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A CLINICAL STUDY OF THE NEWER  
HYPNOTICS.-

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Thesis submitted for the

M.D. Edinburgh

by

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## Introduction.

Among the large number of new drugs which have recently been introduced by enterprising firms of manufacturing chemists, a rather large proportion belong to the class of hypnotics and analgesics. Probably the reason for this is the fact that hypnotic and analgesic properties are possessed by a very large number of carbon compounds, and every manufacturer who wishes to exploit this class of drugs finds it very easy to prepare a modification of some previously existing hypnotic and claim it as an entirely new drug under a new trade name. Each is boomed with plenty of advertisement, and remarkable results are claimed by the makers for each.

The result of this is that the practitioner who has to use these drugs becomes rather bewildered at the claims made about them, and hesitates to use any of them.

There is no doubt, however, that some of the recent synthetic preparations of the hypnotic group are really very serviceable, and it is my object in the present thesis to give the results of a series of clinical trials with a few of the more important ones.

Mental diseases "par excellence" afford scope for an extensive trial of these preparations, and being the Medical Officer of a large Asylum I have utilised several of these preparations and will record my results and endeavour to draw some conclusions as to the scope and indications of the principal hypnotics.

Before proceeding to take up the discussion of the advantages of the various drugs, I think it will be appropriate to make a few remarks concerning the causation and treatment of insomnia in insanity -

About 50 years ago Dr. Carpenter wrote as follows:

"It is a peculiar feature in the physiology of the cerebral and sensorial ganglia that their activity undergoes a periodic suspension, more or less complete; the necessity for the suspension arising out of the fact that the exercise of their functions is in itself destruction to their substance, so that if this is not replaced by nutritive regeneration they speedily become incapacitated from further use."

Insomnia is therefore an insufficient function of the higher nerve centres.

The cause of sleep is not exactly known. Many theories have been advanced most of which are familiar. It is not proposed in this thesis to discuss any of these theories. As regards the action of narcotics it is fairly certain that these bodies, especially those of the methane series, act directly upon the neurons causing depression, and that the neurons depressed by drugs undergo changes similar to those of natural sleep. What these changes really are is not exactly known although many suggestions such as coagulation of proteins, solution of lipoids, or changes in the dendrites or chromatin, have been made.

Insomnia occurs in many diseases but perhaps in none more frequently than mental conditions. In the acute forms of Insanity it is always present and is one of the most important symptoms to be dealt with in order to effect a cure.

Allbutt (system of medicine) describes four groups of insomnia.

1. Irritative Insomnia.
2. Toxic Insomnia.
3. Psychological Insomnia.
4. Insomnia due to change in the habits of life.

Psychical Insomnia is the form that will only be considered in this paper.

Psychical Insomnia may be classified as follows.-

1. The Insomnia of Acute Mania and Acute Melancholia.
2. The Insomnia of Dementia Praecox and the milder forms of Mania and Melancholia in young persons and middle age.
3. The Insomnia that accompanies cerebral atrophy due to arteriosclerosis. This is accompanied by dilatation of the perivascular spaces, and increase in the glia, pigmentation of the ganglion cells, but the medullary fibres are intact. Sometimes small areas of softening occur. (Paton).

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1. The Insomnia of Acute Mania and Acute Melancholia is always very severe. The patient may go for weeks

without any sleep. Generally patients suffering from these two forms of insanity will not remain in bed and also refuse food. To procure sleep is most important in the treatment of these cases, and in order to do this a very large dose of the hypnotic drug is required; an ordinary dose is of no use; and therefore the object is to obtain a drug that can be given in very large doses without producing poisonous effects. I find that the best drug for this purpose is Paraldehyde.

2. The Insomnia that occurs in Chronic Mania and Melancholia, Secondary Dementia and Dementia Praecox is of a very much milder type than the forms of insanity just described, and so large a dose is not required in the treatment of these cases, although the dose has to be greater than is usually given in private practice to sane people.

I have found trional, veronal, amylene hydrate, and sulphonal useful in these cases and to a less extent Chloretone, Proponal, Neuronal, Bromural and Chloralamide.

3. Insomnia that occurs in cerebral atrophy of arteriosclerosis, in which there is generally a perivascular gliosis, is generally seen in patients between 50 and 60 years of age; sometimes it occurs at an earlier age, and if so the patient ages rapidly and looks much older than is the case. In this form of insanity patients are generally melancholic with delusions of unworthiness. Insomnia is always present, sometimes

in marked degree. I have found Sulphonal a useful drug in these cases, and I have given it more than any other. Lately, however, I have not used this drug, and I generally use Veronal and Neuronal.

## II. Classification of Hypnotics.

The classification of hypnotics usually adopted is that of Fraenkel. This observer has classified them in the following order, viz:-, the Alcohol Group, the Chloral Group, and the Paraldehyde Group, this classification being according to the chemical factor that is supposed to determine the physiological action.

### I. The Alcohol Group.-

In this group the hypnotic action depends upon the presence of an alkyl group, especially the ethyl radicle  $C_2H_5$ . It is divided into four subgroups.

1. The alcohols.
  - Ethyl Alcohol.
  - Amylene Hydrate.
2. The Sulphones.
  - Sulphonal.
  - Trional.
  - Tetronal.
3. The Substituted Amides.
  - Urethane.
  - Hedonal.
4. Urea Derivatives.
  - Veronal.
  - Proponal.

