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*A Clinical Study of Paraldehyde and
Sulphonal.*

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A CLINICAL STUDY OF PARALDEHYDE AND SULPHONAL.

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As the value of the new hypnotic sulphonal is still being tested, an account of a clinical comparison between it and paraldehyde may perhaps add something to our knowledge.

The very favorable experience of Cramer and others with the drug, together with the statement of Rabbas, "that it is more desirable than amyl hydrate or paraldehyde," led me to use it and the latter drug quite extensively in the insomnia of mental disease, with the view of determining more accurately their relative worth and the kind of cases to which they were especially adapted, and in which they could be used with the best hope of success and with most benefit.

The observations which are the subject of this paper extended over a period of six months, beginning Nov. 1, 1888. During this time paraldehyde was used in 100 cases, and sulphonal in 166 similar cases. Each drug was used in 20 cases of acute and chronic disease in which the insomnia was due to other than purely mental causes. The patients to whom either drug was administered were watched by competent nurses, and the exact time of sleep noted, and all these results carefully recorded. The standard of success was the same with each drug, and was as follows: From six to nine hours was counted a successful trial, from three to five hours a partially successful result, and under three hours a negative effect. The dose used varied with the age, sex, and condition of the patient and with the intensity of the insomnia; in the case of paraldehyde, from one to two and a half fluidrachms, and sulphonal from gr. xv to one drachm. The after-effects were also recorded as they occurred.

First let us study the result of paraldehyde in 100 cases, 48 males and 52 females, embracing nearly all the varieties of disease of the mind, as follows: acute and chronic melancholia, acute and chronic mania, the various dementias, periodic mania and circular insanity, general paralysis of the insane, alcoholic mania and primary dementia.

In 25 cases of chronic dementia (including all its varieties excepting epileptic), 1021 trials were made, an equal number in each case. These cases of insomnia varied from simple wakefulness to the noisy unrest of



the terminal dement. Of these trials 834, or 81.7 per cent., were successful, 12.7 were partially so, and 5.6 per cent. were negative.

In 11 cases of chronic melancholia habitually sleepless, 397 trials were made, with success in 67.2 per cent., partial success in 23.4 per cent., and failure in 9.3 per cent.

In acute melancholia, in the first month of the disease, 139 trials were made in 6 cases, of which 81.2 per cent. were successful, 7.1 fairly so, and 11.5 per cent. negative, while all of the cases were markedly benefited by its use.

In epileptic dementia 66.9 per cent. of 372 trials in 7 cases was successful, 25 per cent. partially so, while but 8.1 per cent. were negative.

Out of 1080 trials in 27 cases of chronic mania all markedly sleepless, and many accustomed to other hypnotics, 57 per cent. were successful, 25.6 per cent. fairly so, while 17.3 per cent. were negative.

In acute mania 66 per cent. of 198 trials in 10 cases, 4 males and 6 females, were successful, fairly so in 14.5 per cent., and entirely negative in 25.5 per cent. of the trials made. Two of these cases were not influenced at all by the drug.

In the wakeful and restless states of the second and third stages of general paralysis of the insane 62.6 per cent. of 193 trials upon 7 cases, all males, were successful, 26 per cent. partially so, while 11.4 per cent. were negative.

In 5 cases of periodic mania (one was a case of circular insanity), all in the stage of excitement, 109 trials were made, with success in 59.6 per cent., partial in 27.5 per cent., and negative effect in 12.8 per cent., while 23 trials in a case of primary dementia with great restlessness resulted in success in 86.9 per cent., while only 4.3 per cent. were negative, and the remainder doubtful results.

From this we learn that paraldehyde was of most service in the insomnia of the dementias, of least service in acute mania, and that its efficiency is nearly equal in acute and chronic melancholia and epileptic dementia; also that it was less serviceable in the insomnia of the maniacal states than in melancholic conditions,—for only 57 per cent. of trials in chronic mania were successful. Strange to say, in periodic mania it failed in only 12.8 per cent., while in acute mania the percentage of failures was 25.5 per cent.

