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REMARKS

ON

THE UNPLEASANT EFFECTS OF SULPHONAL.

BY

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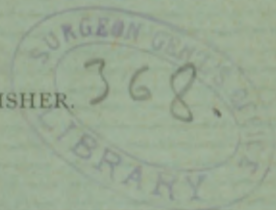
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REMARKS

ON THE

Unpleasant Effects of Sulphonal.

IT is the almost invariable history of every newly-introduced drug of real therapeutic value that, at first received with almost unanimous approbation and enthusiasm, the disadvantages which it possesses have gradually come to the fore ; so that many physicians whose experience with it has chanced to be unfortunate have gone to the other extreme, and have discarded a remedy really capable of rendering great service. One has but to recall the history of cocaine to become convinced of the truth of this statement. Antypyrin, too, was and, indeed, still is used with a freedom and carelessness which the experience of many has shown to be dangerous ; and the once "harmless" acetanilid now produces collapse and death. Yet these and many other of our materia medica, though capable of doing harm, are much oftener productive of the greatest good if properly used, and if their possible dangers are kept in view. In like manner sulphonal came to us



highly recommended by its earlier users, and with scarcely a dissenting voice concerning its admirable hypnotic action and its entire freedom from unpleasant effects. Having reported a year ago, in conjunction with Dr. Elwood R. Kirby, the result of some clinical experiments with urethan and amylene hydrate as hypnotic agents, I began with great interest and great expectations the administration of sulphonal as a drug of the same class. Experience in a large number of cases has convinced me, however, that though a very valuable agent, it is by no means without the power of producing undesired and quite unpleasant secondary effects ; and cases now not infrequently reported in the journals confirm this opinion.

It is not at all the object of these remarks to decry a useful medicine, but to aid in establishing its true value in comparison with other hypnotics ; and, by pointing out some of its possible disadvantages, to warn against the unpleasant surprises and disappointments which might otherwise lead to its abandonment. The cases to be detailed by way of illustration have occurred entirely in my own experience. Those quoted from medical literature do not at all complete the list of unfavorable cases reported in the journals.

1. First to be noticed among the disadvantages of sulphonal, and undoubtedly a very prominent one, is its *slowness of action in producing sleep*. This is to be carefully borne in mind in determining the hour of its administration ; and the patient should perhaps be notified of its peculiarity, or disappointment and dissatisfaction may arise. This

slowness of action has so usually been noticed in the cases under my care, that to cite instances of it would be only tedious. So generally, indeed, has the experience of clinicians agreed as to this point, that Kast, who first employed the drug, has written a second article (*Therap. Monatsh.*, July, 1888), which might almost be called a *defence* of sulphonal, and in which he discusses the reasons of this long delay in action. As a result of experiments on animals and with digestive solutions outside of the body, he advises that it be administered in a finely-pulverized condition, in at least 200 c.c. of a warm fluid, with the evening meal between seven and eight o'clock. The presence of a large quantity of fluid, of hydrochloric acid, peptones, and of salts favors the rapid absorption of the medicine.

2. Another and even greater difficulty to be overcome in the use of sulphonal is the *marked tendency which its hypnotic action has to persist during the succeeding day*. The following case is an excellent example of this :

CASE I.—Mr. Robert S. Ulcerative endocarditis with aortic insufficiency and very troublesome insomnia. 20 grains of sulphonal given at about 10 P.M. He did not fall asleep for some hours, but throughout the whole of the next day until late in the afternoon he was so overcome by sleep and so stupid that replies could scarcely be obtained to questions addressed him, and the family became quite alarmed. The same condition was seen on another occasion after a dose of the same size. In fact, sulphonal seemed always in this case to produce sleep lasting only a few hours at night, while upon the next day the

patient could scarcely rouse himself. In such a case as this it is not pleasant on entering the room to be greeted by the friends with the words, "Oh, doctor! Those powders, those powders!"

