, gardenal, soneryl, and nembutal are all more toxic than veronal. Launoy and Contière, taking veronal as unity, have found that the relative toxicity for dial is 3.1, for soneryl 4.7, for amyral 10.1, and for nembutal 10.1.

The combination of a barbituric acid compound with an analgesic drug (such as amidopyrine, phenacetin, etc., in veramon, allonal, cibalgine, and quadronox) appears to me to be dangerous, since the barbituric acid compound is much more toxic than the analgesic drug, and this may lead to an overdose of the barbiturate when the preparation is taken in large doses to relieve pain.

The barbituric acid derivatives are perhaps the most commonly used hypnotics at the present day. When taken by the mouth they are quickly absorbed, and within an hour or so of taking a clinical dose sleep usually ensues. After a single therapeutic dose, a period of sleep, lasting from six to twelve hours, usually occurs without unpleasant after-effects. There is more certainty of action than with most of the other hypnotics. These are the reasons for the popularity of this group of hypnotics.

All of the above group of drugs have been used for hypnotic purposes. When one remembers that the toxicity of the derivative increases with the substitution of larger radicals than ethyl, it is probably safer to use, for hypnotic purposes, barbitone or its sodium salt than the more complex derivatives.

Many of the group mentioned have been used for basal anaesthesia. Those which are most commonly used at the present time for this purpose are nembutal, pernocton, amyral, and evipan.

DANGERS FROM THE BARBITONE GROUP

Like other poisons, if taken on an empty stomach and in solution, the effect is more rapid and intense. The taking of alcohol with the drug seems to increase the toxic effect.

Some persons have a natural increased susceptibility to all drugs; often there is present a highly strung nervous temperament, and there is a history of abnormally excessive reaction to medicinal preparations.

Allergic patients are often abnormally susceptible—for example, a history of asthma, urticarial attacks, angio-neurotic oedema, etc., are an indication of this state. With defective renal function the usual symptoms of acute or chronic nephritis may be present, but a chronic cystitis, accompanied by a latent pyelitis, will greatly increase the susceptibility to barbiturates, even if the blood urea is little above the normal. With defective liver function a history of cirrhosis or tendency to jaundice or to attacks of acidosis may be present as an indication. Hyperthyroidism greatly increases the susceptibility to these drugs; for example, nembutal is dangerous as a basal anaesthetic. Myocardial disease also may heighten susceptibility. Glycosuria is evidence of defective pancreatic or hepatic function, and is an indication of likely idiosyncrasy. The prolonged toxic effects of some existing disease greatly enhance the susceptibility of the patient to this group of drugs, especially the basal anaesthetics.

TOXIC EFFECTS ON CENTRAL NERVOUS SYSTEM

Idiosyncrasy may lead to symptoms of acute or sub-acute poisoning from a normal full dose—for example, I have seen prolonged coma, suppression of urine, and bronchopneumonia follow a normal dose by mouth of 2 capsules (3 grains) of nembutal. The repeated use of therapeutic doses not uncommonly causes some symptoms,

such as mental depression, drowsiness, visual hallucinations, vertigo, ataxic gait, thick and indistinct speech (anarthric), diplopia, squint, nystagmus, difficulty in protruding the tongue, paralysis of a limb, facial paralysis, tremors of the hands, etc. Albuminuria sometimes occurs, and rarely haematoporphyrinuria. A reddish-brown-coloured urine is present where a phenazone derivative is combined with the barbituric acid compound. Skin rashes of an urticarial, erythematous, or bullous type may occur.

The symptoms from chronic or subacute poisoning very closely resemble those of organic nervous diseases such as encephalitis lethargica, bulbar paralysis, cerebellar disease, general paralysis of the insane, alcoholism, peripheral neuritis, etc. In 1927 a paper was read before this Section by Dr. F. A. Pickworth, in which it was shown by animal experiments that actual degenerative changes occurred in the nerve cells after the prolonged administration of barbituric acid compounds. This work had been carried out by the late Sir Frederick Mott in conjunction with Dr. Pickworth, and I have no doubt as to its accuracy. There is therefore a pathological basis for the toxic nervous symptoms which are observed clinically.