Summarizing these statistics of its use, we find that of the 3515 trials made upon these 100 cases, 2407, or 68.5 per cent., produced from six to nine hours' sleep; 711, or 20.2 per cent., from three to five hours; and 397, or 11.3 per cent., failed utterly to produce sleep.

Besides the foregoing cases, paraldehyde was used in 20 cases in which the insomnia was not due to a mental condition, but was a symptom of some acute or chronic disease. These cases were made up as follows: phthisis, 2; erysipelas, 6; acute rheumatism, 3; pneumonia, 3; cerebral

gumma, 1; typhoid fever, 1; painful leg ulcer, 2; cellulitis of arm, 1. To these paraldehyde was given 267 times, with success in 50.9 per cent.; partial success in 19 per cent.; and complete failure in 30.1 per cent. of trials.

Following the example of H. B. Williams, M.D. (Assistant Physician, Arkansas Insane Asylum), I have also employed it in epilepsy and in the status epilepticus, but with no encouraging result.

Leaving paraldehyde for the present, we will consider its newer rival, sulphonal. The clinical data of this new chemical are already getting numerous. I will refer to the following: Cramer had 92.6 per cent. of "positive success" in 92 insane cases, with "no instance of any unpleasant after-effect." Schwalbe had, in 66 per cent. of 50 cases, a "prompt and satisfactory effect;" while, in 24 cases of purely nervous insomnia, 90.3 per cent. of his trials were effective. Rabbas employed it 200 times with "good effect." Papers have also been contributed by Kast, Ziemssen, Oestreicher, Schmey, Fränkel, Rosenbach, Rosin, Salgo, Mathes, and others. Schmey asserts that it is dangerous in arterio-sclerosis, and Mathes and Ziemssen admit unpleasant after-effects in 19 per cent. and 20 per cent. respectively; yet the great weight of their united testimony is in favor of sulphonal; while Kast says that it does not affect pulse or respiration, and that only very large doses lower the blood-pressure (*Amer. Journal Med. Sciences*, July, 1888).

In this country papers have been written by W. H. Flint, M.D. (*New York Med. Journ.*, December 15, 1888), H. M. Wetherill, M.D. (*Med. and Surg. Rep.*, October 13, 1888), Sachs (*Med. Record*, October 6, 1888), Wilson and Hutchinson (*Med. and Surg. Rep.*, June 9, 1888), and others. Dr. W. H. Flint had success in 82 per cent. of his trials in 33 cases. He recommends it especially in the insomnia of debility, and in recovery from the morphine habit; says it is useless in cardiac dyspnoea, and that it has no anodyne properties.

My own observations of the action of sulphonal were carried out under the same conditions, and in about 50 of the same patients as in the case of paraldehyde. The number of patients to whom the drug was given was 166. Of these 69 were males and 97 females. The dose was administered at 7 o'clock P. M., in some hot menstrum (milk, beef-tea, etc.), as advised by Kast. The results obtained were as follows:

In 27 cases of epileptic dementia with marked insomnia, 143 trials were made, the dose being gr. xxx in all the trials. Of these, 123, or 86 per cent., produced from six to nine hours' sleep; 9.1 per cent. from three to five hours; and 4.9 per cent. were negative.

In the more restless and noisy states of chronic mania 269 trials upon 21 cases gave 206, or 76.5 per cent. of successes; 13.8 per cent. partially so; and 9.6 per cent. were negative. Dose from gr. xxx to gr. xlv.

In acute mania larger doses were necessary—average dose gr. xl; 108

trials upon 4 male and 6 female patients gave 75 per cent. successful; 10.1 per cent. of doubtful efficiency; and 14.9 per cent. negative.

In the maniacal phases of periodic mania and circular insanity 70 per cent. of 47 trials upon 5 cases were successful: 11 per cent. were negative; and 19 per cent. of doubtful value. The same doses were used as in acute mania.