The following less striking case illustrates the same continuance of action after a still smaller dose :

CASE II.—William S. Phthisis and chronic rheumatism. Insomnia usual, though not as a result of cough or pain. After 15 grains of sulphonal, given at 8.30 P.M., the patient slept well, but continued drowsy until noon of the following day.

The same condition is exemplified by some of the other cases to be presently related. (See Cases III., V., VI., XV., and especially XII.)

This prolonged hypnotic action has frequently been referred to by writers. L. L. Johnson (*Med. News*, September 8, 1888), for example, reports a case in which the patient promptly fell asleep after 30 grains of sulphonal given in the evening, but was very somnolent until afternoon of the next day. In smaller amount the drug acted very well. Algeri (*La Riforma Medica*, No. 233, 1888) says that the action of large doses continues through the following day, and Oestreicher (*Berlin. klin. Wochenschr.*, June 18, 1888) has seen sleep remain absent during the night, but persist through the following morning. Lovegrove (*Brit. Med. Jour.*, May 26, 1888), too, states that the effects on patients to whom he gave the drug were very discouraging. For several hours after taking it no appreciable action could be noticed, but during a great part of the next day there was extreme drow-

siness and considerable cyanosis. The case of Schotten's, presently to be quoted, is of especial interest in this connection. Kast discusses this "postponed action" in the article referred to, admitting that it is often witnessed, and that it constitutes a great disadvantage when it is necessary that the patient be actively employed during the day. For this difficulty he has no special remedy to propose in addition to the method of administration described, except that the dose be carefully adapted to the individual.

3. But this *determination of the individual dose*, in order to overcome the difficulties mentioned, itself constitutes a sometimes insurmountable obstacle to the use of sulphonal. I have frequently found that the amount necessary to produce satisfactory sleep was followed by the prolonged effect on the following day, or by various unpleasant after-effects presently to be described, while any smaller amount failed to bring the desired result during the night. In quite a number of cases it was observed that a small dose merely served to render the patient uncomfortable in the night and upon the following day, while a full dose procured satisfying sleep, and the morning was free of prolonged action or disagreeable after effects. It would seem sometimes as though sound sleep were necessary to exhaust, so to speak, the action of the medicine. Matthes (*Centralbl. f. klin. Med.*, No. 40, 1888; *Wien. med. Blätter*, December 13, 1888), too, reports a case in which very marked disagreeable after-effects appeared to develop because the sulphonal-sleep had been much disturbed by outside causes.

The following cases are examples of the fact that a large dose is sometimes less objectionable than a small one, and are also illustrative of the difficulty in determining the proper amount to give :

CASE III.—George H., aged 15. Rheumatoid arthritis. Troubled with nervous insomnia. 15 grains of sulphonal were almost entirely without hypnotic action, and 25 grains had but little more effect. After these smaller amounts there were short, bewildered, troubled periods of sleep throughout the night, with a tendency to talk at random ; and upon the days following the patient was drowsy and uncomfortable. 30 grains, however, produced six hours' continuous, restful sleep, entirely without unpleasant after-effects.

CASE IV.—Miss O. Hysteria ; great nervousness and insomnia. Sulphonal in a dose of 30 grains, given on three successive evenings, was only productive of short, delirious dozes, and upon the morning following there were nausea, headache, and generally unpleasant sensations ; so that the patient begged that no more of the drug be given her. A further trial was made, nevertheless, and 40 grains were administered. This gave her six hours' sound, uninterrupted sleep, with no unpleasant sensations on the next day. The 40-grain doses were continued during some weeks with great satisfaction to the patient. She later found that 20 grains were often sufficient, but if very nervous she was obliged to take the larger amount.