## II. The Chlorine Group. (Halogen Substitution Products.)

The hypnotic action of this group depends upon the presence of a halogen which has been substituted for one or more atoms of hydrogen in the simpler substance of the fatty series. This substitution very greatly increases the hypnotic power.

This Group consists of:

Chloral Hydrate, Chloralamide, Chloralose, Somnal, Hypnol, Isopral, Chloretone, Bromural, Brometome.

## III. The Paraldehyde Group.

In this group the hypnotic action is due to the aldehyde or ketone radicle; it contains

1. Paraldehyde.

2. Hypnone.

Hypnotics have also been classified by Dr. H. J. Campbell (Lancet, April 2nd, 1910) in a paper that he recently read at a meeting of the Bradford Medico-Chirurgical Society in the following manner.

1. Bromides.

2. Chloral, Sulphones and Urethanes.

3. Opium and its allies.

1. This observer states that Bromides act in two ways; firstly in causing a rise in the blood pressure and diuresis because of their action as salines, and secondly because they act as depressants to the cells of the central nervous system.

2. Chloral, Sulphones, and urethanes, although comparatively insoluble in water are soluble in fat-like compounds such as brain lipoid, and their physiological action is due to this combination.

3. Opiates depress the nerve cells in the higher centres, and also the cells in the sympathetic ganglia.

Dr. Fortescue Brickdale (Guide to the Newer Remedies) has given hypnotics what might be called a clinical classification and this appears to me to be one of the most useful methods.

The classification is as follows:

1. Dangerous Hypnotics.

1. Tetronal. 2. Isopral. 3. Chloralose. 4. Chloralurethane.

2. Hypnotics having no special advantage.

1. Addition Products. 2. Trigeminal. 3. Brometone. 4. Propion  
5. Hypnone.

3. Mild Hypnotics.

1. Urethane. 2. Hedonal. 3. Amylene Hydrate. 4. Chloral-  
amide. 5. Dormiol. 6. Viferral.

4. Medium Hypnotics.

1. Paraldehyde. 2. Sulphonal. 3. Bromural.

5. Powerful Hypnotics.

1. Chloral Hydrate. 2. Trional. 3. Veronal, and Sodium  
Veronal. 4. Proponal. 5. Neuronal.

The Alcohols.

The hypnotics in this group consist of ethyl,  
alcohol, and Amylene Hydrate.

Ethyl Alcohol ( $C_2H_5HO$ ) is extensively used in therapeutics but not so much for its hypnotic action as for other purposes. It is however useful in the insomnia of elderly people if given at bedtime in the form of whiskey or gin and it certainly increases the action of other hypnotics when combined with them.

### III. Clinical Trials.

#### Amylene Hydrate.

This is the only other alcohol that has been introduced into therapeutics.

Its chemical formula is  $((CH_3)_2C(OH)C_2H_5)$  thus it is a tertiary amyl alcohol. It occurs as a colourless liquid with a rather unpleasant taste and is generally given in capsules. It has to be kept in the dark, as it decomposes when exposed to light. It is said to resemble paraldehyde in its action, but it depresses the heart more than this drug. Two cases of poisoning by this drug are recorded, one by Anker and the other by Lederer, after a dose of 27 gm. in one case and 8 gm. in the other. Both patients recovered. The symptoms were those of collapse and the treatment adopted was that of stimulation.

I have used this drug myself and I have not found it very convenient for asylum use. Its unpleasant taste is a disadvantage, and it is not easy to administer drugs to lunatics by means of gelatine capsules and my experience is, that as a hypnotic it is not powerful enough for asylum use. It is however useful in asylum practice in cases of mild insomnia and as a variant to other drugs.

PATIENTS TREATED WITH AMYLENE HYDRATE.

The following case was treated with Amylene Hydrate with very good results:-

She was suffering from General Paralysis of the

Insane of the melancholic Lucy R. - no delusions of exalt-

Patient was admitted on May 21st, 1910, suffering from extreme Melancholia - groaning and moaning, and also in a state of stupor, not appearing to know where she was. She refused food and had to be fed forcibly. She slept fairly well, and it was unnecessary to give her any sleeping draught. After a time she got out of the state of stupor, and had delusions of unworthiness - had an idea that all the unhappiness in the world was due to her. This delusion increased, and she became troublesome in many ways - clutching at people. She also about this time (in November) suffered slightly from Insomnia, and on Thursday, December 1st, she was given 40 minims of Amylene Hydrate, and she slept from 10 o'clock until 6. The drug was administered at 8.30, therefore the patient went to sleep  $1\frac{1}{2}$  hours after it was administered. On December 4th she had another dose of Amylene Hydrate and she slept for 6 hours. The drug was continued twice a week for three or four weeks with good effect. The drug was given in the form of gelatine capsules, and there was no difficulty in getting the patient to take them. It is seldom however, that one can get maniacal patients to take drugs in this form.

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Amylene Hydrate did not have any effect in the following case.-

Mrs. C. L. M. Admitted October 27th 1910.

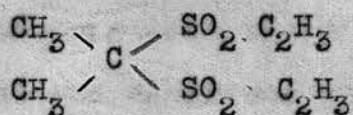
She was suffering from General Paralysis of the Insane of the melancholic type - no delusions of exaltation. She had exaggerated knee and ankle jerks, wrist, elbow and jaw jerks. She had unequal pupils, and lacked concentration of attention. She also slept badly. In December she was given 40 minims of Amylene Hydrate. That drug had no effect, and she did not sleep at all. Two nights after this she was given 4 drachms of Paraldehyde, and patient slept well.