In 43 cases of chronic dementia (including all varieties except epileptic) 199 trials gave 70.3 per cent. successful; 18.2 per cent. fairly so; and 11.5 per cent. negative. Average dose gr. xxv.

In 33 cases of chronic melancholia without very marked mental depression, all sleeping habitually from one to four hours, 330 trials were made, an equal number upon each patient. Of these, 67 per cent. were successful; 17.2 per cent. of doubtful value; and 15.8 per cent. were negative. Seven of these cases could not be influenced by the drug, although as high as gr. 50 were given.

In acute melancholia sulphonal was used in 21 cases—8 male and 13 female patients, all of whom were in the first three months of the disease, and the majority of them were instances of extreme mental depression, amounting in many to absolute agony. In these cases 178 trials of the drug were made, with the result that only 49 per cent. were successful, while 36 per cent. were wholly negative, and 15 per cent. were doubtful results.

In 6 cases of general paralysis of the insane, presenting the same stages as those in which paraldehyde was employed, 39 trials were made. Dose, gr. xxx. Of these, 30.8 per cent. only were successful, 46.2 per cent. partially so, and 23 per cent. failed.

Summarizing these results, as in the case of paraldehyde, we find that the whole number of trials of sulphonal upon these 166 patients amounted to 1313: of these, 910, or 69.3 per cent., produced from six to nine hours' sleep; 206, or 15.6 per cent., from three to five hours' sleep; and 197, or 15.1 per cent., were negative in effect.

From the above it would appear that sulphonal is most successful in the insomnia of epileptic dementia, and least so in acute melancholia; that it is about equally efficient in the insomnia of all the remaining dementias and periodic mania (in the latter states its success exceeds that of paraldehyde by 21 per cent.); also, that it is far more useful in maniacal conditions than in depressed states, and upon this I wish to lay especial emphasis, as I consider that sulphonal does harm instead of good in any form of melancholia. The reason of its failure to produce sleep in such conditions may be partly due to its slowness of action, but the mental condition of the patient must be considered as the first factor. It is the after-effects of the drug, however, that make it very undesirable in such cases, and tend to deepen the mental depression of the patient.

The power of sulphonal as a hypnotic in acute and chronic diseases

in which pain, cough, dyspnœa, or fever were the underlying causes of the wakefulness, was tested in 20 cases, other than those already referred to. They consisted of 6 cases of erysipelas, 4 of acute rheumatism, 2 of phthisis, 2 of acute abscess, 2 of suppurative tonsillitis, 1 each of lead colic and cardiac dyspnœa, and 1 each of neuritis of upper extremity and asthma. In these, 190 trials were made, 42 per cent. being successful, 48 per cent. being negative, and 10 per cent. giving uncertain results.

In the 2 cases of opium habit in which I have employed the drug, one case was very much relieved by it, and the patient expressed himself as much pleased with its effects, while in the other case it was useless, although large doses were given. From 120 observations upon 40 patients, the average time in which they slept after taking sulphonal was found to be sixty-three minutes.

Having considered the actual proportion of the successes and failures of these two drugs, I will now compare their after-effects.

Although, as we have seen, these two drugs differ considerably in their action in the various mental diseases, as well as in other diseases, their greatest differences lie in their after-effects. Here they widely diverge, one being capable of producing very few and comparatively innocuous after-effects, while those produced by its fellow are, to say the least, capable of being dangerous to life. A paraldehyde habit has been noted in a few cases since the advent of the drug, but I have not yet seen a case, although many of the patients in this institution have been taking it for many months continuously. Among this class of patients I have in vain sought for a case; and from the very limited number of cases that have been reported, when we consider its very general use since 1882, I conclude that it must be a rare occurrence compared to the frequency of the chloral, chloroform, or morphine habit. It certainly possesses two great safeguards in its taste and the odor it leaves upon the breath for from eight to sixteen hours after its ingestion. Whether sulphonal is liable to form a habit I am at present not able to say; but I have one patient who has been taking it about six weeks, and who has recently repeatedly asked to have the dose increased. Neither have I seen the continuous use of paraldehyde followed by serious nasal ulceration, as Dr. J. G. Kiernan has reported (*Wood's Therapeutics*), although in several cases I have seen a scattered papular eruption over the upper part of the body in debilitated subjects.

