

ACID INTOXICATION, AND LATE POISONOUS EFFECTS OF ANESTHETICS.

HEPATIC TOXEMIA. ACUTE FATTY DEGENERATION OF THE LIVER FOLLOWING CHLOROFORM AND ETHER ANESTHESIA.*

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(Concluded from page 696.)

Stocker,⁵ in 1895, reports an operation for strangulation of pedicle of ovarian cyst. A gangrenous pedicle was found and cyst and pedicle were removed. Stocker makes no mention of the anesthetic, but in Cohn's article referred to later he mentions chloroform as the anesthetic used. Probably this statement was made to Cohn personally. Shortly after the operation icterus was noted, the patient became restless, finally became comatose and died. An acute yellow atrophy of the liver was found at autopsy. Stocker believes that the atrophy resulted from the absorption of toxins from the strangulated and gangrenous pedicle. He does not lay much stress on the anesthetic used.

Victor Bandler,¹⁴ in 1896, reports a case of late chloroform poisoning from Wölfler's clinic.

Patient.—Male, 42 years old; glass blower by occupation; apparently in good health, but a heavy beer drinker, often taking as many as 101 daily, was operated on at noon, July 18, 1895, for an incarcerated inguinal hernia. Omentum was found in hernial sac and was resected. The operation lasted about one hour. Anesthesia was easily produced and about 80 grams of chloroform were used. The morning following the operation icterus was noted. On the second day the icterus had increased and bile pigment was found in the urine. Patient was quiet, no pain in abdomen or wound; tongue moist; some headache and a striking apathy. Temperature 38.2 C., pulse 92. On the third day icterus was marked; urine brownish color; some blood in stool; urine rich in bile pigment; albumin, and in the sediment yellowish, granular and hyaline casts. There was some pain in the liver region, but the liver apparently was not enlarged. During the day icterus increased and little urine was passed. During the evening the patient suddenly became delirious, attempted to get out of bed and was restless.

On the following morning the patient was unconscious: there were hemorrhages into the abdominal wall, but the wound was clean. Leucin and tyrosin were found in the urine, and a diagnosis of acute yellow atrophy was made. The patient became comatose. There were petechiæ in the skin. Terminal rise of temperature to 40 C. Death occurred four days after operation.

Anatomic Diagnosis.—Acute yellow atrophy of the liver; icterus; multiple hemorrhages; fatty degeneration of the heart; chronic Bright's disease.

Erlach,¹⁷ in 1896, in a personal communication to Bandler,¹⁴ reports the death of a patient from acute yellow atrophy of the liver, following the use of Billroth's mixture; total extirpation of the uterus was done for fibroids. The predisposing cause was probably gastritis and catarrhal icterus. At the autopsy acute yellow and red atrophy of the liver was found.

Marthen,¹⁸ in 1896, reports the following clinical history:

Patient.—Woman, 34, insane. The roots of fourteen carious teeth were removed under chloroform anesthesia. Anesthesia

lasted about forty minutes, and about 70 c.c. of chloroform were used. Patient vomited frequently after anesthetic. The day following operation some icterus of the face and back was noted. Vomiting continued, and on the third day the patient became restless, uttered piercing cries and attempted to leave bed. There was convulsive tic of face and upper extremities. Pupils, maximum dilatation. Cheyne-Stokes respiration. Death.

Anatomic Diagnosis.—Fatty degeneration of heart muscle and kidneys. Acute fatty degeneration of liver.

W. Mintz,¹⁹ in 1900, reports the following case:

Patient.—Male, 40 years old, heavy drinker, always well previous to present trouble. Operation, opening of appendiceal abscess and removal of gangrenous appendix. During evening of second day patient vomited three times; the vomitus contained blood. Vomiting persisted on the third day, accompanied by singultus. Slight jaundice, which increased in intensity. Death occurred seven days after operation, eighteen days after beginning of disease.

Anatomic Findings.—Erosions in duodenum and along lesser curvature, corresponding to which were numerous obliterated arterial lumina.

