DEATH DUE TO WITHDRAWAL OF BARBITURATES*

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ALTHOUGH it is known that abrupt withdrawal of barbiturates from persons who have been chronically intoxicated with large amounts of these drugs may precipitate a serious abstinence syndrome,[1, 2] a review of the American literature revealed no report in which death was attributed to abstinence from barbiturates. Three cases in which death was associated with withdrawal of barbiturates were found in the German literature. Two of these cases were complicated by the presence of organic disease (Buerger's disease with gangrene, and acute yellow atrophy of the liver with blood dyscrasia), so that abstinence from barbiturates could be regarded only as a contributing factor to death. In the third patient[3] no complicating disease was found on physical examination, and death was in all probability due to withdrawal of barbiturates.

The usual course of the barbiturate abstinence syndrome may be described as follows: Upon abrupt withdrawal of barbiturates from individuals who have been ingesting 0.8 gm. or more daily of one of the potent barbiturates (secobarbital, pentobarbital, amobarbital), signs of barbiturate intoxication disappear in the

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first 8–12 hours of abstinence, and, clinically, the patient seems to improve. Thereafter, increasing anxiety, insomnia, tremulousness, weakness, difficulty in making cardiovascular adjustments on standing, anorexia, nausea and vomiting appear. One or more convulsions of grand mal type usually occur during the second or third day of abstinence. Following the seizures, a psychosis characterized by confusion, disorientation in time and place, agitation, tremulousness, insomnia, delusions and visual and auditory hallucinations may supervene. The psychosis clinically resembles alcoholic delirium tremens, usually begins and is worse at night, and terminates abruptly with a critical sleep.

With respect to the incidence of the various signs and symptoms, Fraser and Isbell [4] found that all of 19 patients who had been ingesting 0.8 to 2.2 gm. of amobarbital, secobarbital or pentobarbital chronically, exhibited anxiety, weakness, tremor, insomnia and paroxysmal bursts of abnormal waves in the electroencephalogram following abrupt withdrawal. Fifteen (or 80 per cent) had one to four convulsions; 12 (or 60 per cent) developed a delirium; four patients had seizures but no delirium; one patient had a delirium but no seizures, and three patients escaped both seizures and delirium, although they exhibited anxiety, weakness and electroencephalographic abnormalities. These data indicate that the type with a delirium without a seizure is the least common variant of the barbiturate abstinence syndrome.

In 17 of the 19 patients, symptoms disappeared within 10 to 14 days even though no treatment was given. The two remaining patients became so exhausted during the course of a protracted delirium that their lives were judged to be in danger; both were treated by rapid reintoxication with barbiturates, followed by gradual reduction [2, 4] of barbiturates, with satisfactory results.

The purpose of this communication is to present the clinical and pathologic findings in a case in which death was apparently due to the severe stress of the barbiturate abstinence syndrome superimposed on an already damaged cardiovascular system.

Case Report

A white male physician, 49 years of age, was admitted to the USPHS Hospital, Lexington, Kentucky, at 11 p.m. on June 21, 1951. He gave a history of intermittent addiction to codeine since 1942. The maximal codeine intake had been 360 mg. daily, but this dose had been voluntarily reduced and no symptoms of abstinence from opiates were ever detected. He denied the use of barbiturates on admission but four days later, while psychotic, admitted using 0.3 to 0.5 gm. of secobarbital four times daily. When this information was obtained, the diagnosis of barbiturate abstinence syndrome was considered but could not be proved because of the unreliability of the patient's history. Subsequent to the patient's death a detailed history of secobarbital addiction was obtained from his wife. She stated that he had taken a high dose of barbiturates for eight months, and for the four months prior to admission had been ingesting 5.0 gm. (50 capsules) daily.

The patient had had the usual childhood diseases with no complications, and no adult diseases except appendicitis, with appendectomy in 1936. The only positive physical findings were obesity and a blood pressure of 170/90 mm. of Hg. The urinalysis, chest x-ray and blood Kahn were negative.

Course in Hospital: On admission the patient appeared to be in good physical condition; he had no signs of abstinence from codeine; he was coöperative in carrying out all admission procedures, talked coherently and wrote legibly. After 36 hours

