scarcely be doubted, I think, that the murmur that appears in the advanced stages of the disease is at times due to relative incompetency, since many other indications of a dilated heart are in association. In some cases the murmur heard over the aortic area is attributable to an associated chronic nephritis, since the presence of a basic systolic murmur in the latter disease is a matter of common observation. Again, the bruit may be hæmic in origin or due to an abnormal, relaxed state of the heart-muscle or to weakness or insufficiency of the papillary muscles.[1] The moderate degree of enlargement in four of my cases showed itself by an increase of dulness more to the left than to the right and more in the transverse than in the vertical direction. It is probably occasioned principally by dilatation which may be preceded by and associated with some hypertrophy caused by the over-fatness. The rôle played by the infiltrated fat as well as the abnormally great subpericardial fat deposit must also be taken into account. It is always exceedingly difficult and sometimes impossible to establish the boundary lines of dulness by percussion, owing to the extreme corpulency. Not to be neglected in the treatment of these cases are measures directed to the removal of the over-fatness, the accomplishment of which enables us not only to determine accurately the size of the heart, but also to improve both the cardiac action and general condition of the patient.

A fatal termination is often due to spontaneous rupture of the heart, as occurred in all of the cases given in the above list that came to necropsy. This accident, however, does not, as shown by the clinical notes of Cases IV. and V. in the above table, invariably cause sudden death.

MULTIPLE NEURITIS AND HÆMATOPORPHYRINURIA FOLLOWING THE PROLONGED INGESTION OF TRIONAL.

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That poisoning by trional is an exceedingly rare condition is readily borne out by the fact that it has been freely administered in thousands of cases in the past decade for insomnia, as a sedative, and as an antipyretic in a wide range of diseases, and is generally considered a reliable and effective remedy, without untoward effects. I have been impressed by the readiness with which patients acquire the trional habit and the difficulty of inducing them to abandon its use. Their attitude has, I think, often been determined by the physician who first

[1] See Schroelten, Ziemssen's Hand-book, vol. i. p. 26.

administered it to them with the assurance (which his experience has led him to believe) that trional is a safe, harmless drug, or at least as little harmful as any of our hypnotics.

While trional is an exceedingly useful drug, I believe we should always bear in mind its possible bad and even fatal effects, and for this reason I have thought it worth while to report a case of trional poisoning which came under my observation, together with several somewhat similar cases which I have been able to collect from the literature.

These cases are also interesting in that they bring vividly before us the etiological relationship existing between the ingestion of another of our synthetized organic drugs and the development of nervous affections. It is a well-recognized fact that the occurrence of neuritis has notably increased since the introduction and general use of the coal-tar products as remedies.

The following cases collected from the literature have certain points of interest not unlike my own case:

Schultz[1] reports a fatal case in a woman, aged fifty-four years, who took a gramme of trional a day for one month. After two weeks she had epigastric pain, vomiting, and loss of flesh and strength. A few days before death hæmatoporphyrin appeared in the urine.

Hecker[2] reports a case of "progressive paralysis" following the use of trional. There was unsteady gait, disturbances of speech, and general weakness. The patient recovered.

Reinicke[3] had a patient who took trional for four months. She had, as a result, headache, vertigo, epigastric pain, and temperature of 101.6° F. The urine was black and contained albumin, casts, and blood. She recovered after the removal of the drug.

Bresslauer and Joachim,[4] while using trional in a very large number of cases, had no severe cases of poisoning, but occasionally noted anorexia, constipation, giddiness, ataxia of the lower extremities, and oliguria.

Young[5] noted trophic changes in the skin of a woman, aged thirty-five years, which was caused by the continuous use of trional in 15-grain doses.

Herting[6] reports a fatal case in a patient, aged thirty years, who had taken tetronal and sulphonal and later a gramme of trional daily for a considerable period. The urine contained hæmatoporphyrin.

Gierlich[7] saw a patient who, after the use of trional, had tremor and ataxia in the arms and legs, depression, and loss of memory. The reflexes were normal; there were no changes in sensation, no trophic disturbances, and no hæmatoporphyrinuria. All these symptoms disappeared two weeks after the withdrawal of trional.

A. Claus[8] instances a child, aged five years, who after 10 grains of

trional walked unsteadily. A reduction in the dose caused a disappearance of the symptoms.

Stocktou[9] reports a case of acute ascending paralysis which was fatal in a woman, aged twenty-seven years. Paralysis began in the lower extremities and advanced upward. Hæmatoporphyrin was present in the urine. The etiology was not clear, but the patient had taken small amounts of trional.