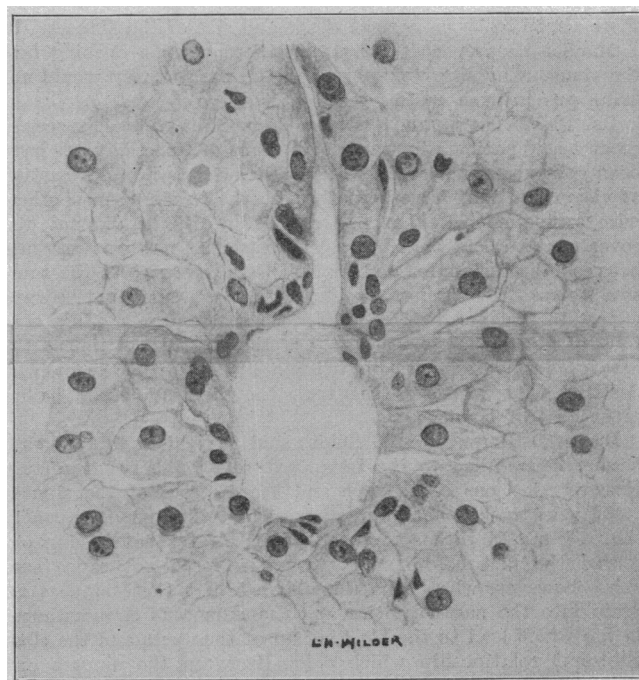


Fig. 1.—Section of liver of healthy rabbit, showing nuclear and cytoplasmic characteristics. Stained with hematoxylin and eosin.

Anesthetic is not mentioned. The author speaks of direct relation to epityphilitis.

Cohn,⁴ in 1902, reports a case of protracted chloroform action resulting fatally.

Patient.—A woman, aged 21, with no apparent predisposing cause, was operated on Jan. 3, 1902, for the removal of diseased uterine adnexa. The patient took chloroform well, about 175 grams being used. During the day the patient was excited and restless, and gained complete consciousness only once. There was slight vomiting after anesthesia.

January 4: She had a sleepless night, tossed about in bed, and finally was restrained by nurse. The evening temperature, 38 C.

January 5: Patient slept a great deal, talked with nurse at times, and was conscious.

January 6: Jaundice was noted. At half-past 8 the patient suddenly became very restless and delirious. She tossed about

* Read in the Section on Surgery and Anatomy of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.

17. Erlach: Personal communication to Bandler.

18. Martin, G.: "Ueber tödtliche Chloroform nachwirkung," Berl. klin. Wochft., 1896, xxxiii, p. 204.

19. Mintz, W.: "Akute gelbe Leber atrophie als Komplikation v. Epityphilitis zugleich ein Beitrag. z. Frage der postoperativen Magen-Duodenal Blutung." Mittell. aus den Grenzgebiete der Med., 1900, vi, p. 645.

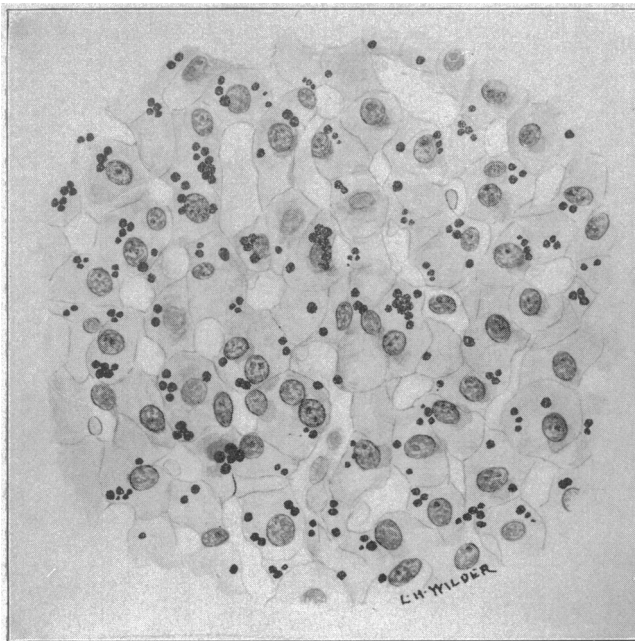


Fig. 2.—Section of liver of healthy rabbit, showing the amount and distribution of fat in the liver cells. Fat globules are represented by the heavy black. Drawing made from a frozen section, stained with Sudan III and Delafield's hematoxylin.