of hospitalization he still showed no opiate abstinence signs or other symptoms and was transferred to a convalescent ward. One hour later he vomited, became very nervous and perspired profusely. He was dizzy and refused lunch, and was given 0.2 gm. of phenobarbital. At bedtime on the two previous days he had received 0.1 gm. of pentobarbital. On June 23, at 3:30 p.m. (40 hours after admission), he developed auditory and visual hallucinations and was transferred to a ward for acutely disturbed patients. At this time his oral temperature was 99° F.; pulse was 80 per minute; respiratory rate was 20 per minute, and blood pressure was 162/90 mm. of Hg. He was perspiring profusely, his pupils were somewhat dilated and he had a slight facial tremor. He was very nervous and tremulous but had no complaints of pain. He ate no lunch or dinner. During the night he did not sleep, was disoriented in place, and said there were a lot of boys and girls having a party in his room. On June 24 his condition was unchanged; he was given 0.1 gm. of Dilantin three times a day; he was oriented at intervals and confused at times. On June 25 these symptoms continued and the patient complained that his home town neighbors were watching him. He was given 128 mg. of phenobarbital at 8 p.m., and after 10:30 p.m. he slept fitfully. On June 26 the hallucinations continued and he was given 96 mg. of phenobarbital at 9 p.m. He was quite nervous and restless and did not go to sleep until 3 a.m. On June 27 he appeared improved and was transferred from the disturbed ward to the convalescent psychotic ward, but during the evening meal he again became disturbed and attacked a fellow patient and had to be separated from him. Later in the evening he attacked another patient, and then was locked in his room. At 10:40 p.m., while still locked in his room, he had hallucinations and claimed that someone was being killed and cut up by the attendant. At 12:45 a.m. on June 28 he was put in a wet pack for 45 minutes but continued to be restless and noisy. The pulse rate declined from 120 at 1:15 a.m. to 64 per minute at 1:30 a.m., shortly before the patient was removed from the wet pack. He was rubbed down with a towel and returned to his room. At 2:00 a.m. the blood pressure was 90/70 mm. of Hg; at 2:15 a.m. patient had gross tremors, and was jerking and twitching and stuporous; axillary temperature was 107° F.; pulse volume was poor and the rate was 120 per minute; the extremities were cold and cyanotic. At 2:30 a.m. cyanosis was general; there was incontinence of feces, and the twitching continued in all extremities; the pulse was rapid (rate, 120 to 146 per minute), weak and thready. The respiratory rate was 44 to 48 per minute. The blood pressure could not be obtained because of the convulsive movements; the skin was hot and dry; the pupils were round, regular and equal, and there was no nuchal rigidity. At 2:30 a.m. the patient was given 0.5 gm. of sodium amytal intravenously, following which his color and pulse improved and he became quieter. These effects wore off in about 45 minutes, but after repetition of the dose of sodium amytal he again improved temporarily. He was given 1 c.c. of ephedrine and 300,000 units of penicillin G intramuscularly, and 1,000 c.c. of 5 per cent glucose with 10 units of insulin intravenously. At 4:15 a.m. the jerking and twitching recurred, and 0.5 gm. of sodium amytal was given intramuscularly, but without any significant improvement. The axillary temperature continued at 107° F. The patient died at 4:37 a.m. on June 28, six days and six hours after admission to the hospital.

The clinical diagnoses (prior to obtaining a history of barbiturate addiction from the patient's wife) were essential hypertension, toxic psychosis of undetermined etiology, and fever of undetermined origin. The immediate cause of death, clinically, was attributed to "acute heart failure," probably resulting from abstinence from barbiturates.

Autopsy: Necropsy was performed six hours after death on the body which had been satisfactorily embalmed.

Gross examination was largely negative and supplied no completely adequate explanation of the cause of death. The *right lung* weighed 460 gm.; the *left lung*, 410 gm. Both lungs were fully crepitant throughout, except for a very small edematous area at each base. The *heart* weighed 500 gm. and was quite firm. The *pulmonary artery* was explored but no evidence of a pulmonary embolus was found. All the heart valve cusps were freely movable, of normal size and texture, and presented no evidence of sclerosis or incompetency. No coronary thrombi or areas of infarction were found. The left ventricular wall was greatly thickened, measuring 26 mm., but there was no dilatation of any heart chamber. The *liver* weighed 2,235 gm. and appeared enlarged with indistinct markings on section. *Genitourinary tract*, including kidneys, ureters and bladder, appeared grossly normal. *Spleen* was normal. *Adrenals:* The left adrenal, plus a small amount of fat, weighed 20 gm. Externally, both adrenal glands appeared normal, but on section the center of the medulla presented a cavity, probably resulting from postmortem autolysis. The medulla did not appear to be quite so distinctly brown as usual. The *gastrointestinal tract* was normal except for absence of the appendix and a few pericecal adhesions. The *brain* weighed 1,550 gm. The hemispheres were symmetrical and the brain was firm throughout. The gyri appeared to be somewhat flattened and the sulci moderately narrowed. The vessels at the base of the brain were normal in distribution and translucent, but there were a few atheromatous areas. An opening was made into the third ventricle and only a small amount of clear fluid exuded. Following fixation in formalin, sections at 1 cm. intervals revealed the brain tissue to be generally well preserved. The midline structures were not displaced; the ventricular system appeared approximately normal in size, with normal ependymal lining; there appeared to be some grayish mottling in some areas of the thalamus, substantia nigra, and possibly the lentiform nuclei. The substantia nigra was very prominent, both in the cerebral peduncles and in the upper midbrain, particularly on the right side. Serial sections made through the cerebellum, pons and medulla failed to reveal any significant gross abnormalities.