In healthy persons barbituric acid compounds are fairly rapidly excreted, and accumulation does not readily occur. Where repeated doses are taken, there is an accumulation of the toxic effects as shown by the objective nervous symptoms mentioned. In these cases discontinuance of the drug for a few days leads to disappearance of the symptoms. I have seen toxic jaundice follow the daily taking of 1 grain of luminal for over a year.

Only a slight degree of tolerance to this group of drugs is established even after long use. It is for this reason that a moderate overdose is usually followed by severe symptoms.

I have seen a large number of cases where a definite craving for the drug has arisen after repeated daily administration, and the daily use of the drug has been continued in spite of strong medical advice to the contrary. Addiction to the barbituric acid group of drugs differs from morphine and heroin addiction in that sudden discontinuance is not followed by severe withdrawal symptoms.

I have been very greatly impressed by the risk of fatality from suicide. Persons who have been taking the barbituric acid derivatives daily for a long period very commonly take a large overdose when they are faced with mental stress and worry, and often death results thereby. I have met with such cases where suicide has been effected by taking an overdose of lysol or other poison. The danger of overdosage must always be borne in mind with persons taking barbituric acid drugs in repeated daily doses; it is a very real danger. A recent example of this occurred in the case of a physician whom I saw when a large overdose of veramon was taken with fatal result.

ILLUSTRATIVE CASES

1. F., aged 35, suffering from effects of domestic worry. Had been taking two tablets of veronal nightly for several weeks. Very depressed, tremors of facial muscles, very ataxic gait, visual hallucinations. Symptoms completely cleared up after five weeks.

2. M., aged 34, in an institution for treatment for chronic alcoholism. Had been given allonal, four tablets nightly for several weeks. No alcohol taken while in institution. He developed thick and indistinct speech, diplopia, and ataxic gait. Wassermann reaction negative. Symptoms cleared up on discontinuance of allonal.

3. M., aged 45, suffering from acute rheumatic fibrositis. Had been given 10 grains of medinal for six nights. On examination drowsy, with bilateral ptosis, speech indistinct and thick, diplopia on looking to left. Mental condition somewhat confused. Had been seeing objects which were

non-existent (visual hallucinations). No history of alcoholism or evidence of syphilis. The symptoms completely cleared up in a week after discontinuance of the medinal.

4. M., aged 60, with history of epilepsy. Had taken $1\frac{1}{2}$ grains luminal daily for eighteen months. On examination jaundice present for fourteen days, some abdominal pain in hepatic region. Drowsy for three days. Sick several times daily the last three days. Liver slightly enlarged. This patient was obviously in a condition of commencing acute yellow atrophy. On discontinuance of the luminal, and with intensive treatment with alkalis and glucose, the symptoms cleared up after a few days.

5. F., aged 60, doctor's wife, said to have taken a few (? six) tablets of dial. On examination four hours afterwards deep coma, loss of conjunctival reflexes. Stomach washed out, strong coffee given, and colon washed out. Consciousness recovered in fourteen hours, when delirium and restlessness occurred. Good recovery.

6. F., aged 65. Operation for gall-stones and intestinal obstruction. Nembutal given intravenously for anaesthesia. On the day after operation, defective articulation; two days after operation, confused defective articulation. Suppression of urine after operation. Death occurred four days after operation.

7. M., aged 55, suffering from chronic streptococcal toxæmia. On December 23rd, 1932, two capsules of nembutal were given. A deep sleep lasting twenty-eight hours occurred. On December 26th one capsule of nembutal was given at noon. On December 27th, at 4.30 a.m., one capsule of nembutal was given, and at 1 p.m. another capsule by mouth. Coma followed in two hours. At 6 p.m.: temperature, 101° F.; respirations, 40. 8 p.m.: temperature, 103° . 9.45 p.m.: temperature, 102° ; respirations, 60. Dullness over right lower lobe, deficient air entry, and crepitation. 11.30 p.m.: lumbar puncture, 30 c.cm. of fluid drawn off. December 28th: 6 p.m., recovery of consciousness. Temperature normal. Lung signs beginning to clear up. Retention of urine occurred for four days and some suppression (58 oz. of urine passed in four days by catheter). Good recovery occurred.