It is decomposed in the body and occurs in the urine as sulphonic acids, the hypochlorite action however is not due to this substance but to the sulphonic acid of sulphonal. ... Sulphonal is a very useful drug in the treatment of insanity ...

Sulphonal.

Syn. Diethyl - Methane - diethylsulphone.

Its structural formula is



This substance is an aldehyde derivative which has received considerable attention during the past 10 years as a hypnotic.

It is produced by oxidation of a mixture of ethyl-mercaptan and acetone. It occurs as crystals which are colourless, odourless and tasteless. It is not very soluble, about 1 in 450 of water, but it dissolves freely in hot alcohol and in 1 in 50 of cold alcohol.

It is decomposed in the body and occurs in the urine as ethylsulphonic acid, the hypnotic action however is not due to this substance but to the unchanged molecule of sulphonal. Kast has found sulphonal in the blood many hours after its administration.

Sulphonal is a very useful hypnotic <sup>in</sup> the milder forms of insomnia occurring in mental disease. When given in doses of 15 to 20 grains it usually produces a refreshing sleep of 5 to 7 hours duration. Owing to its insolubility it is slowly absorbed and consequently it often produces some depression and drowsiness on the following day. Occasionally I have known it not to produce sleep until the night following its administration but this does not often happen.

This drug should not be given more frequently than every alternate night, otherwise a tolerance is soon produced, and its administration should not be continued for more than two or three weeks as a series of unpleasant and dangerous symptoms may be produced.

These symptoms occur more readily in some patients than in others and usually in anaemic women. They consist of muscular weakness and inco-ordination and the appearance of a red pigment in the urine called haematoporphyrin.

Other symptoms are vomiting, abdominal pain, partial paralysis, collapse and death.

The pigment haematoporphyrin has the chemical formula  $C_{68}, H_{72}, N_8, O_{12}$ . It was first recognised by Hoppe-Seyler. It forms a crimson solution in the urine and has a distinct spectrum. It is formed by the removal of the iron from Haematin. The amount found in the urine varies very much in different individuals. Tyson and Crofton found in one case that the amount passed in one day indicated the destruction of one-seventeenth of the total haemaglobin of the body.

Its formation is due to some obscure change in the liver, and not to any alteration in the renal function. Sulphonal exerts an injurious effect upon the liver. The amount of urea to the total nitrogen of the urine is changed. It also affects the metabolism of the purine bodies. Haematoporphyrinuria also occurs in lead poisoning, acute rheumatism, pulmonary tuberculosis and pleurisy.

On account of the danger of these after effects being produced sulphonal is not so much in favour as a hypnotic as it was some five years ago.

Personally I have given the drug to a great many cases during the past eighteen years; but I do not use it so much now as formerly; and I never continue its administration for long. I have noticed many patients become tottering and ataxic in their gait, but when the drug is discontinued this symptom soon disappears. I have never noticed any case to have haematoporphanuria.

My experience is that sulphonal is a useful hypnotic if used for short periods at a time.

The following is an account of a lady who came under my care a few years ago, who, previous to her admission had been in the habit of taking large doses of sulphonal, the exact amount however, I do not know.

#### SULPHONAL.

C.S. Admitted November 15th, 1906.

She was unnaturally dull and stupid, and took a long time to reply to questions, and appeared to be suffering from Ataxic Paraplegia. She was unable to stand with feet together when her eyes were closed, and she could not put her fingers to her nose when her eyes were shut. The gait was ataxic. There was also slight spasticity of the lower limbs, with increased knee jerks, and the urine was very high coloured. By December 14th she could walk much better than formerly and was

Tribonal

not ataxic at all; by January 4th she had improved considerably. On questioning the patient's friends I was told that she was in the habit of taking very large quantities of Sulphonal before her admission, and this evidently accounted for the symptoms which I mistook for Ataxic Paraplegia. The patient made a complete recovery and was discharged.

It occurs as minute crystals soluble 1 in 240 of water, in alcohol 90%, and 1 in 11 in ether. Dose 10 to 30 gr.

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I have found this drug rather less powerful than Sulphonal, but in some cases of insomnia it produced very excellent results. I have also found it of great service when combined with Bromide of Potassium in treating the excitement and noisy restlessness of acute mania. I generally give gr. X of tribonal with gr. XX of Bromide of Potassium twice a day. The following two cases were treated in this manner.

TRIBONAL

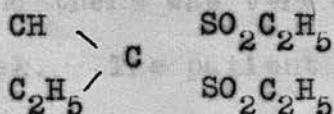
Case 1. Cambridge, N. Y., Aug. 14.

This patient was admitted on September 10th, 1912 suffering from Acute Mania. She was in a state of acute excitement, noisy and restless, and was making indecent remarks. She was unable to sustain a conversation rationally, and was very incoherent. She had Paraldehyde for a few weeks, and always slept after the drug, but was still noisy and excitable in

Trional.

This substance is an oxidation product of mercaptol made by the condensation of methylethylketone with ethylmercaptan.

Its structural formula is



It occurs as minute crystals solubility 1 in 840 of water, in alcohol 90%, and 1 in 11 in ether. Dose 10 to 30 gr.

I have found this drug rather less powerful than sulphonal, but in some cases of insomnia it produced very excellent results. I have also found it of great service when combined with Bromide of Potassium in treating the excitement and noisy restlessness of acute mania. I generally give gr. X of trional with gr. XX of Bromide of Potassium twice a day. The following two cases were treated in this manner.

TRIONAL.

Constance S. Age 39.