Microscopic Examination: The *myocardium* showed mild interstitial fibrosis. The pericardium and the endocardium appeared normal. An occasional small scar was seen in the myocardium. Sections from the *coronary arteries* showed atherosis with considerable calcareous deposit. Sections of the *lungs* removed from the dependent portions showed edema but practically no inflammation. The *bronchioles* were not unusual. The *liver* showed marked fatty metamorphosis, but the remaining liver cells appeared quite normal. In the pancreas, the islands and acinar tissues presented no lesions. The *adrenal* cortical cells were pale. The *spleen* showed considerable sclerosis of the arterioles. The *kidneys* showed mild sclerosis of the medium sized arteries.

Brain: Microscopic sections were prepared from blocks removed from Rolandic cortices bilaterally, from the basal ganglia bilaterally, including the substantia nigra, and from the midbrain, pons, dentate nucleus and cerebellum. These were stained with hematoxylin (both alum and iron) and eosin, toluidin blue, phosphotungstic acid and hematoxylin, alizarin red and thionin, alizarin red alone and with Schiff's stain, the latter being a stain for mucin.

Frontal Cortex: Two blocks were stained as described. These revealed no marked changes in the leptomeninges. Throughout the cortex, patchy areas of nerve cell loss were observed. Many of the neurons appeared fairly normal, but Nissl substance was poorly preserved in most of these, although it could be seen distinctly in a few of the cells. The nuclei were eccentric in many of the nerve cells; others appeared swollen and distorted, and some showed disintegration. A few ghost forms were present. No intracellular vacuoles or abnormal globules were observed. Oc-

casionally neuronophagia and, rarely, satellitosis were seen, but there was no significant increase in glial or endothelial cells generally throughout the cortex. The smaller blood vessels showed a marked thickening of their walls with fibroblasts and endothelial cells.

Basal Ganglia: Foci of nerve cell degeneration and loss similar to those described in the frontal cortex were observed. The white matter in the internal capsule and elsewhere had a vacuolated appearance similar to that seen in cerebral edema. The ependyma of the third and lateral ventricles appeared normal.

Pons: These sections generally showed less severe degeneration of the nerve cells, while rare vacuoles were scattered through the section. Extracellular amorphous bodies, resembling corpora amylacea, were observed frequently toward the periphery of the section. No intracellular vacuoles or globules were observed. The neurons generally were slightly swollen, with some loss of Nissl substance, while a few possessed eccentric nuclei and were more distorted in outline. Satellitosis occurred rarely, and there was no generalized increase in glial or endothelial cells. The ependyma appeared normal.

Medulla, Adjacent Cerebellum and Dentate Nucleus: Numerous amyloid bodies were seen scattered at the periphery of the cerebellar folia; the cerebellar tissue generally had a vacuolated appearance. The Purkinje cells generally appeared swollen and showed diminution or loss of Nissl substance. A few cells were lost. Similar changes were observed in the cells of the dentate nucleus, although some of these appeared more distorted with eccentric nuclei. In some, no nuclei were demonstrable, but bluish granules were present in the cytoplasm in sections stained with thionin blue. There was some generalized increase in the number of endothelial cells in the cerebellar tissue, but no increase in glial cells was observed. Changes in the nerve cells and interstitial tissue of the medulla resembled those found in the pons. No intracellular globules or vacuoles were seen. The ependyma of the fourth ventricle appeared normal.

Comment: A special study was made in this case, in a search for mucoid bodies or globules scattered throughout the white matter or in the nerve cells themselves, as evidenced by the variety of stains used. No such collections were seen, and there was no evidence of degeneration of the basal ganglia grossly, as is sometimes described in barbiturate intoxication.