8. F., aged 39. Operation for vesico-vaginal fistula, which had been present for nine months. One capsule of nembutal given the night before operation. Two capsules of nembutal given an hour before operation the following morning. Gas and oxygen given also for anaesthesia. After operation deep coma supervened, with all the signs of acute barbituric acid poisoning. Typical pneumonia occurred. Death resulted fifty-one hours after the operation. Blood urea, 57 mg. per 100 c.cm. eighteen hours before death. This was clearly a case of nembutal poisoning, the idiosyncrasy being due to the toxic effects of the genito-urinary infection on the heart and kidneys.

NEED FOR CARE IN USE OF HYPNOTICS

The need for exercising care in the use of hypnotics is obvious, particularly when there are any of the danger signs above mentioned. In psychical cases an obsession of insomnia sometimes occurs, and in such cases ordinary therapeutic doses seem to have little or no effect. It is probable that such cases would be better treated by psychotherapeutic measures than by drugs.

With the drugs used for basal anaesthesia the need for care in dosage cannot be too strongly emphasized. If a therapeutic dose (which in a susceptible person may be an overdose) be given, either intravenously or by mouth, it cannot be withdrawn, since absorption is rapid and one has to combat the full effect of the toxic symptoms. Where any of the dangers mentioned are present, if a basal anaesthetic is used at all, a minimum dose should be given and full anaesthesia obtained by a general anaesthetic such as gas and oxygen or ether.

In a recent case where avertin was desired by the patient, after consultation it was decided to give a half-dose since glycosuria and myocardial weakness were present. Some of the solution was returned after rectal administration, and probably only about one-third of the normal dose was absorbed. This patient was able to talk up to the time of the abdominal operation, which was performed under gas and

oxygen and ether. After recovery from the operation the patient stated that he had no recollection of the events preceding the operation, and a full amnesia was attained with the small dose.

In cases where there is a possibility of danger it appears to me that if a basal anaesthesia is used a reduced dose should be given which would effect amnesia without causing complete loss of consciousness.

CONCLUSIONS

In prescribing hypnotics it is wise to select one or a combination of the less toxic type of drugs whose action is well known. I have been so impressed by their toxic effects that I never prescribe any of the barbituric acid group of drugs or of the sulphonal group.

These drugs should only be obtained on the prescription from the medical adviser, and the prescription should be retained by the pharmacist and not repeated, except on medical authority and signature. The total quantity ordered on a prescription should be well under a possible fatal dose.

Legislation regarding the sale of poisons is under consideration as a result of the recent Pharmacy and Poisons Act, which was passed this year (1933).

A close co-operation between the medical profession and those practising pharmacy is essential if dangers from hypnotic drugs are to be avoided.

CARBON DIOXIDE THERAPY IN LOBAR PNEUMONIA

BY

REGINALD HILTON, M.D., F.R.C.P.

ASSISTANT PHYSICIAN AND ASSISTANT DIRECTOR OF THE MEDICAL UNIT, ST. BARTHOLOMEW'S HOSPITAL

Of recent years increasing attention has been given to the use of carbon dioxide in respiratory conditions. In some ways it is the ideal respiratory stimulant; its chief action is to increase the depth of breathing without accelerating its rate excessively. This result is apparently achieved in two ways: first, by the changes it produces in the pH of the blood, secondly, by the specific effect of the HCO_3^- ion itself. It is therefore to be expected that its value would be tested in many respiratory conditions, in some of which, indeed, its utility has already been fully demonstrated. These include atelectasis, certain forms of asphyxia, and post-operative bronchopneumonia. Its value, however, is still under dispute in lobar pneumonia. This paper is concerned with the latter condition.