This patient was admitted on September 19th, 1910 suffering from Recurrent Mania. She was in a state of acute excitement, noisy, and erotic in conversation - making indecent remarks. She was unable to sustain a conversation rationally, and was wet and dirty in habits. She had Paraldehyde for a few weeks, and always slept after the drug, but was still noisy and excitable in

the daytime although she slept fairly well at night. The Paraldehyde was discontinued; the excitement, however, still remained, and she was given 12 grains of Trional combined with 20 grains of Bromide. This was given night and morning, and there was very great improvement in the course of a week. The patient was better, up and dressed, and was more rational in many ways.

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Hannah G.      Age 63.

She was admitted on May 2nd, 1910 suffering from Senile Melancholia. She was in great mental distress, continually moaning and groaning, and talking nonsense. She refused food, and had to be fed forcibly. She also had to be kept in seclusion. She did not sleep at all, and was given Paraldehyde three times weekly. She always slept at night after she had the drug, but did not sleep on other occasions. The excitement still continued, she refused food, and had to be fed forcibly until July 4th. She was having 6 pints of milk daily, 6 eggs, and the juice of a beef steak. At this time she was sleeping well every night, but she became very much more excitable during the daytime, and her language became most filthy and disgusting. It was impossible to dress her and get her up, as she pulled off all her clothing and threw it about the ward. She was given 10 grains of Trional combined with 20 grains of Bromide of Potassium. In a very short time she improved. In a fortnight she

was up and dressed, and behaving quietly - although she was still incoherent in speech and could not sustain a conversation.

It is a colorless liquid with a specific gravity of 0.985 and with a very unpleasant taste. It boils at 100° F and freezes at 30° F. It is freely soluble in alcohol and 1 in 10 of water. It is a very powerful hypnotic and acts very quickly. I have frequently used it to maintain patients in a state of unconsciousness, and in this respect it is markedly superior to sulphonal, chloral, and veronal. It is stated to have no bad effects upon the heart and can therefore be given in cases of acute myocardial infarction, debility, and exhaustion due to refusal of food, and in the treatment of insomnia.

The sleep which it produces lasts for several hours and it produces no unpleasant after-effects, and it does not affect the gastro-intestinal tract. It is stated that in large doses it affects the cells in the exterior of the spinal cord and abolishes reflex action. I have given large doses of this drug over a long period of time and have never noticed this effect to be produced. However, it is stated to be especially useful in the treatment of cases of epilepsy, and the fact that it has a very bitter taste and is very disagreeable to the patient may be a disadvantage in its use.

The dose is from 0.5 gr. to 1 gr. and this is quite sufficient in most cases of insomnia, and in

Paraldehyde  $C_6H_{12}O_3$ .

Paraldehyde is a produce of the polymerization of aldehyde by means of various acids and salts. It is a colourless liquid with a specific gravity of 0.998 and with a very unpleasant taste. It boils at 250 F and freezes at 50°F. It is freely soluble in alcohol and 1 in 10 of water. It is a very powerful hypnotic and acts very quickly. I have frequently known it to act within five minutes of its administration, and in this respect it is markedly superior to sulphonal, trional, and veronal. It is stated to have no bad effects upon the heart and can therefore be given in cases of mania where there is cardiac weakness, debility and exhaustion due to refusal of food, maniacal excitement and insomnia.

The sleep that it produces lasts for several hours and it produces no unpleasant after-effects, and it does not affect the gastro-intestinal tract. It is stated that in large doses it affects the cells in the anterior cornua of the spinal cord and abolishes reflex action. I have given large doses of this drug over a long period of time and have never noticed this effect to be produced. Sometimes it causes an erythematous rash. The great objection to its use is its horrible taste and the unpleasant odour of the breath that it produces.

The dose is from  $\frac{1}{2}$  to 2 dr. and this is quite sufficient in ordinary cases of insomnia; but my

experience is that in cases of insomnia accompanying acute mania, nothing less than 4 drachms is efficient, and that this dose should be given three times a week and continued for some time. When given in this dose this drug is most valuable in the treatment of acute mania as the following cases will show.

I used to treat cases of this description some years ago with Chloral Hydrate 30 grains and Bromide of Potassium 15 grains, but the result was nothing like so good as that obtained with 4 drachms of Paraldehyde, and I invariably use this drug now with those cases of profound Insomnia which accompany the excitement of Acute Mania or the depression of Acute Melancholia.

I have come to the conclusion that the Pharmacopoeial dose of this drug is too small, and that it should be four drachms not two.

#### Cases treated with Paraldehyde.

Miss D., female, age 21 single, admitted May 20th, 1909 had symptoms of Grave's disease. The pulse rate was 120. She also had proptosis and an enlarged thyroid; also tremor of the hands. She was suffering from an attack of acute mania, was exceedingly restless and would not remain in bed, was unable to recognise people, and refused to take food. She was not sleeping at all and had not done so for weeks. As she would not remain

in bed she was placed in a Peacocks room artificially heated; she was also fed through the nose. She was given six pints of milk, six eggs, and six ounces of brandy a day, and also the juice of one pound of beef-steak squeezed from the uncooked meat with a squeezing machine. She retained the food well but she did not sleep. On May 27 she was given Paraldehyde 2 Drachms; this small dose being given on account of the cardiac weakness and rapid pulse. The drug had no effect at all, the patient did not sleep.

On June 3rd she was given 3IV of Paraldehyde. She was asleep within half an hour of taking the drug and she slept for 7 hours.

