THE PROLONGED USE AND TOXIC ACTION OF SULPHONAL.

BY JAMES E. TALLEY, M.D.,

DIRECTOR OF THE CLINICAL LABORATORY OF THE PRESBYTERIAN HOSPITAL, PHILADELPHIA.

ABOUT twelve years ago, a woman then just past middle life, was operated on for uterine fibroids. She had developed a mild melancholic state with insomnia, and was given sulphonal for sleep. A year and a half later, when I first saw her, she had largely recovered from her depression, but still found it necessary to take from 10 to 15 grains of sulphonal every night, or else remain wakeful. The dangers of such prolonged use were pointed out to her then and many times since, but any attempt even to change to another hypnotic always ended in a return to the sulphonal. In the words of the patient, "the number of nights missed in taking sulphonal during all these years is not greater than the number of the years." Formerly she had often to take as much as 15 or 20 grains, but for the last four or five years she has taken 10 grains regularly. Finding that there was little chance of ever getting her to make a determined effort to get rid of a habit which she looked upon as rather necessary, and comparatively harmless, matters were left to drift. I saw her from time to time for minor ills. I examined the urine occasionally and found it normal until about five years ago, when it first showed a trace of albumin and hyaline casts. This condition still persists, but shows no increase, and is not an uncommon condition at her time of life. Repeated examinations of the patient show only that she has the stamp of chronic invalidism, with recurring mild attacks of melancholy. The abuse of the drug appeared to affect her so little as to suggest substitution, but that theory is untenable, since the husband has means of procuring the drug in original packages. That the dosage was correct was proved by furnishing him with accurately weighed pieces of tin foil with which to test his scales. This woman has taken on the average yearly at least a half pound avoirdupois of sulphonal for twelve years, or five and a half pounds in all, and suffered no ill consequences so far.

In November, 1907, the patient was admitted to the Presbyterian Hospital for insomnia and mental depression. She had been taking sulphonal fairly regularly, and was kept on a nightly dose of 20 grains during a short time while we sought to investigate two points: First, although the urine did not suggest hematoporphyrinuria, if the theory of Stokvis is tenable, namely, that the hematoporphyrin of the urine is due to hemorrhage into the intestinal mucosa and the transformation of the hemoglobin there into hematoporphyrin which is absorbed and excreted in the urine, we thought that the stools might give a positive reaction for occult blood. The patient was put on a milk diet and the stools tested, but with negative result.

Again, knowing that traces of hematoporphyrin are found in normal urine, we thought that after this prolonged use of sulphonal we might find at least small amounts present. With the coöperation of Dr. Sydney Repplier and Dr. D. W. Fetterolf, demonstrator of chemistry in the University of Pennsylvania, first the method of Salkowski and then that of Riva and Zoja were tried with negative results. Following this Dr. Fetterolf carried out the more accurate method of Garrod with two specimens of urine taken at intervals of three days; still with negative results. The only reason that can be assigned for the entirely negative results with the Garrod method was the fact that only 200 c.c. of urine was sent to Dr. Fetterolf each time instead of 1000 to 1500 c.c. as desired. Further experiments were impossible, because the patient left the hospital. It is reasonable to suppose, however, that the urine did not contain a large amount of hematoporphyrin when the comparatively sensitive method of Garrod failed entirely to give a positive reaction with even 200 c.c. of urine.

Considering the time that sulphonal has been in use, and the frequency of its use, especially in asylum practice, the number of cases of poisoning by it are comparatively few. However, the cases of poisoning reported are sufficiently numerous to make us cautious in dosage, and especially in the length of time of exhibition of the drug.

Dr. Hunt has found references to at least 50 cases in the literature without making an exhaustive research. Garrod and Hopkins¹ report the case of an epileptic woman, aged fifty years, who had taken almost continually 20 to 40 grains of sulphonal for six years before she developed symptoms of poisoning. The attack proved fatal. The other cases described show varying degrees of susceptibility. Occasionally, idiosyncrasies toward the drug may appear. The man reported by Murphy² had taken a single dose of 10 grains on three separate occasions at long intervals, and had suffered each time with itching, swelling of the hands and feet, and a general erythema with vesicular eruptions.

Among the cases of acute poisoning with recovery, Tresilion's³ case took only 20 grains one night and 15 grains the succeeding night; Hearder's⁴ case, 15 grains on each of four succeeding days; Gillett's⁵ case 1 dram in four hours; Richmond's⁶ case, 2 drams at one dose; and Hill⁷ reports the case of a child, aged eighteen months, who received 34 grains in a few hours. Among the fatal cases Pettitt⁸ reports that of an insane woman who succumbed to poisoning by 30 grains given in two doses about one hour apart. Schulz⁹ records

¹ Jour. Path. and Bact., 1895 to 1896.

² Brit. Med. Jour., 1896, 209.

³ Brit. Med. Jour., 1898, ii, 808.

⁴ Med. Record, 1894, xlii, 339.

⁵ Neurol. Centralbl., October, 1896.

⁶ Indian Med. Gaz., 1904, xxxix, 96.

⁷ Lancet, 1896, ii, 1372.

⁸ Ibid., 1337.

⁹ Med. News, 1889, ix, 165.

that an hysterical woman died from the effects of one-half ounce given during the course of a month. Other cases vary in time from weeks to months of fairly constant use of average doses before the development of symptoms of poisoning which proved fatal.

The symptoms are pretty uniform in all the well-developed cases of poisoning. They consist in epigastric pain, nausea, vomiting, acetone odor to the breath, usually constipation, low temperature, shallow respiration, feeble pulse, cyanosis, scanty dark reddish urine due to hematoporphyrin, which may or may not contain albumin, casts, degenerated blood corpuscles, and much urobilin; ataxia, delirium, or stupor, and gradual development of motor and sensory paralysis, and finally death, usually from respiratory, sometimes from cardiac arrest. Some autopsies have been reported, but few, if any, cases have been so exhaustively studied, both clinically and pathologically, as the case reported by Taylor and Sailer.¹⁰

A point in prognosis is the observation that all the cases that have recovered have had some or all of the gastro-intestinal, nephritic, respiratory, and circulatory symptoms, but no nervous symptoms beyond stupor and ataxia. The development of paresis appears always to run on to complete paralysis and death.

The predominance of constipation among the toxic cases, should put one on the alert to keep the bowels active during the exhibition of the drug, but that free purgation is not able to eliminate the poison when once absorbed and the mischief begun is shown in the first case reported by Smith. The woman had diarrhoea the greater part of the twelve days between the first signs of poisoning and death.

The conclusions are that, although the patient the subject of this report has taken perhaps an unprecedented amount without any symptoms of poisoning so far; the prolonged use of sulphonal is never a safe procedure, as the literature attests. The appearance of even the first symptoms of poisoning is apt to be the beginning of a condition over which we have no control. It is safer, therefore, occasionally to discontinue its use, changing for a time to other of the hypnotics, if the necessity of the case demands their constant use.

¹⁰ William Pepper Clinical Laboratory Reports.