Putnam[10] saw a case of multiple neuritis following the use of trional and sulphonal. There was advancing paralysis, muscular tenderness, great emaciation, and death from the gradual involvement of the nerves of the heart and the respiratory muscles. The autopsy showed no changes in the cord, but a well-marked degenerative neuritis.

The history of the case which I wish to present is as follows:

Mrs. ——, aged fifty years, born and bred in New York City, had for twenty years been more or less of a chronic invalid, suffering from nervous depression, insomnia, and gastric disorders. According to her own statement, she had never had a wish, which money could gratify, unsatisfied. She had consulted many of the leading practitioners of medicine in this country and various parts of Europe, had submitted to all kinds of cures and systems of treatment, and had taken a great variety of drugs. At one time she had taken a large amount of trional and was continuing its use when she first came under my care; this she was induced to gradually diminish and finally gave it up entirely for a period of several months. At this time she was neurasthenic to a marked degree, but beyond a moderate anæmia there existed no organic disease.

About the middle of February, 1899, she suffered from obstinate insomnia and resumed taking trional, limiting the dose to 15 grains every other day, with an occasional intermission of three or four days. This continued until the evening of April 20th, when quite suddenly she developed pain in the abdomen of a severe colicky character, with extreme nausea and vomiting. At this time the temperature was normal and there was no abdominal tenderness or distention. The vomiting and pain continued for several days, rendering it necessary to interdict all food by the mouth and to resort to rectal alimentation. At this stage the case suggested the possibility of some acute poisoning. No further symptoms, however, could be elicited, but the administration of trional was stopped, and to control the severe pain morphine was used hypodermatically. On April 25th the heart became intermittent and there was developed a systolic murmur at the apex, transmitted to the left. At the same time the urine, which had been hitherto normal, became a dark red and contained a trace of albumin and a few granular casts. On the next day she passed only twelve ounces of nearly black urine, of a specific gravity of 1023, acid, with a small amount of albumin, no glucose, many granular casts, leucocytes, and small cuboidal epithelium; no blood. From this specimen I was able to separate by the usual methods[11] a substance giving the characteristic spectrum and color of hæmatoporphyrin.

The abdominal pain still continued and she complained of it bitterly.

The pulse increased in frequency and would frequently intermit; the heart action became weak and irregular, the apex murmur loud and rough, and there was added a loud murmur of aortic insufficiency. The area of cardiac dulness was moderately increased to the left. On April 30th she complained of tingling and pricking sensations about the vulva. The left knee-jerk was absent and the right was elicited with great difficulty. May 1st there was tingling in both arms; both knee-jerks were absent. On May 2d the patient complained of severe pain in the left elbow and weakness of the legs. The surface of the extremities showed diminished sensibility to tactile and thermic stimuli, but no absolute anæsthesia; this was particularly noticeable in the soles of the feet. The pain in the extremities increased, and two days later some loss of power was evident in the extensor groups of the left arm and left leg, but no actual paralysis. All the muscles reacted to Faradism, but the extensors only when a very strong current was employed. For several days there was a slight, irregular elevation of temperature, ranging from 99° to 101° F. By May 12th a well-marked drop-wrist (double) and drop-foot (double) had developed. The flexors and extensors of the wrists and ankles failed to respond to the Faradic current. Tested with galvanism the extensors showed the reaction of degeneration, while the flexors responded slowly and only to a strong current. There was marked weakness of the extensors of the legs, but they all reacted to strong Faradism. While at rest the knees were held in the position of flexion. The surface of the body (particularly of the extremities) was so hypersensitive that it was necessary to keep the bed-clothing from touching the skin. There were periods of delirium, with hallucinations of time and space. She complained of excruciating pain in the extremities and abdomen and of slight girdle sensation and constriction about the chest. Loss of weight was commencing to be very apparent. The urine contained a trace of albumin and a few casts, merely a trace of hæmatoporphyrin. Heart slightly improved in rhythm and force; murmurs still present.

For a few days the patient remained in the condition just described and then began a slow, tedious improvement. Something over a week later she had recovered some slight, voluntary power of extension over the fingers and toes, although to the electric current the muscles still showed the reaction of degeneration, and it was many weeks before the extensors reacted normally to the galvanic current and contraction to Faradic stimulation was not re-established for three months—long after voluntary contraction was well advanced. There were moderate contractures of the ham-strings and Achilles tendon in spite of the use of passive motion and the application of correcting apparatus. These contractures gradually disappeared when the patient was able to use her hands and relearn to walk. There was considerable ataxia at times, but probably only such as would be accounted for by muscular weakness. The emaciation was extreme, the weight falling from 153 to 90 pounds. After some weeks the kidneys regained their normal condition. The heart slowly returned to the normal, leaving no evidence of valvular disease or enlargement. For a period of ten days there was a marked œdema of the lower extremities, which, however, disappeared with the improvement in the action of the heart. At the end of a year from the onset the patient was just beginning to walk without assistance. The recovery has since become complete.