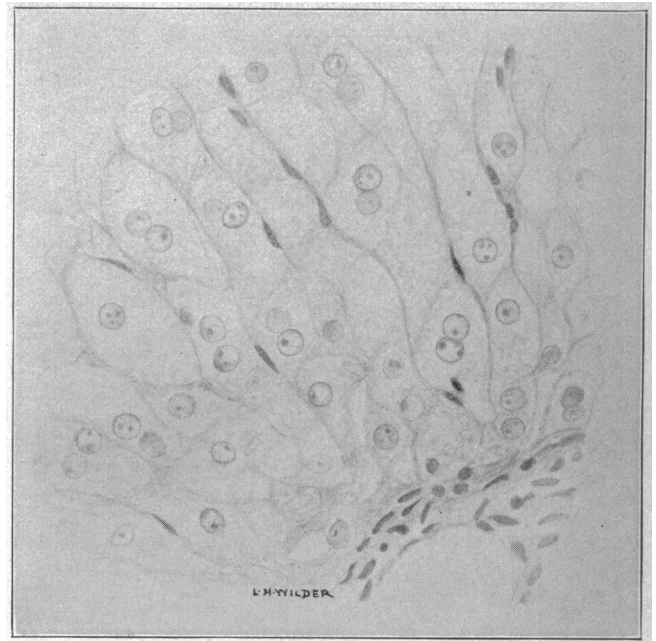


Fig. 4.—Section from liver of rabbit, which had been chloroformed for two hours and killed forty-eight hours later, stained with hematoxylin and eosin. The liver cells are swollen and vacuolated, the fat droplets having been dissolved out during the process of embedding. The nuclei stain poorly, the chromatin network having been partially destroyed. In some cells karyorrhexis is well advanced.

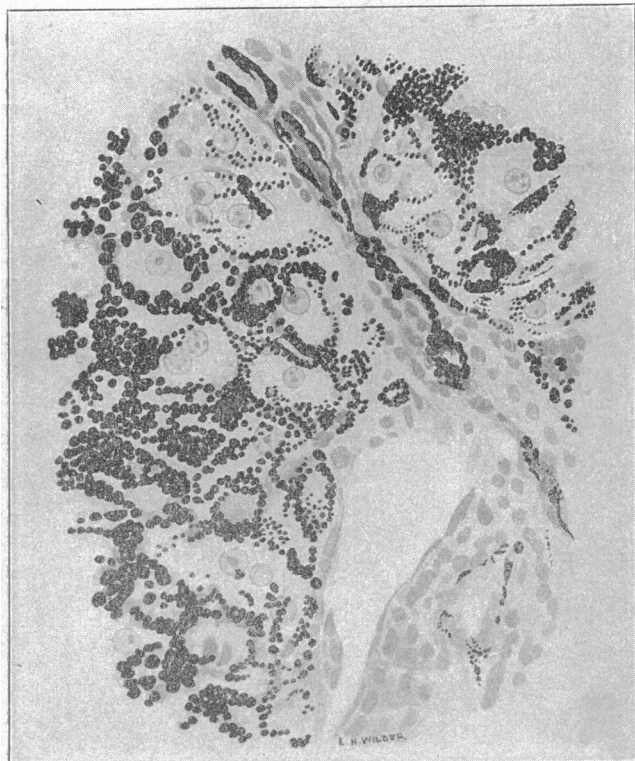


Fig. 3.—Section of liver of a rabbit, which had been chloroformed for two hours and killed forty-eight hours later. The rabbit became drowsy about twenty-four hours after the anesthetic, refused food and was partially paralyzed in the forelegs. The liver presented the typical appearance of fatty degeneration. Drawing made from a frozen section stained with Sudan III and Delafield's hematoxylin. Fat is represented by the heavy black. Fatty degeneration of the liver cells is marked; the fat droplets are grouped about the periphery of the liver cell and are separated from the nucleus by a clear, unstainable, degenerating cytoplasm. The fatty changes are found throughout the lobule, and are not confined to any particular zone.