The principal after-effects of paraldehyde in my cases have been due to its irritant action upon the gastro-intestinal mucous membrane, and for this reason it should be given well diluted. Diarrhœa, vomiting, and impairment of the digestive functions have occurred in about 7 per cent. of cases. Strange as it may appear, I have seen its continuous use followed by increase in appetite and a corresponding increase in digestive power in several cases of atonic dyspepsia. Whether this was

wholly due to its stimulant action upon the gastric mucous membrane, or was the result of the relief of sleeplessness, it is difficult to say, but I think that probably both combined gave the result. I have never seen paraldehyde produce any serious alteration in the pulse, temperature, or respiration, and these observations are abundantly confirmed by many who have extensively used the drug. It will be sufficient to quote from a paper by H. C. Harris, M. D., on its use upon 152 patients at the Norristown, Pa., Insane Asylum. He says: "Its advantage over chloral, in our experience, is mainly that there is no danger from its action on the heart; in fact, 100 minims have been given to cases of acute mania without the slightest noticeable effect upon the heart or respiration." The very fact that this drug has been so extensively used since 1882, and that so few bad effects have been noted, proves pretty conclusively its safety, even in the fullest therapeutic dose.

What evidence have we that sulphonal is capable of producing more serious symptoms? The very high commendation which it received at first led to an extensive use of the drug, and very soon cases were reported in which unpleasant symptoms occurred. Dr. Bornemann (*Deutsche medizinische Zeitung*, Nov. 26, 1888) relates a case—male, aged fifty-three, suffering from the morphine habit—who was given 90 grains in four hours. Muscular weakness and incoördination and great mental depression were produced, while the ataxia did not disappear until the sixth day. Dr. Schotte, of Cassel, has reported a case in which difficult movement of the tongue, stupor, headache, and loss of appetite persisted for four days, and were succeeded by an eruption, like that of measles, over the entire body, lasting two days. Dr. Engelman (*Wiener medizinische Blätter*, Nov. 1, 1888) gives a case—female, aged forty, suffering from chronic metritis—in whom only gr. xxx produced, the following morning, a diffuse scarlet eruption, extending symmetrically over the body, which subsided with violent itching on the third day.

It may be stated that 30, or 18 per cent., of my 166 cases experienced unpleasant after-effects. Some persons seem very susceptible to it (as in Case III. detailed below), while I have given in violent maniacal states as much as one drachm daily for twelve days, with no alarming symptoms. The after-effects of sulphonal are far more variable and are more significant of its more powerful action upon the great nerve centres than those of paraldehyde. The effects which it in some cases produces bear no direct proportion to the amount ingested, so that the production of the various symptoms in these cases must, at least in great part, depend upon other conditions of the organism itself; while I have no doubt that the conditions of its solution in and absorption from the intestinal tract have great influence also in their production. The after-effects which I have seen follow its use will be best understood from the following detailed cases:

CASE I.—Female; aged forty; periodic mania. In the intermissions patient was in good health. During an attack of active mania one drachm daily in divided doses was given for two days. On the morning of the third day she was much depressed mentally, pulse small and feeble, respiration distinctly slow, and temperature 96.4° F. Upon attempting to walk, great muscular weakness was evident. This condition lasted for two days, after which her mania re-appeared. Sulphonal was resumed in the same dose, and the same symptoms returned on the fourth day, with very marked muscular incoördination added. These symptoms abated gradually in three days after the withdrawal of the drug.