Hanson and Calhoun,¹ in a series of early cases treated for short periods by 5 per cent. CO_2 and 95 per cent. O_2 , carefully controlled by repeated x-ray examinations, failed to abort the spread of consolidation. Alison² claimed that the disease could be arrested if treatment were begun in the first thirty-six hours. In his opinion the patients "were more comfortable and appeared to progress better" with CO_2 added than with oxygen only. On the experimental side Henderson³ and others assert that in pneumococcal pneumonia with bronchial obstruction CO_2 prevents the development of the disease. He considers that atelectasis plays an important part in lobar pneumonia. Since hitherto there has been a lack of blood-gas studies in man after CO_2 administration, the following observations attempt to supply some of the missing evidence.

As there is a considerable amount of information about the benefit of O_2 alone, it was considered advisable to study the effects of CO_2 unaided by oxygen. The procedure adopted has been to measure first the rate and depth of respiration. A sample of arterial blood was

then taken from the femoral artery. Approximately 3 per cent. carbon dioxide was administered with a loose face mask, and the examinations of the breathing and the blood were repeated fifteen minutes later. The blood gases were determined by the van Slyke method. There are obvious difficulties in the way of investigations of this sort; for instance, the accuracy of measurements of the tidal air cannot be strict. Any apparatus is apt to disturb a patient with pneumonia, and in particular any resistance to expiration is quickly resented. To obtain the measurements mentioned here a specially devised low resistance mask was employed, which has proved its value in collection of air in dyspnoea.⁴ Some results are shown in the accompanying table.

	Arterial Saturation (Vol. per cent.)		Respiratory Rate per Minute	Litres per Minute Ventilation	Tidal Air in c.cm.
	O_2	CO_2			
1. (a) before CO_2	87	35	41	11.47	280
(b) after (15 minutes later)	88	46	42	15.1	360
2. (a)	91	37.4	31	12.1	390
(b)	92.5	48.2	29	13.75	473
3. (a)	85	32	33	12	365
(b)	85.6	41.5	31	13	420
4. (a)	84	31.4	35	10.4	290
	83.2	43	33	12.05	365

These observations were made during the first five days of lobar pneumonia.

The first point to be noted in the table is that arterial anoxaemia is unrelieved after CO_2 administration in these quantities, in spite of the fact that the depth of the tidal air is considerably increased. This raises the question as to what part shallow breathing plays in the production of anoxaemia.

SHALLOW BREATHING

Haldane, Meakins, and Priestley⁵ have shown that the artificial limitation of the tidal air in normal subjects to about 200 c.cm. resulted in periodic breathing, which was removed by adding oxygen. They also demonstrated that the mixed alveolar air under such conditions may contain a higher pressure of O_2 than would be expected to cause anoxaemia. This they explained by uneven ventilation.

Meakins⁶ investigated the question further in pneumonia by correlating the ventilation with the cyanosis. He considered that the shallow restricted breathing in pneumonia was an important factor in causing the anoxaemia. Since anoxaemia in its turn gradually leads to failure of the respiratory centre and rapid shallow breathing, there is a vicious circle which has to be broken if recovery is to follow. The same observer and Davies⁷ published valuable studies of the tidal air and arterial oxygen in pneumonia. Consecutive examinations of the same patient revealed that, as the cyanosis deepened, the arterial oxygen fell and the breathing became more shallow. In that series of observations there were only two measurements of a tidal air below 200 c.cm.: they occurred on the ninth day, when the patient died. These measurements were associated with respiratory rates of over sixty per minute, which is rare in adults who recover. The lowest tidal air during the first five days in four patients was 220 c.cm. In my experience the breathing of patients with pneumonia during the first few days is often of normal depth or even greater, as the table shows. It must be remembered, also, that when a large part of a lung is solid a given tidal air represents a better ventilation for the remaining lung.