The drug had no harmful effect upon the heart or respiration. The patient took four drachms three times a week until July 4th when she became more sensible and began to take her food.

It was noticed at first that she only slept on the nights that she had taken the drug.

She made a complete recovery and has remained well ever since.

Emily C. Admitted October 24th 1909. Age 57.

This patient was in a very feeble state of bodily health. She was suffering from Melancholia. She was depressed, silent, dull, and almost in a state of stupor. She could not recognise people, and was restless and out of bed. She scarcely ever slept at all, and refused

food. On Nov. 2nd she was tried with Sulphonal 20 grains, which had no effect. On Nov. 13th she was tried with Paraldehyde 2 drachms - no effect. On Nov. 15th she was given 4 drachms of Paraldehyde, and slept for 6 hours. She was very much better after this, and gradually improved. She had Paraldehyde three times a week. On January 4th she was up and dressed, and on February 19th was discharged Recovered.

Catharine H. Admitted September 21st, 1909. Age 28.

She was suffering from Recurrent Mania. She was in a state of acute excitement - shouting and noisy, and she had delusions chiefly of a sexual character, saying that she was an illegitimate child. She threw the cups and plates all over the room, and refused food. She was fed through the nose, as she always vomited when fed through the mouth. She had no sleep at all, and after being admitted a week she was given 4 drachms of Paraldehyde three times a week. She slept well on these nights, but did not sleep on the intermediate nights. She gradually improved, and by January 4th was up and dressed. She still continued taking the Paraldehyde. On February 4th she was able to leave off the drug, and was sleeping fairly well. On March 14th, 1910 she was discharged Recovered.

Alice S. Admitted August 9th. Age 49.

She was suffering from Recurrent Mania (2nd attack)

She was exceedingly excited on admission, talking incoherently, and addressing imaginary objects in her room. She took her food, but did not sleep at all. After she had been in the Hospital two days she was given 3 drachms of Paraldehyde twice a week. This was not sufficient and it was increased to 4 drachms three times a week. She slept well, and was much improved. On August 23rd she was much quieter, and was able to be up and dressed. From this date she gradually improved. The Paraldehyde was discontinued in September, and on January 6th she was discharged Recovered.

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George T. Admitted August 15th 1910. Age 49.

He was suffering from Acute Melancholia. He had an exceedingly dejected aspect, would not look up, and only spoke in monosyllables. He was extremely wretched, and had delusions of unworthiness, thinking he had been very wicked and had poisoned people. Patient did not sleep at all, and stated that he had not slept for some weeks. He was given 4 drachms of Paraldehyde on August 17th, and was asleep within 10 minutes of taking the drug, and slept for 7 hours. He was afterwards given 3 drachms three times a week. He slept well and gradually improved.

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Thomas T. Admitted April 14th 1910. Age 42.

Patient was suffering from Acute Melancholia. He was depressed, and for the most part was in a semi-stuporose condition. He had a dejected aspect, and was morbidly taciturn. He did not appear to know exactly what was said to him, and only answered questions with difficulty, and after a great deal of hesitation. He slept very badly indeed. He had an exceedingly rapid pulse, and protrusion of the eyeballs, and also slight tremor of hands. There was no enlargement of the Thyroid. On April 25th he was given 4 drachms of Paraldehyde, and was asleep within half an hour of taking the drug, and slept all night. He took 4 drachms three times a week for some weeks. On September 7th he was very much better, could answer questions more readily, and was much more cheerful. The draught was discontinued, he gradually improved, and was discharged on October 13th.

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Henry B. Admitted August 14th 1909. Age 54.

This patient was admitted suffering from great emaciation, want of food, and want of sleep. The heart was very feeble, the beat being irregular and intermittent. The pulse was of low tension. He was acutely melancholic with delusions - saying that his bowels were confined and had not acted for 5 years, and that it was useless for him to take any food. It was found necessary

to feed him forcibly, and he had about 6 pints of milk, 6 eggs, and a little brandy every day. He improved slightly, but still suffered very much from Insomnia. He was given 4 drachms of Paraldehyde three times weekly, after which he always slept well all night. He did not sleep at other times. In about six weeks he had improved considerably, he soon took his food, and became better mentally. He was able to wash and dress himself in the morning, which was not the case at the time of his admission. He could answer questions, and was better in many ways.

The following is a case of Insomnia in a patient suffering from Acute Mania, where Paraldehyde was successful in producing sleep although Veronal and Neuronal had both failed.

Mrs B.A.B. Admitted December 9th 1910.

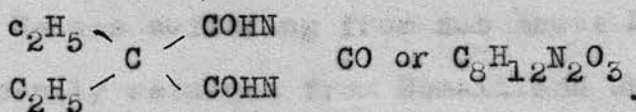
She was suffering from Acute Mania, was in a state of acute excitement - noisy and troublesome in behaviour, and wandered about her bedroom and did not sleep. On December 10th she was given 10 grains of Veronal - it had no effect at all upon her. On December 13th she was given 10 grains of Neuronal - which also had no effect. On December 16th she was given 4 drachms of Paraldehyde, and she slept 8 hours. The drug was repeated two nights afterwards, and she had a good night's sleep. In the course of a few days she had improved, and was able to be up and dressed.

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Veronal.

(Diethyl-malonyl-urea) (Diethyl Barbituric Acid).

Structural formula -



Veronal is made by condensing Urea with the Diethyl ester of Malonic Acid.

It occurs in white crystals. It is soluble 1 in 450 of water in 1 in 9 of alcohol. It is easily soluble in Ether, Acetone and Acetic Ether.