CASE II.—Male; aged twenty-six; acute mania. Was given gr. xv three times a day. Beginning on the second day, this patient had successively headache, vertigo, slight and, later, decided weakness of the heart-beat, pallor of the surface, coated tongue, dryness of the mouth and pharynx, and repeated emesis, all passing away when the drug was stopped.

CASE III.—Female; aged thirty; epilepsy. After one dose of gr. xxx of sulphonal slept well, but, when seen sitting in a chair the following morning, could not be roused. The pupil was half dilated, and reacted to light very slowly; the eyelids drooped, and the head inclined forward upon the chest; sensation to the prick of a pin was abolished; the muscle reflexes could not be obtained, and respiration was slow and somewhat irregular. These symptoms persisted for forty-eight hours, and then gradually passed away. There was in this case total disability to walk, even with the assistance of two persons.

CASE IV.—Male; aged thirty-three. The continued use of gr. xxx of sulphonal at night followed by lassitude, distaste for food, weakness, occasional vomiting, and diarrhoea.

CASE V.—Male; aged forty-five; chronic melancholia. Gr. xlv of sulphonal daily for three days produced extreme weakness, dryness of the mucous membranes, and a peculiar semi-delirious condition, in which the patient seemed conscious at times that he was acting strangely.

CASE VI.—Female; aged sixty-five; chronic melancholia of a mild form. This patient is sensible in conversation and only looks upon the dark side of life; insomnia very marked. Sulphonal, gr. xxx, at night for ten days was given, when symptoms resembling closely those of acute alcoholism came on. She conversed volubly, incoherently, and without her accustomed sense, while a decided stagger in her gait was manifest. This latter symptom seemed due partly to lack of coördination, while muscular power seemed also affected.

CASE VII.—Female; aged thirty-two; periodic mania. In the intermissions is afflicted with persistent insomnia. Sulphonal, gr. xxx, at night was given with good effect, but on the fifteenth day an eruption appeared. This consisted of deep red blotches, slightly elevated, well defined, varying in size from a pin's head to a split pea, and uniformly distributed over the body. Intense itching accompanied it. This eruption faded in three days, the drug being stopped, but when sulphonal was resumed, a week later it came back and presented the same appearances.

CASE VIII.—Female; aged thirty-eight; acute melancholia, associated with phthisis and exophthalmic goitre and intense insomnia. Was given sulphonal, gr. xxx, at night, and after the third dose left

foot became swollen and red, with considerable œdema of subcutaneous tissues. In a few hours similar patches of erythema, with less œdema, appeared on both thighs, arms, and anterior surface of the trunk. In the latter situation it assumed a papular form upon an erythematous base. These patches were the size of the hand, and rapidly appeared and disappeared in the various regions named. This condition passed away gradually in four days after the drug was stopped. During this time the woman had a slight degree of fever, lassitude, and loss of appetite.

CASE IX.—Male; aged fifty; chronic mania. After having had gr. xxxv of sulphonal for a week at night, began to show lassitude, congested eyes, dry tongue, weak pulse, diarrhoea, anorexia, and muscular weakness and incoördination. When the latter symptoms appeared sulphonal was discontinued, and they gradually passed away in three days.

CASE X.—Female; aged twenty-eight; epilepsy. After gr. xxx of sulphonal one day, followed by gr. xxx the next day, appeared dull and weak, and twelve hours later had great difficulty in swallowing even liquids. These symptoms passed away in twenty-four hours.

The last case that I will refer to is of especial interest as illustrating the severity the after-effects of this drug may attain.