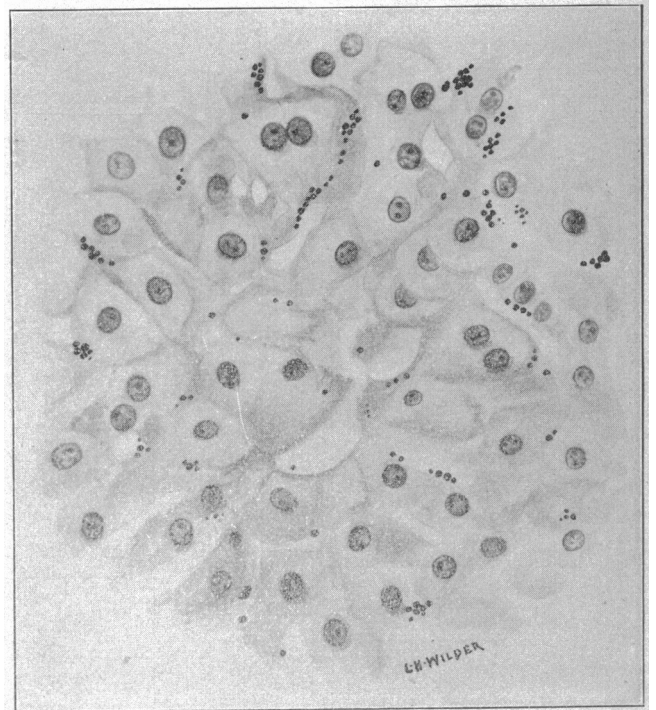


Fig. 5.—Section of liver from a rabbit, which had been etherized for two hours and killed seventy-two hours later. The animal was not sick after the anesthetic. The liver was macroscopically normal. The fat does not exceed in amount the fat found normally in the liver. It should be noted, however, that the greater part of the fat is intercellular, whereas in the normal liver it is intracellular.

in bed and cried with fright, and had to be forcibly restrained. Sleep was induced by chloral and morphin.

January 7: The patient became deeply comatose. Face reddish, cyanosis, conjunctivæ icteric; pulse small and frequent, 150. Death occurred at 8:30 p. m.

Anatomic Diagnosis.—Cloudy swelling of heart, liver and kidneys. Icteric nutmeg liver.

G. E. Brewer,² in 1902, reports the following case:

Patient.—S. S., schoolboy, aged 12, was admitted to Roosevelt Hospital, April 29, 1901. Two days previously he had been seized with acute abdominal pain, accompanied by nausea and vomiting. There was slight elevation of temperature and increased pulse rate. Previous health was good.

Operation.—April 29, 1901: A perforated gangrenous appendix was found in a small abscess and removed. Anesthesia produced by chloroform lasted about twenty-five minutes. The second night after the operation was a comfortable one, and the following morning temperature was normal, pulse 76. During the day the temperature remained normal and pulse did not rise above 80.

Postoperative History.—The following night (third) he slept well until shortly after midnight, when he awakened suddenly without apparent cause and uttered an agonizing, piercing shriek expressive of terror. He failed to recognize people about him; he soon fell asleep, and rested quietly until morning. He was somnolent on the following morning. When aroused he would cry out and appear much frightened. Temperature 98.5, pulse 74. He was seen by Dr. Brewer at about 11 o'clock, and when awakened he screamed so loudly that he could be heard over the whole building and was the picture of abject terror. The paroxysms lasted from a few seconds to two or three minutes. There were no symptoms on part of nervous system. Consultation was held. Peculiar sweetish odor of breath was noted. At 6 p. m. temperature was normal; pulse during day was 80. Acetone and diacetic acid were found in the urine.

At 8 p. m., 400 centimeters of blood were withdrawn from median basilic vein, and 1,000 c.cm. of normal salt solution, to which were added 15 grams of chemically pure sodium bicarbonate were injected. The paroxysms of screaming became shorter and occurred less frequently. Circulation in extremities was slower; face became slightly cyanotic and eyes expressionless. Between 4 and 5 a. m. the condition began to grow worse. Respirations became shallow and rapid. The pulse was weaker; temperature rose rapidly to 103 F., and deep and progressive coma developed. Death occurred at 11 a. m. No autopsy.

Ballin,²⁰ 1905: Dec. 9, 1901: Appendectomy was done on a young man, aged 20 years; lead poisoning was a possible predisposing cause, under chloroform anesthesia. A small amount of chloroform was used.

Dec. 10, 1901, 9 a. m.: Temperature normal, pulse 100, patient restless and nauseated. Urine was drawn by catheter.

December 11: There was slight jaundice of skin and conjunctiva and slight vomiting several times. He was somewhat restless in the afternoon. Temperature 97.6 F., pulse 88. The jaundice increased; patient was restless and slightly delirious in the evening. There was vomiting of greenish fluid at 5 p. m.