This case brings out a number of points of special interest. The whole amount of trional ingested was not what one would ordinarily consider excessive—*i. e.*, about thirty doses of 15 grains each, a total of 450 grains for the two months. The onset presented the picture of a case of acute gastro-intestinal poisoning. Following this there was an acute degeneration of the kidneys and the presence in the urine of hæmatoporphyria—a substance which is usually associated with poisoning by sulphonal and trional. The first of the nervous manifestations was a neuritis of the vagus and a subsequent trophic disturbance in the heart muscle resulting in dilatation and valvular insufficiency. The nature of the heart lesion seems clear in the light of the subsequent course, for with the improvement in the muscular tone the dilatation and valvular incompetence entirely disappeared, leaving a normal heart. Among other trophic changes may be noted the extreme emaciation and a marked thickening of the tissues about the joints of the fingers, which still remains.

The more marked affection of certain definite groups of muscles—*e. g.*, the extensors of the wrists and feet—suggests the selective action of trional for certain nerves or groups of cells in the anterior horns of the cord, not unlike that of the metallic poisons.

The nerves recovered their function in the same order in which they were impaired, viz., first the vagus, next those of the extremities of the left side of the body, and lastly those of the right side.

In view of the similarity in chemical constitution of trional and sulphonal it is not surprising that their toxic effects should have a close parallel; this is borne out by the manifestations of a number of cases of sulphonal poisoning to be found in the literature. As to how trional produces its various injurious effects is a question of some doubt. One theory[7] ascribes to it a specific toxicity to the cells in the anterior horns of the spinal cord. In a case of sulphonal poisoning in which there had been weakness and ataxia of the lower extremities Helwig[12] reports an autopsy showing a degeneration of the cells of the anterior horns of the lower cord.

Another theory is that trional causes a very slow oxidation of the cells of the central nervous system, and this when long continued produces permanent changes, the manifestations in the stomach, bowels, and urine being secondary. It seems to me, however, that our theory must be even broader than this in order to include cases like that of Putnam,[10] in which on autopsy the lesion was found entirely confined to the peripheral nerves, the cord and brain being found normal.

Hæmatoporphyrin has been described as occurring in a variety of conditions associated with lesions of the nervous system. Ogden[13] reports hæmatoporphyrin as present in a fatal case of post-diphtheritic paralysis and Nakarai[14] isolated the pigment from the urine of six

cases of lead poisoning. In sulphonal poisoning its presence has been frequently demonstrated. The exact cause and mode of its production are still unknown. By some it is claimed that the original toxic substance acts as a direct irritant to the kidneys; by others that the function of the kidneys is modified by changes in the central nervous system. My own cases would argue for the latter theory, as the change in the urine did not appear until some time after the development of the nervous symptoms and a considerable period after the withholding of the drug.

Some years ago Morro[15] demonstrated that trional had a cumulative action, and this should be borne in mind when administering the drug for an extended period. It should not be given continuously, and while being used the bowels and kidneys should be kept active. To aid in the elimination of trional Goldman[16] recommends that citric acid be exhibited with it, and suggests that, if the urine becomes dark or cloudy, bicarbonate of soda and the drinking of aërated waters should ward off more serious developments.

References.

1. Deutsch. med. Wochenschr., Leipzig, February 15, 1894.
2. Centralb. f. Nervenheil. u. Psych., August, 1894.
3. Deutsch. med. Wochenschr., Leipzig, March 28, 1895.
4. Centralb. f. d. gesammt. Therapie, Vienna, August, 1895.
5. University Medical Magazine, 1896, p. 715.
6. Allgem. Zeitschr. f. psychiat. u. psychisch.-gericht. Med., Berlin, 1894, B. li., H. 1.
7. Neurol. Centralb., Leipzig, 1896, xv. p. 770.
8. Internat. klin. Rundschau, 1894, No. 45.
9. Transactions Association American Physicians, 1900, vol. xv. p. 6.
10. Transactions Association American Physicians, 1900, vol. xv. p. 10.
11. Salkowski. Zeitschr. f. Physiol. Ch., 1891, xx. p. 297.
12. Hosp. tid., 1892, 3, R. 39.
13. Boston Medical and Surgical Journal, February 24, 1898.
14. Deutsch. Arch. f. klin. Med., lviii. p. 165.
15. Deutsch. med. Wochenschr., 1894, No. 34.
16. Therapeutisch. Monatsheft., Berlin, 1891, No. 11.