The dose probably most often recommended by writers is 1 to 3 grammes, and it has been repeatedly claimed that unpleas-

ant effects only follow the administration of a dose unnecessarily large. The cases which I have described show that this is not the fact. I should say, too, that I have repeatedly, and indeed usually, commenced with a small dose, but have generally found it insufficient: and can recall but one instance in which 10 grains exerted a hypnotic action. Rosin (*Berl. klin. Wochenschr.*, June 18, 1888), who has carefully tested the size of the necessary dose, found that 1 gramme was seldom, if ever, enough to cause sleep, except in those cases in which starch, given under the name of sulphonal, had an equally good effect; and Funajoli and Raimondi (*Archiv. italiano per le mal nervos.*, etc., 1888, xxv. 325) believe that the efficient dose for men is 4 grammes and for women 2 grammes, and that the best results are not obtained until the third night of administration. Too much attention cannot be given to the proper method of testing hypnotics, as so well described by Rosenbach (*Berlin. klin. Wochenschr.*, June 11, 1888), and to the absolute necessity of eliminating the influence of psychic impressions before concluding that sleep is due to the medicine given. The relief of pain and the production of sleep by morphine powders composed of sugar of milk is a ruse too well known to need remark. Matthes (*loc. cit.*) comments on the difficulty in determining the dose of sulphonal, since it not only seems to vary greatly with different persons, but at different times with the same individual. He gave 5 grammes to one patient without any effect whatever, while in another case which he reports the drug had been used

repeatedly with good results; but on one occasion a dose of only .5 gramme occasioned very unpleasant symptoms.

A somewhat similar instance is the following:

CASE IV.—Lizzie H. Insomnia. 40 grains of sulphonal were taken on retiring on four consecutive nights. On the first three a rather restless slumber, in which the patient talked somewhat, began in one to one and a half hours; followed at about 3 to 4 A.M. by a deep sleep lasting until 8 or 9 in the morning, when she woke refreshed. On the fourth night, instead of passing into the deep, quiet sleep at 3 o'clock, she rose, still unconscious, walked about the room with a candle in her hand,—a rather dangerous proceeding,—and screamed at the top of her voice. As she had never been known to act in this way before, her relatives were not without reason in considering the medicine at fault, and in urging her to take no more of it.

4. *Unpleasant secondary effects* have been already alluded to in these notes as constituting one of the disadvantages of sulphonal, and some of them have been mentioned in the cases already described. Many writers have observed them, so that the claim made by the makers of the drug and by some of its users, that it is totally without disagreeable secondary action, is not substantiated. Zerner (*Wien. med. Wochenschr.*, November 10, 1888), indeed, estimates that these effects are seen in 10 per cent. to 12 per cent. of all cases, and Matthes (*loc. cit.*) says that they were noted in a majority of his patients. Prominent among them may be mentioned a *con-*

dition of excitement developing instead of the wished-for sleep. The following case illustrates this condition :

CASE VI.—Mrs. McC. Disseminated sclerosis; extreme and persistent insomnia, for which various hypnotics had been used in vain. Small amounts of sulphonal had no effect whatever. Finally 60 grains were given on each of four consecutive nights, but the patient appeared only to become more excited and nervous, and more wakeful, if possible. On the days following the nights of administration she was drowsy and uncomfortable.

Other illustrative cases are the following :

CASE VII.—Jennie S. Neurasthenia; anæmia. Annoying insomnia was relieved nicely by paraldehyde, but 30 grains of sulphonal were absolutely without action. 40 grains given early on two successive nights made her very excited and semi-delirious, without producing any desire for sleep until about 4 A.M. From this time until the evenings of the days following she experienced nausea, headache, and vertigo, and was so generally uncomfortable that she flatly refused to take any more of the drug.

CASE VIII.—Mrs. E. Rheumatoid arthritis; simple insomnia. 35 grains of sulphonal had a very exciting effect throughout the whole night, producing short, dreamy snatches of sleep. On the next day there was nausea and drowsiness.

CASE IX.—Mrs. B. Simple insomnia. 20 grains of sulphonal only excited the patient through the whole night, and produced no sleep whatever.