Dose 5-10 grains.

Veronal is an excellent hypnotic producing a very refreshing sleep without as a rule any after effects. Cushny (193) states that it is devoid of action except on the central nervous system, and thus approaches the ideal more closely than any others. The dose is small, 5-10 grains, and this is sufficient to induce a natural sleep without subsequent depression. Several fatal cases of poisoning have occurred through taking this drug, the sleep getting gradually deeper and ending in coma with respiratory failure.

I have myself seen a case of poisoning by veronal in private practice. It was undoubtedly a case of suicide as shown by letters found in the patient's bedroom. The amount taken was not known. The patient appeared to be in a sound sleep, the breathing was slightly stertorous, there was no conjugate deviation of the head and eyes.

PATIENTS TREATED WITH VERONAL.

Frank S. Admitted July 25th, 1908.

He was suffering from sub Acute Mania. Patient had recently returned from Somaliland where he had a Government appointment. He had delusions of persecution - imagining that everybody was plotting against him. He was unnaturally excitable and had ideas of a somewhat grandiose type, e.g. he stated that everybody knew him in Africa. He improved during August, but about the end of this month he began to suffer from Insomnia. He was given Veronal 10 grains on September 1st and he slept for 7 hours. The drug was continued three times a week for four weeks - patient improved rapidly, and by November 3rd was discharged recovered.

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Miss Elizabeth H. Admitted April 1st, 1909.

She was suffering from Melancholia with delusions of unworthiness - thinking she had committed serious crimes and was going to be arrested for murder. Patient did not sleep well, and had Sulphonal from time to time. Tolerance of this drug appeared to have been produced, and it was discontinued. She was given 10 grains of Veronal on Sunday November 6th. The drug was administered at 8.30, she slept from 10 o'clock until 3, and also from 4 o'clock to 5.30. The dose was repeated on November 8th, when she slept from 9 o'clock until 4.

The drug was continued for some few weeks twice a week. Her mental condition improved considerably, but she was not well enough to be discharged. The sleep that the drug produced evidently relieved her condition to a considerable extent.

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Miss Fanny G. Admitted August 20th, 1893.

She was suffering from Chronic Mania, which was in the course of a year or two followed by Secondary Dementia. Patient was unable to converse and did not appear to know where she was. During the summer of 1910 she developed Phthisis. She lost weight considerably, and also suffered from Insomnia. She was given Veronal 10 grains twice a week with the result that she was usually asleep within an hour of taking the drug, the sleep usually lasting from 6 to 7½ hours. She never used to sleep for some weeks before she had the drug. Her mental condition was much relieved by the administration of this drug.

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Miss Anna G. Admitted June 24th, 1908.

She was suffering from Recurrent Mania with delusions. She was excitable and had to be kept in bed. She was unable to converse rationally and her habits were wet and dirty. She took her food and slept fairly well, and in the course of a week was well enough to be up and dressed. About September she became

Bromural.

violent and often struck the nurses and some of the other patients, and she was noisy. At this time she began to suffer from Insomnia. She was given 10 grains of Veronal, which was administered at 8.30. She was usually asleep before 9.30 and slept for 6 to 7½ hours. The drug was taken twice a week for another three weeks, when it was discontinued. Patient greatly improved, was quiet and orderly, and occupied herself by doing needlework, but was not sufficiently well to be discharged. Later on Chloralamide was given to this patient (See page 20.)

The hypnotic effect of this drug is due to the urea and bromine elements, and there are no unpleasant after-effects. The bromine is not split off the compound in the digestive tract, so the isolated action of this element does not occur, and there is no trace of bromine in the urine after the administration of bromural.

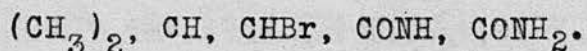
I have found bromural to be a very good hypnotic for some people, producing a very pleasant sleep in about 30 minutes after its administration which lasts from 5 to 7 hours.

In insane people it appears to vary in its action considerably, sometimes it produces sleep, in other cases it fails to do so, and I have known it cause great cardiac depression. It is, however, useful in some of the forms of insomnia in insanity.

Bromural.

Synonym a-Brom-iso-Valerianyl Urea.

This substance occurs as white needleshaped crystals; the chemical formula is



It has rather an unpleasant odour, but the taste is not so unpleasant as the smell. It is insoluble in cold water. I have also always found it to be insoluble in hot water. It is freely soluble in alcohol. The dose is from 5 to 10 grains. Children are said to stand it well. There is a limit to its usefulness, as the dose cannot be extended beyond ten grains. The hypnotic effect of this drug is due to the urea and bromine elements, and there are no unpleasant after-effects. The bromine is not split off the compound in the digestive tract, so the isolated action of this element does not occur, and there is no trace of Bromine in the urine after the administration of Bromural.

I have found Bromural to be a very good hypnotic for sane people, producing a very pleasant sleep in about 30 minutes after its administration which lasts from 5 to 7 hours.

In insane people it appears to vary in its action considerably, sometimes it produces sleep, in other cases it fails to do so, and I have known it cause great cardiac depression. It is, however, useful in some of the forms of Insomnia in insanity.

PATIENTS TREATED WITH BROMURAL.

Rachel L. Admitted November 30th, 1910.

This patient was admitted suffering from Recurrent Mania. She was in a state of acute excitement shouting and gesticulating, and rushing about the ward. It was necessary to keep her confined to bed. She took her food, but slept badly. She was given 10 grains of Bromural which had no effect on the first night, but on the second night the patient slept very well. She was given Bromural twice a week, and it acted very well in her case for a time. It then ceased to act and was replaced by Neuronal.