December 13, 8 a. m.: Temperature 98 F., pulse 86; patient was delirious all night and was noisy; he slept at short intervals; he was apparently in deep coma at these times. He threw his arms and legs about wildly and was violent. By this time he presented the classical symptoms of acute yellow atrophy.

December 14: Temperature 100.4, pulse 108. Delirium and coma seemed to increase. Gradually there was subsidence of symptoms; patient was discharged from hospital on February 11.

Ballin discusses in this paper the possible relation to chloroform anesthesia and to toxins from diseased appendix.

Guthrie,²¹ in 1903, reported the following cases:

CASE 1.—Woman, aged 41, was admitted to Glasgow Royal Infirmary on October 29, 1897. She had a tuberculous knee, from which she had suffered for the past twenty-seven years. During the past four years she had had occasional attacks of gallstone colic. Otherwise her health was good. The limb was put in carbolic acid dressings preparatory to operation. After twenty-four hours the patient vomited bile-stained matter; urine was greenish, becoming darker on standing. The dressings were immediately removed, but the patient remained seriously ill for eight days. After subsidence of vomiting, she remained well for nearly three weeks; urine was free from albumin and casts.

November 24: The knee was excised under chloroform. During the night, vomiting commenced and increased; nothing would stop it. Afternoon of November 26 patient was drowsy. At night she could not be aroused to answer questions. Urine was passed in small quantities and contained casts. She died comatose, November 27, three days after operation.

Autopsy.—Liver was markedly fatty. Heart was small, musculature healthy. Kidneys were fatty, with some interstitial nephritis. Spleen was normal.

CASE 2.—Boy, aged 3, admitted under care of Mr. Burghard, for webbed fingers and toes, April 6, 1903. Patient was healthy looking and well nourished. Described as "dyspeptic," subject to "bilious attacks," "night terrors," and very passionate.

Operation.—April 7, at 3 p. m., webs between second and third fingers of each hand were divided under chloroform. Operation lasted twenty minutes. Chloroform was taken well.

Postoperative History.—On April 9 patient was slightly sick, drowsy and apathetic. On the afternoon of the same day, he became slightly, but distinctly, jaundiced. In the evening, he began to scream loudly, the screaming occurring in fits and paroxysms; he was seemingly semi-conscious. There was possible slight tenderness in liver region. Liver was slightly enlarged. Urine was passed involuntarily. Screams of shrill meningitic type continued until after 3 a. m., when they ceased after administration of chloral and bromids.

April 10: He lay in a practically unconscious state. Jaundice was about the same as on previous day. Liver could be felt two fingers' breadth below the ribs. Leucin and tyrosin were not found in urine. Toward night he became comatose. The conjunctival reflexes were lost. There was slight lateral nystagmus, especially in the left eye with a tendency in both eyes to turn upward. Respirations were loud, quick, but not typical Cheyne-Stokes. Death occurred at 2:45 a. m. on April 11; 84 hours after the operation. Temperature was between 97 and normal throughout.

Autopsy.—Liver weighed 1 pound 12 ounces; pale and fawn-colored.

Microscopic Examination.—Osmic acid preparations showed a ring of fatty cells, occupying the outer zone of each lobule; intermediate zone, a few fatty cells; none in inner zone. Cloudy swelling and fatty degeneration. Small petechiæ were found in pleuræ. Brain, meninges, kidneys, suprarenal capsules, spleen and intestines were normal.

CASE 3.—Healthy-looking female child, aged 1 year and 10 months, was admitted to the Children's Hospital, Paddington-Green, under care of Mr. Burghard, February 24, 1898. Partial removal of nevus had been made in June of previous year. At 10 a. m., February 25, Mr. Burghard removed remaining portion of nevus under chloroform. The operation lasted twenty minutes. Carbolic acid was used only in strong mixture to purify skin at beginning of operation. Wound was dressed with cyanid gauze.

Postoperative History.—At 4:30 p. m. the child was slightly nauseated. Temperature, 9 p. m., 102. Child slept well during night; at 5 a. m. she awoke, restless and nauseated; at 7:15 a. m. she was restless, somewhat cyanosed, conscious. Pulse was feeble and rose to 136 and 160. At 11 a. m. the

20. Ballin, Max: "Acute Yellow Atrophy of the Liver as a Sequela to Appendectomy." *Ann. of Surg.*, 1903, xxxvii, p. 362.