CASE X.—Tak Sing. Obstruction of the superior vena cava; persistent insomnia. 15 grains of the drug were given at 10.30 P.M., and repeated in an hour. The patient slept about half an hour after each dose, but for the remainder of the night was unusually restless.

CASE XI.—James B. Alcoholic delirium of a mild type. The patient was restless, never violent, often wanting to get out of bed, but easily restrained. He was sleeping quietly at 4 A.M., when 40 grains of sulphonal were given as a test, and in about half an hour he became very unruly and delirious. He had not acted so badly before, nor afterwards until the like amount was administered on two other occasions, when the same results were observed. On another day 20 grains, given at 7.30 P.M., produced so much restlessness and wakefulness that 45 minims of amylene hydrate had to be administered at midnight, after which he went to sleep.

It is worthy of note in this case that paraldehyde, chloral, or the bromides also exerted a quieting influence; while hyoscine produced on two occasions effects similar to those of sulphonal.

One more illustration may be given.

CASE XII.—Mr. H. Mitral regurgitation. Troubled greatly with insomnia. 40 grains of sulphonal administered on each of several nights produced for some hours intense drowsiness and the desire to go to sleep, without the power to do so. The patient walked the floor, and felt "trembling" and nervous, and queried afterwards whether the powders could have made him so "light-

headed." After about two hours of this condition he fell asleep, and was very drowsy during all of the day following the administration of the drug. His wife, too, remarked that "the medicine had an effect on his brain."

A tendency to an excited mental condition *accompanying* but not *replacing* sleep is shown by Cases III. and IV., but especially by X.

Temporary *delusions* after the ingestion of the drug are reported by Fürbringer (quoted by Zerner, *loc. cit.*), and may be classified in the same category with the excited mental conditions I have reported.

Nausea, dizziness, and headache have been already mentioned in Cases IV., VI., and VII. as effects which may follow the ingestion of sulphonal. A similar instance is as follows:

CASE XIII.—Sallie C. Mitral stenosis. 30 grains of sulphonal had no effect for several hours. On the following day the patient felt uncomfortable, and suffered from headache and dizziness. 40 grains given on another occasion produced five to six hours' sleep, but the after-effects were the same.

Matthes (*loc. cit.*) says that in some of his cases *ringing in the ears*, headache, and dizziness were experienced on the next day; and that in two instances *vomiting* occurred. Among the patients of G. W. Rachel (*N. Y. med. Presse*, November, 1888) was one in which 1.5 grammes of sulphonal were followed by fourteen hours' sleep, and later by a sense of dizziness. Otto-Dalldorf (*Deut. med. Wochenschr.*, August 23, 1888) and Rosin (*loc. cit.*) have likewise witnessed diz-

ziness, which sometimes lasted nearly the whole of the next day. Rabbas (*Berlin. klin. Wochenschr.*, April 23, 1888) has seen vomiting on the morning after the ingestion of sulphonal, and in another patient *diarrhœa* occurred; but he is not certain that these symptoms were attributable to the action of the medicament. *Heaviness in the head* and dizziness were observed by Sachs (*N. Y. Med. Rec.*, October 6, 1888) in a patient who had taken two doses each of 2 grammes three hours apart. Schwalbe (*Deut. med. Wochenschr.*, June 21, 1888) has in several instances observed dizziness, headache, nausea, and in one case vomiting, after a dose of only 1 to 1.5 grammes, and S. G. Burnett (*N. Y. Med. Journ.*, March 2, 1889) has seen two instances of vomiting.

The production of a marked *sense of fatigue*, of *depression*, and of *confusion of mind* is not infrequently referred to by authors. J. Fränkel (*Berlin. klin. Wochenschr.*, July 23, 1888) has found these symptoms so decided in a number of patients that the drug could no longer be given them; Matthes (*loc. cit.*) refers to the sense of exhaustion and depression as the secondary effects most frequently observed, and Oestreicher (*loc. cit.*) has seen them in one or two out of eighteen cases. In one of these it was very pronounced, and the patient refused to take the medicine again. Ott (*Prag. med. Wochenschr.*, October 3, 1888) refers to the sense of fatigue on waking as the chief bad symptom which the drug leaves behind it. He reports a case in which 3 grammes caused vomiting and an attack of *fainting*. The confusion of mind is exempli-

fied in several of the cases I have reported, especially in Case XII.