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C. M.

This patient was not a lunatic, but a sane person suffering very badly from Insomnia, and inclined to be Neurasthenic. She was sleeping very badly, and on November 5th was given a dose of 5 grains of Bromural - this had no effect. Two nights after she had another dose of 10 grains, after which she had a very good night, and it was not necessary to repeat the dose any more.

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I have often found Bromural is very useful to give as a hypnotic when other hypnotics fail owing to tolerance having been established. The following case is illustrative of this.-

Fanny H. Admitted October 7th, 1909.

She was suffering from Chronic Melancholia, was depressed and dull. She had delusions of unworthiness - thinking she had committed some unpardonable sin. She was exceedingly agitated and unable to occupy herself. She had been taking Sulphonal for some time up to 20 grains - tolerance was established. This was changed to Veronal, and after a time tolerance was produced in this case. The drug was changed to Bromural gr. X on December 5th and she had a very good night's sleep.

Edith G. Admitted November 7th, 1910.

Patient was suffering from Melancholia, was unnaturally silent, dull and unoccupied, but was able to converse. She had no particular delusions. Her form of insanity showed itself in extreme Melancholia. She was utterly wretched and sleeping very badly indeed. On 27th of November she was given 5 grains of Bromural, but had hardly any sleep at all. This was increased to 10 grains in a few days, but it did not appear to suit her and she did not sleep. Veronal was then given with good results.

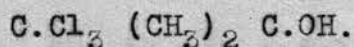
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Helen F. Admitted November 19th, 1910.

She was suffering from Acute Mania, and was in a state of acute excitement, incoherent in speech, and had to be fed forcibly as she refused food. She was given 10 grains of Bromural two nights after admission. She only slept  $1\frac{1}{2}$  hours, and the drug was changed to Paraldehyde, which had a good effect.

Chloretone.

Trichlor - Tertiary - Butyl - Alcohol.



This substance occurs as white crystals. It is soluble 1 in 200 of water 1 in 10 of glycerine and 3 in 2 of alcohol. It has a strong camphoraceous odour.

As a hypnotic it is rather like chloral but it is less irritable to the stomach. It also has the advantage of having a smaller dose than chloral. On several occasions I have found it useful as a hypnotic. The small dose and the fact that it is very soluble in alcohol make it convenient to use.

PATIENTS TREATED WITH CHLORETONE.

Miss Madeline C.

This patient has been in the Hospital for many years suffering from Chronic Mania - Incoherent in speech, dirty in habits, and had a habit of eating paper whenever she got the opportunity. Occasionally during October 1910 it was noticed that she did not sleep as well as usual, and on November 8th she was given 10 grains of Chloretone. She had a fairly good night, and on the 11th the drug was repeated, same dose. She generally slept from 9 to 6. The drug was continued twice a week for a fortnight. She slept fairly well, and it was not necessary to repeat it.

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NEURONAL. (Bromo-Diethyl Acetamide.)

This is a powerful hypnotic. The average dose is 15 grains, but it may safely be given up to  $22\frac{1}{2}$  grains. My own experience is that 10 grains is quite sufficient in ordinary cases of Melancholia, but I have not found it of very much service in the severe form of Insomnia met with in Acute Mania and Acute Melancholia, where the patients are so bad that they require forcible feeding.

The drug is said to be insoluble in cold and hot water. I find that if 10 grains are put into 1 ounce of cold water in the morning, by evening it has dissolved sufficiently for all practical purposes though it does not dissolve so easily as gr. XX of Chloralamide in 1 ounce of water, and can be easily taken. It is said to produce great depression, but I have not always found it do so. The following cases are illustrative of this.-

Mary F. Admitted November 1st, 1910.

She was suffering from Recurrent Melancholia, and was unnaturally silent, dull and depressed. She was very agitated and miserable. She was also suicidal, and slept under observation. She did not take the initiative in conversation, but replied to questions when spoken to. She slept badly. At times cried without cause. About December 9th the Insomnia had increased, and she was hardly sleeping at all. On December 11th she was given 10 grains of Neuronal at 8.30 p.m. She slept from 9.30 until 6 the next morning.

There was no depression in the morning - in fact, she was more cheerful than she had been for some little time. She continued to take it twice a week for some time.

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Elizabeth P. Admitted November 13th, 1910.

She was suffering from Acute Melancholia. She was in a stuporose condition, and did not appear to know where she was. She pulled out the greater part of her hair. She did not speak and it was necessary to feed her forcibly. She was given 4 drachms of Paraldehyde on the night of admission, and she was asleep within three minutes of taking the drug. In less than five days she took her food. The Paraldehyde was discontinued. She was not sleeping well about the beginning of December, and on December 11th she was given 10 grains of Neuronal at 8.30. She slept 5 hours - from 12 to 5, and there was no depression in the morning.

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Emma J. Admitted November 10th, 1909.

She was suffering from Chronic Melancholia. She had been taking Sulphonal from time to time, but generally slept badly. She was depressed, and unnaturally dull and silent, although she occupied herself. She also had delusions of unworthiness. On December 10th, 1910 she was given 10 grains of Neuronal. The drug was administered at 8.30 and she slept from 9.15 to 6, and there was no depression next morning.

Caroline T. Admitted February 27th, 1907.