21. Guthrie, L. G.: "Some Fatal Effects of Chloroform on Children Suffering from a Peculiar Fatty Condition of the Liver." *Lancet*, 1903, II, p. 10.

child vomited dark colored matter. At noon she became unconscious, though still restless and thirsty. At 2 p. m. there was a slight general convulsion. Saline injection was given. Death occurred twenty-eight hours after operation. Pulse was 160, temperature 106 at time of death.

Autopsy.—Liver weighed 13 ounces. Slight increase of fibrous tissue along portal canals. It was preserved in alcohol, preventing good demonstration of fat, but is reported as "undoubtedly fatty in places."

CASE 4.—Girl, aged 3. Dr. Lack opened postpharyngeal abscess from behind sternomastoid. Chloroform was taken well. The operation lasted from ten to fifteen minutes. Twenty-four hours later the child appeared well, but was often nauseated. Temperature was 102 F. At 8 p. m., thirty-three hours after operation, the child had a "cold fit;" there was some shivering and extremities were blue and cold. Temperature rose to 107. Death occurred one-half hour later. Carbolic acid was used at operation, but no carboluria had developed. No autopsy was permitted.

E. G. Brackett,³ in 1904, J. S. Stone and H. C. Low reported the following:

CASE 1.—M. J. B., girl, aged 8, entered Children's Hospital October 6, 1903. There was extensive infantile paralysis involving most of the muscles of both lower extremities. During preceding year frequent attacks of severe and persistent vomiting, accompanied by marked prostration and rapid pulse, closely resembling condition existing first day of fatal one, may have been predisposing causes.

Operation and Postoperative History.—Oct. 10, 1903: The child was etherized and three tendons were transplanted. She took ether badly, was cyanotic and had rapid pulse. During recovery from ether the child vomited and then seemed comfortable and in good condition for twelve hours. She suddenly began to vomit; the pulse became rapid; rose to 190, and temperature to 106. Vomiting lasted about thirty hours. The child passed from restlessness into a delirious stupor, and died forty-two hours after operation, thirty hours after vomiting began. No test was made for acetone and diacetic acid in this case, but it was later recalled that the breath had a peculiar sweetish odor.

Autopsy.—Liver weighed 510 grams. Surface was smooth and irregularly mottled with yellowish areas from 3 to 5 cm. in diameter, scattered over a reddish-brown surface. Cross-section, yellowish-brown in color. Microscopically, sections of liver, spleen, kidneys and lung were negative.

CASE 2.—Girl, aged 5½ years, entered Children's Hospital, November 16, 1903. Infantile paralysis, four years before, and contracted fasciæ, causing permanent flexion of the thighs. A slight trace of diacetic acid was present in urine.

November 17, 1903: Fasciæ at upper and outer part of each thigh were divided, open method. Operation was short, little ether being used.

Postoperative History.—At 11 p. m., thirteen hours after operation, she vomited a small amount of dark brown thin fluid; during the next ten hours she vomited several times. She slept in all three hours. When awake she was very restless and noisy. Twenty-four hours after operation the condition of patient was very poor. Extremities were cold; pulse weak and rapid; expression anxious; sweet odor of breath noticeable during morning. Twenty-six hours after operation 5 ounces of urine were passed, containing large traces of acetone and diacetic acid. Thirty hours after operation the child became delirious. Pulse was very weak. Thirty-six hours after operation, 12 ounces of 2 per cent. bicarbonate solution were given intravenously; also under each breast. On second morning following operation, child became dull and apathetic; she gradually lost consciousness and coma supervened. Odor of breath became more pronounced. Cyanosis was marked during last few hours. Temperature after operation remained at about 102.

Autopsy.—Liver surface smooth, and pale yellow; in places reddish color. Cut surface, pale yellow; oily and homogeneous. Fresh examination showed marked fatty infiltration. Kidneys, fatty infiltration.

CASE 3.—Girl, aged 4, entered Children's Hospital, February 15, 1904, with double congenital dislocation of both hips.

Right hip had been reduced five months previously under ether. Urine was acid, free from sugar and albumin. Three days after entrance to hospital patient was etherized, and in manipulating both femurs were broken.