In two instances I have seen full doses of sulphonal produce a *disturbance of gait*.

CASE XIV.—James M. Aortic regurgitation; insomnia. 40 grains of sulphonal were followed by sleep lasting most of the night; but on the next day the patient suffered from swimming in the head, and oscillated while walking.

CASE XV.—Mr. C. Plethora. Greatly troubled by insomnia. After 40 grains of the drug, given in the evening, the patient slept well, but could with difficulty rouse himself on the following morning, and felt all day as though stumbling over something.

The occurrence of a drunken, staggering gait has also been reported by Zerner (*loc. cit.*) and by Otto-Dalldorf (*loc. cit.*). Bornemann (*Deut. med. Zeitung*, November 26, 1888) reports a case of the morphia habit in which 60 grains of sulphonal were taken at about 9 P.M., and one-half of this amount at 1 A.M. As a result there developed very marked muscular inco-ordination with great mental depression, lasting to some extent during six days. This is a case in proof of the observation already made by Ziehen (*Arch. f. Psychiat. u. Nervenk.*, B. xx. H. 2), that severe motor inco-ordination and a somnolent condition are liable to appear if sulphonal be given at the same time with opium or to opium habitués. Still another case in point is that recently published by Fischer (*Neurolog. Centralbl.*, 1889, No. 7), in which the drug, given repeatedly to a morphia habitué, produced on two occasions not only ataxia of the limbs,

but indistinctness of speech. Burnett (*loc. cit.*) mentions the occurrence of muscular inco-ordination after the ingestion of sulphonal. He further reports *intense thirst* and great *dryness of the mouth* produced by it in three cases.

Engelmann (*Münch. med. Wochenschr.*, October 16, 1888) details a case in which 3 grammes produced an erythematous *eruption* over the breasts and inner surface of the arms, attended by considerable itching. Another instance of an eruption occurred in a case of Schotten's (*Therap. Monatsh.*, December, 1888), in which 2 grammes of sulphonal, given on each of two succeeding nights, produced but little sleep at night, but depression on the following days. After 3 grammes on the third evening the patient slept all night, but seemed completely exhausted and extremely drowsy on the next morning, and suffered from persistent headache and loss of appetite. This condition lasted four days, when improvement set in, and simultaneously an eruption exactly resembling measles appeared over the whole body. Kisch (*Berlin. klin. Wochenschr.*, No. 7, 1889) reports three interesting cases of ill effects from sulphonal. In the first, a patient with hemiplegia from a recent apoplexy slept the entire night after taking 1 gramme of the drug. On the next morning, however, he had complete *aphasia*, and only after eight to ten hours did this slowly disappear, the patient meanwhile feeling very weak. The second patient, after taking 3 grammes of sulphonal in divided doses during the night, felt wretched and exceedingly languid on the following morning,

and complained of great depression and of a feeling as though his senses were leaving him. The *pulse was also retarded*, beating only 38 in the minute, and this symptom did not disappear for several hours, and under the use of stimulants. The third patient, a man 62 years old, slept soundly after 1 gramme of the drug. On the following morning he was horrified to find that he had had a *nocturnal seminal emission*,—the first for over ten years. He also felt as though stupefied during the whole day, and could not leave his bed.