The *histopathologic diagnoses* were (a) *myocardial fibrosis,* mild; (b) *pulmonary edema,* mild; (c) *lobular pneumonia,* mild; (d) *fatty metamorphosis in liver,* marked; (e) *arteriosclerosis in spleen;* (f) *nephrosclerosis,* mild; (g) *atrophic changes in cortical cells of adrenals;* (h) *cerebral encephalopathy with diffuse neural degeneration,* and (i) *cerebral edema.*

Discussion

That abstinence from barbiturates was responsible in large part for death in this case can scarcely be doubted. This opinion is supported by the confirmed history of ingestion of enormous amounts of secobarbital and by the clinical course, which was atypical only in that no convulsions were observed. What part the hypertension and the accompanying cardiovascular-renal pathology played in the fatal termination is difficult to assess. The nature and extent of the cardiovascular-renal damage were, however, hardly sufficient to account for the death alone. The same is true of the changes in the liver. The case of Meyer [3] also developed an aggravated phase in the psychosis, a high fever and circulatory

collapse after being placed in a moist pack. His patient was a 30 year old female in good general health who had taken cyclobarbital (Phanodorn) in excess for two years. At the time of admission she was taking 4 to 5 gm. daily. Barbiturates were abruptly withdrawn; two days later she was extremely weak and tremulous and had not slept for two nights. She was confused and hallucinating. She was given glucose and 4 gm. of Phanodorn by proctoclysis. On the third, fourth and fifth days hallucinations persisted, particularly at night, with intervals of relatively normal behavior. At 7 p.m. on the fifth day the temperature was 99.3° F. At 8:30 p.m. she was found in a severe delirium; she burrowed her head in the pillow and would not answer questions; she tossed about in bed and groped about with her hands. She was placed in a light moist pack in an effort to quiet her. After one-half hour she suddenly became pale and cyanotic and was gasping for breath, so she was immediately removed from the pack. The body temperature was now over 107.6° F. and the pulse was small and rapid, yet "well filled." The patient remained quiet until 12 p.m., when she suddenly died. The autopsy "revealed findings of a circulatory death with dilatation of the right heart, and congestion of the lungs." (No other autopsy observations were reported.)

Impairment of cardiovascular function (usually manifested by excessive tachycardia, sharp decline in both systolic and diastolic blood pressures, dizziness and faintness on standing, or even on sitting) is a characteristic feature of severe abstinence from barbiturates. It is quite probable that impairment in circulatory function played a significant rôle in the death of our patient and also that of Meyer. Probably warm baths and cold packs are contraindicated in abstinence from barbiturates, since the marked circulatory changes produced by these physiotherapeutic procedures might overwhelm an already functionally impaired cardiovascular system.

Death has also been observed following withdrawal of barbiturates from experimentally addicted dogs. Seevers and Tatum [5] chronically intoxicated dogs with sodium barbital for four and one-half to 30 months. Some of their dogs died following convulsions after withdrawal of barbital. Fraser and Isbell [6] observed one death following withdrawal of barbiturates from 17 chronically intoxicated dogs. The dog that died, a female that had been chronically intoxicated for 195 days with 47 mg./kg. of pentobarbital daily, showed no signs when 24 hours abstinent. When 35 and again when 36 hours abstinent, this dog had a grand mal convulsion. Following the seizures she showed weakness, extreme hyperactivity and abnormal behavior, and had a rectal temperature of 109.4° F. No pathologic changes of any significance (except for congestion of the thoracic and abdominal viscera) were found on gross and microscopic examination of the tissues, including the brain, of this animal.

Some of the histologic changes seen in the brain of our patient resemble some of those reported in experimental animals that were chronically intoxicated with barbiturates. The amyloid bodies are suggestive of those reported by McCrum et al.,[7] or of the "mucinoid" bodies of Mott, Woodhouse and Pickworth.[8] Loss of Nissl substance in Purkinje cells was also a feature in this case, as it was in the animals of Mott et al. None of the histopathologic changes reported in either animals or man can be regarded as being specific for chronic barbiturate intoxication, since they occur in other conditions. Furthermore, the relation of

pathologic changes in animals to withdrawal of barbiturates is obscure, since none of the reported studies was designed to observe the clinical picture and pathology of withdrawal per se. It is noteworthy that most patients chronically intoxicated with barbiturates recover completely within two weeks (as far as can be judged by clinical means) following withdrawal of the drugs. This fact suggests that, if chronic barbiturate intoxication does produce histopathologic changes, the changes are usually either reversible or not sufficiently extensive to produce gross impairment of function.

The occurrence of this death points up the opinion previously ventured,[9] that abrupt withdrawal of barbiturates from chronically intoxicated persons is very dangerous and generally contraindicated. Withdrawal in this case was accidental and due to the patient's concealment of his enormous barbiturate intake from the physicians who were attempting to treat him. Had the diagnosis been made in time, proper treatment would have consisted of parenteral administration of barbiturates in sufficient quantity to induce eight to 12 hours of unbroken sleep, followed by regular oral doses of amounts of barbiturates sufficient to maintain a definite, continuous, moderate degree of intoxication. After several days on this régime, dosage of barbiturates should have been reduced cautiously (no more than 0.1 gm. daily) until withdrawal was completed.

Summary

The clinical course and gross and microscopic pathology of a patient who died during the course of the barbiturate abstinence syndrome is presented.

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