Postoperative History.—Child was under ether between one-half and three-quarters of an hour. She recovered from the ether as usual. In the evening, pulse was weak and rose to 150. Twenty hours after operation, pulse became suddenly weak and rapid; the color was poor. The child seemed dull; no vomiting. Breath was sweet. Acetone and diacetic acid present in urine. During the day, the child grew rapidly worse and sank into restless coma; lips blue in spite of oxygen; drawn expression of face; eyes became sunken. At 6 p. m. salt solution was injected under both pectorals, followed by marked improvement in pulse and color. Temperature was 104; at 9:30 p. m. the child was able to recognize her mother. At midnight the condition grew rapidly worse. Temperature rose to 106 at 3 a. m. Coma returned. Child died at 5:30 a. m., twenty-three hours after first collapse, forty-three hours after operation.

Autopsy.—Liver large, pale yellow, with a pink color in places. Cut surface pale yellow; lobules indistinctly marked. Knife edge scraped up fatty material. Tissue broke easily on pressure. Kidney, considerable fat in epithelium of convoluted tubules.

Kelly,²² in 1905, reported the following case:

Patient.—Schoolboy, aged 9. Service of Dr. H. W. Cushing. Operation, May 16, 1904, for appendicitis. Ether anesthesia. The condition of the appendix did not account for the patient's serious condition, so the abdomen was explored and nothing found. A sterile gauze wick was inserted into pelvis and to stump of appendix, and abdominal wound was closed. An area about 1 centimeter in diameter of slight edema and redness was found about 2 cm. from the tip of the appendix. The appendix contained a grape seed. The patient's general condition so grave that 250 c.c. (1-50,000) adrenalin salt solution were given. He was restless after operation. Urine was negative before operation.

Postoperative History.—May 18: Sweetish odor of breath continues. Patient mildly delirious and drowsy. Urine contains acetone and diacetic acid. Vomiting continues.

May 22: General condition markedly improved. Still occasional vomiting. Acetone and diacetic acid present in urine. No delirium, but patient is drowsy and resists daily dressing.

May 26: Occasional vomiting. Expression dull. Patient sleeps most of time; refuses everything by mouth. Acetone and diacetic acid in urine. Patient slowly failed, and in spite of active stimulation died at 11:05 p. m.

No autopsy. Examination of liver during operation was negative.

REVIEW OF SYMPTOMS.

The symptoms appear in from 10 to 150 hours after the anesthesia. The average of Guthrie's first series of ten cases being 7½ hours.

In Brewer's case, a boy of 12, following an operation for appendicitis lasting twenty-five minutes under chloroform, nothing unusual was noted immediately after. The second night following the operation was a comfortable one. He slept six hours; the next day his pulse was 76, and temperature normal. He was cheerful, happy, had no pain, and was hungry.

The following night, he slept quietly until shortly after midnight, when he suddenly awakened and without any apparent cause uttered a piercing shriek, which alarmed his nurse and mother. He continued to scream for several minutes, looked wildly about him, and apparently failed to recognize those around him. A few moments later he fell asleep and rested quietly until morning. The following morning he was distinctly somnolent, when aroused would cry out and appear frightened, but could easily be soothed by his mother.

22. Kelly, Jas. A.: "Acid Intoxication: Its Significance in Surgical Conditions," 1905, xii, p. 161.

At 11 in the morning he awoke and again uttered an agonized cry. He continued to scream, so that he could be heard all over the building. Delirium was followed by coma. The face seemed slightly cyanosed; acetone and diacetic acid were found in the urine and blood. Death. No autopsy.

Brewer discusses the case and comes to the conclusion that it was an auto-intoxication, and considers ptomain poisoning, uremia and acetonemia, and concludes that acetonemia was the cause of death.

Brewer describes the three characteristic symptoms, as sweetish odor of the breath, delirium and rapidly fatal coma. Another symptom is that of air hunger, described by Kussmaul, evidenced by deep breathing and a bright red color of the mucous membranes (this was noted in our case), Cheyne-Stokes respiration and cold extremities.

Brackett, Stone and Low describe the following symptoms: Vomiting associated with collapse; a very weak and rapid pulse; an absence of fever until just before death; cyanosis in the fatal cases, causing extreme dyspnea; apathy and stupor alternating with periods of restlessness, at first, but in the fatal cases gradually deepening into coma and death; and the presence of acetone in the breath and urine.

Stocker describes the symptoms in his case as follows: The morning of the second day after the operation the patient, who had been doing well, became very restless, threw herself about in the bed, but mind was at first clear. The next day coma and death.