CASE XI.—This patient was a vigorous, healthy female, of fine physique, but subject to epileptic seizures. Her attacks have been rapidly increasing in frequency, and gr. xx of sulphonal three times daily were added to her treatment. After taking six doses, dizziness and drowsiness appeared, which, by the following day, had deepened into stupor, with unsteadiness of gait and an indescribably dull appearance of her usually attractive face. The patient was in a dreamy state with drooping eyelids, an anxious expression, and seemed in constant fear of some impending danger. She frequently exclaimed, "I hardly know where I am." At this time there was also dryness of the buccal mucous membrane, decided dimness of vision, and rapidity and weakness of the pulse. Sulphonal was now stopped, but, nine hours later, she fell upon the floor from weakness, and one hour later her condition was as follows: She was unconscious but could be roused with difficulty, respiration shallow, laborious, and 40 to the minute; mouth very dry, but she swallowed without difficulty. The tendon reflexes were nearly absent, while the pupils, which were equal and somewhat dilated, reacted to light very slowly indeed. Sensation in the skin and conjunctivæ was abolished. The bodily temperature was 97° F. After six hours patient uttered a few inarticulate words and relapsed into profound unconsciousness, which lasted for fifteen hours more, when she again became partially conscious, and for the next twenty-four hours she kept alternating between coma and consciousness. During the comatose periods the respirations were more rapid, and at one time were 42 to the minute, while the pulse was weaker than when she became partially conscious. On the third day she could be roused by the voice, but recognized no one. Now her respiration was 25 to the minute and the heart was acting much better. In the afternoon of the fourth day pulse and respiration were about normal. There was extreme mental confusion and a mild delirium at times. By the seventh day the woman was nearly in her usual good health again. At no time was there any fever.

These cases certainly proved that sulphonal is capable of being a dangerous remedy, even when used in therapeutic doses. Many of our patients, however, received larger doses and yet suffered no bad effects. In one case of chronic mania gr. lxxv daily were given for over a week without bad effect, and it did not produce sleep. The remainder of the cases in whom marked after-effects were noted suffered in milder degrees sulphonal intoxication, as detailed in the above eleven cases. The most common of the effects observed were lassitude, dizziness, and vertigo, diarrhœa, vomiting, and great mental depression, with a dreamy half-unconscious expression upon the face. In two cases partial loss of muscular coördinating power was the only effect produced, and these patients did not sleep from its use. The very various symptoms produced by sulphonal suggest a very general action upon the nervous system, but it remains for the experimental therapist to explain their causation. Cervello says: "Paraldehyde affects the cerebrum, spinal cord, and the bulbus successively, abolishing the reflexes, causing anæsthesia by anæmiating the brain and cord. It is eliminated by the lungs, and is not a cardiac poison." In some of my cases in which sulphonal was employed weakness of the circulation was very marked, while in Case X. respiration appeared chiefly affected. Why the drug in one instance produces delirium, in a second incoördination of the muscular system, in a third difficult movement of the tongue, and in a fourth stupor, cannot be explained from our present knowledge of its action.

The practical deductions that my experience with these two drugs would suggest are:

I. That paraldehyde is the safer hypnotic where a continuous action is desired.

II. That paraldehyde has a wider range of application in mental disease than sulphonal, and that in the insomnia of acute or chronic disease, where pain, cough, dyspnœa, or fever exist, sulphonal is less effectual than paraldehyde.

III. That in all depressed mental states sulphonal acts ineffectively, and acute melancholia should be a contra-indication to its use, while in maniacal conditions it is more satisfactory than paraldehyde. That the use of the former in general paralysis of the insane should be carefully considered, while in acute melancholia the latter is usually effective.

IV. That a high degree of physical debility with insomnia should contra-indicate sulphonal.

V. That in 18 per cent. of cases various degrees of sulphonal intoxication appear, and that it would seem that the drug is capable of being dangerous to life, and that, therefore, the commencing doses should be small, some persons being extremely sensitive to its influence.

VI. That the effects produced by sulphonal are not always in proportion to the dose administered, and that in some cases at least it very

seriously interferes with the normal bodily secretions, while paraldehyde does so to a very much less extent.

In conclusion, my thanks are due to Dr. Eliot Gorton and Dr. L. L. Mial for aid in collecting the results referred to, and for references to cases in their wards. *

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