Schmey (*Therap. Monatsh.*, July, 1888) details most unpleasant results following the administration of sulphonal to a case of angina pectoris from arterio-sclerosis. Nitrite of amyl had reduced the attacks to one to two a day, and amylene hydrate produced sleep very satisfactorily. As the patient complained of the taste of the latter, the author administered 2 grammes of sulphonal, soon after which *attacks of angina* came on with great violence and with only a few seconds' intermission during the entire night, without any real sleep. For the next two days the attacks were unusually frequent and severe. It is true that the occurrence of these symptoms may have been only a coincidence, and Müller (*Therap. Monatsh.*, August, 1888) claims that this is proved by the fact that in a case of arterio-sclerosis in which he used sulphonal no unfavorable action was observed. This is, of course, only negative proof. Burnett (*loc. cit.*) reports a case of arterio-sclerosis in which the patient became cyanosed and semi-comatose for twelve hours after taking it. He

believes it to be contra-indicated in this condition. Lovegrove (*loc. cit.*) has also witnessed cyanosis produced by sulphonal, as has been already stated.

5. Finally, the *uncertainty of hypnotic action* is one of sulphonal's disadvantages,—a fault which it shares more or less with all hypnotics. Cases of failure of action on the part of sulphonal are too numerous in the literature to allow of quoting from them. Among those who have been unfavorably impressed by the drug on the ground of its inefficiency may be mentioned Wilson and Hutchinson (*Med. and Surg. Reporter*, June 9, 1888), Lovegrove (*loc. cit.*), Salgo (*Wien. med. Wochenschr.*, No. 22, 1888), and Regis (*Journ. de Méd. de Bordeaux*, July 1, 1888). Several of the cases I have reported might serve as examples, but the following are perhaps still better illustrations of its occasional lack of hypnotic power, though given in full or even very large amount.

CASE XVI.—Mr. W. Fracture of spine. No pain, but persistent insomnia. 30 grains of sulphonal in the evening had no effect whatever.

CASE XVII.—Mrs. F. Paraplegia; persistent insomnia, and some pain. 30 grains at bedtime did not produce sleep.

CASE XVIII.—Mr. B. Cancer of face; insomnia independent of pain. Opium often used in full but not excessive doses. 40 grains of sulphonal at bedtime only made him drowsy and uncomfortable. On the next night the same dose was given and repeated at midnight. Even this large amount produced but little sleep, and the patient com-

plained on the following day of dizziness and headache, and of feeling "queer." The same absence of beneficial action was observed after 80 grains given on another occasion.

The large majority of writers, nevertheless, pronounce favorably for sulphonal. My own experience with it has been for the most part satisfactory; for the number of cases in which no unpleasant effects have followed or supplanted the refreshing sleep obtained by its use much exceeds the number from which I have reported examples here. The instances detailed, with those reported from the experience of others prove, however, that it is to be used with a proper appreciation of the bad results which may follow, that the time of administration is to be carefully determined, and that the dose should be accurately adapted to each individual case.

The chief disadvantages of sulphonal may, then, be recapitulated as follows: 1. Its hypnotic action usually develops very slowly. 2. This action is very liable to be prolonged throughout a greater or lesser part of the following day. 3. It is difficult to determine the dose which may be given with effect and with comfort in each individual case, and this dose may vary at different times in the same case. 4. The drug is liable to produce unpleasant secondary effects, which may even replace the primary hypnotic action. Chief among these are mental excitement, nausea, vomiting, dizziness, headache, languor, exhaustion, depression, and a staggering gait. These symptoms may appear either after large or after quite small doses. 5. It very often fails to exert any hypnotic action, either in any

dose whatever, or in any amount which can be given with comfort to the patient.

Though I have expressed myself as in general favorably impressed with sulphonal, yet I confess to a decided preference for paraldehyde, and especially for amylene hydrate. With the latter drug my experience has been especially satisfactory, and disagreeable results following its administration are much less frequently reported in the journals than in the case of sulphonal. The objection that its taste is disagreeable is entirely removed by giving the full dose (45 minims) in 3 capsules of 15 minims each. It is especially to be preferred when a rapid hypnotic action is desired, or where there is not time to learn by repeated trial the amount of sulphonal suited to the patient in question. In cases, however, in which the stomach is irritable, it is probable that the latter will usually be more easily tolerated.