She was suffering from Chronic Melancholia. She slept badly and from time to time she had Trional, Sulphonal and various other drugs. On December 11th 1910 she was given 10 grains of Neuronal, and she slept from 10 to 5, and there was no depression next morning. The drug was continued twice a week for some weeks, and no depression was caused.

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Rachel L. Admitted November 30th, 1910.

She had already had doses of Bromural, and slept occasionally. This drug was changed on December 10th to 10 grains of Neuronal. It was administered at 8.30, and the patient slept from 10.30 to 6 o'clock, and she complained of no depression. The drug was continued twice a week for some weeks and she always slept well.

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Chloralamide (Chloral Formamide).

This occurs in colourless shining crystals prepared by combining Anhydrous Chloral with Formamide.

Its formula is  $\text{CCl}_2\text{CH}(\text{OH})\text{NH}\cdot\text{COH}$ .

I find this a very useful hypnotic in cases of Insomnia in Mania where there is cardiac Dilatation and weakness, and I have found 20 grains sufficient.

I generally find that 20 grains will dissolve in 1 ounce of water when left for a few hours, and this is the best way of administering the drug.

The following case shows the use of this drug in Chronic Mania with Dilatation of the Heart.-

Anna G. Admitted June 24th, 1908.

She was suffering from Chronic Mania and was excitable at the time of her admission. She was unable to converse rationally, was wet and dirty in her habits, and had to be kept in bed. This state of affairs passed off after a time, but from time to time she was sleepless, complained of headache, and had a dilated heart and rapid pulse. She also had slight Oedema at times. The Insomnia in her case was probably more on account of her heart than her mental condition. On December 9th, 1910 she had 20 grains of Chloralamide dissolved in 1, ounce of water. The drug was administered at 8.30, and she slept for 7 hours, viz. from 9 to 3 and from 5 to 6 in the morning. She stated that she had no headache at all - she had complained of headache

on the previous day. The drug was repeated on December 13th and she slept for  $6\frac{1}{2}$  hours.

In ordinary cases of Mania I find it is of very little service. The following cases are illustrative of this.-

Miss B. Admitted May 16th, 1904.

She suffered from Chronic Mania. This was followed by Secondary Dementia. She was more or less in a stuporose condition, could not reply to questions, and at times slept exceedingly badly. On December 9th she was given 20 grains of Chloralamide and she only slept 4 hours, from 11 to 3. The dose was repeated on December 13th, and she had no sleep at all.

Mrs. Emily F.

This patient was suffering from Dementia, and had been in the Hospital for many years, and very often had no sleep. On December 9th she was given 20 grains of Chloralamide, but it had no effect. On December 13th she had 40 grains; this had no effect, and she did not sleep at all.

CONCLUSIONS.

With regard to the use of the newer hypnotics in cases of insanity, my experience is that insane people require a very much larger dose than other people - especially those people who are suffering from the acute forms of Mania or Melancholia, in these cases a very large dose is required in order to produce any effect.

I used to find Sulphonal fairly useful some years ago if not continued for too long. I have never had a case of Haematoporphyria from using this drug, but I have found that in some patients it produced muscular inco-ordination and weakness. I have not quoted any cases where I have used this drug because I have not used it for some considerable time. Dr. Robertson of Edinburgh is very averse to using the drug at all on account of its after effects.

I found Trional a more useful drug in some cases of Insomnia where this Ataxic effect of Sulphonal has been produced, but I used to notice that some patients preferred Sulphonal to Trional, as they stated that the hypnotic effect of the latter drug was not so good.

I have found Trional very useful at times when combined with Bromide of Potassium.

I found Veronal a more powerful drug than either Trional or Sulphonal, but it appears to lose its power after it has been given some little time.

Bromural is very useful in some cases, but I have known it cause great Cardiac depression.

Chloralamide is very useful in cases of Insomnia where there is Cardiac weakness, but it does not act so well as Veronal or Trional, although it is less dangerous.

Chloretone, I have found, suits some patients remarkably well, especially where Insomnia has been accompanied by headache - after a night's sleep the patients have stated that the headache has disappeared. In some cases, however, I have found this drug of no service.

Amylene Hydrate if given in no less than a 40 minim. dose I have found of some service. In my experience this drug does not appear to lose its power to a very great extent after being given for some time. It is, however, rather difficult to get many insane patients to take the gelatine capsules, in which form this drug is usually administered.

Neuronal is a drug that I have recently tried with very good results. It is a very powerful hypnotic, and in some cases I have found it of great service where Veronal and Trional have failed. I have not found it produce any depression, headache, or ataxia, and lately - in one case especially, I have had very good results with the use of this drug.

Proponal, I have never used. According to Farquharson there is too narrow a margin between the Therapeutic and Toxic dose.

Chloralose and Tetronal I have not used either, because they are stated to be dangerous.

Paraldehyde has too unpleasant a taste to give in ordinary cases of insomnia where the patients are fairly sensible and up and dressed, and do not require forcible feeding. In my experience, however, this is the only drug that is of any real value in the treatment of the profound insomnia which accompanies cases of acute mania and acute melancholia where the mental condition of the patient is so bad that it is necessary to keep them confined to the padded room, and where it is also necessary to feed them forcibly. I have found that when Paraldehyde is given to these patients in doses of four drachms, they are usually asleep within five minutes of the administration of the drug, and generally sleep six to eight hours. I have continued the use of this drug in this dose three times weekly for as long a period as eight weeks, and have had no harmful results; the patients generally making a complete recovery.

Chloral Hydrate I have not used for some time on account of its effect upon the stomach.

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