Guthrie says of symptoms:

After recovery from the immediate effects of the chloroform there was usually an interval of a few hours at the end of which the child would begin to utter piercing cries at short intervals, disturbing the whole building by its shrieks, grinding its teeth, tossing, struggling and requiring constant attention lest dressings be torn off or fractured bones displaced. The pupils were often dilated, sometimes unequally, the face being flushed or pale, with a look of wild terror and anxiety. Consciousness was sometimes lost early and never regained; sometimes there were intervals in which the child would be dull and apathetic, but would answer rationally when addressed, and usually deny being in pain. Vomiting was a marked feature in all but one case. It was copious, frequent, persistent and the vomited matter sooner or later almost exactly resembled the dregs of beef tea.

In eight out of ten cases, the symptoms of a marked cerebral type were present, resembling maniacal delirium.

Temperature (10 cases): In 1 case it rose to 103 four hours after operation, and remained there throughout. In 2 cases it rose to 103.2, and 104.6, just before death. In 1 case it remained between 98 and 99. In 6 cases it varied from 99 to 102.

Two cases suggested meningitis, running unusually acute and rapid courses; except for absence of jaundice and hemorrhage, they might have been diagnosed as "acute yellow atrophy."

In Kelly's cases there was apathy, alternating with restlessness, vomiting occurring without apparent cause, following immediately on taking anything into the stomach, coma and death. The pulse was increased in rapidity, of decreased tension, and in some cases became very weak. Fever was absent except in severe cases, when the temperature would rise to 102 or 103. The face alternately pale or flushed, was at times expressive of great anxiety.

PREDISPOSING CAUSES.

Age, 1 to 10 years, 17 cases; 11 to 20 years, 3 cases; 21 to 30 years, 1 case; 31 to 40 years, 2 cases; 41 to 50 years, 2 cases. Age not mentioned in 5 cases.

Sex: Male, 9 cases; female, 18 case. Sex not mentioned in Bastianelli's three cases.

Possible predisposing or accessory causes are, alcohol, lead, carbolic acid, mercurial and iodoform intoxication. Other causes are homesickness, fright, change of food (Brackett, Stone and Low), intestinal fermentation and putrefaction; extensive fatty changes associated with infantile paralysis; starvation; sepsis. In pregnancy, in the presence of a dead fetus; the existence of a gangrenous mass, diabetes, carcinoma, anemic states from any cause and hemorrhage are also to be considered.

POSTMORTEM FINDINGS.

Liver: Fatty degeneration or infiltration occurred in 16 cases; acute yellow atrophy in 3 cases; icteric nutmeg liver in 1 case; no distinct liver changes mentioned in 4 cases; recoveries in 2 cases; no autopsy in 4 cases; total, 30 cases.

CHANGES IN OTHER ORGANS.

The following changes were noted in other parts of the body: Fatty degeneration of heart; different grades of nephritis; fatty degeneration of muscles of lower limbs; considerable venous congestion of brain; pyelitis; tuberculosis of bronchial lymph nodes and vertebræ.

CONCLUSIONS.

From the analysis of clinical and laboratory reports bearing on this subject, we believe that we are warranted in the following conclusions:

1. Anesthetics, especially chloroform (ether to a very limited degree), can produce a destructive effect on the cells of the liver and kidneys and on the muscle cells of the heart and other muscles, resulting in fatty degeneration and necrosis, very similar to the effects produced in phosphorus poisoning.

2. The constant and most important injury done is that to the liver.

3. This injury to the liver cells is in direct proportion to the amount of the anesthetic employed, and the length of the anesthesia.

4. Certain individuals exhibit an idiosyncrasy or a susceptibility to this form of poisoning which it is difficult to explain.

5. There are certain predisposing causes which favor this destructive effect of chloroform, among which are, (a) age—the younger, the more susceptible; (b) causes which lower the general vitality of the individual and probably the vitality of the liver cells, such as diabetes, previous recent anesthetics, infections from pus germs, diphtheria, intoxications from a dead fetus in the uterus, a gangrenous mass in the abdominal cavity, etc.; (c) exhaustion due to hemorrhage; (d) exhaustion due to starvation; (e) exhaustion due to wasting diseases, such as carcinoma; (f) lesions which have resulted in extensive fatty degenerations, such as occur in the limbs in infantile paralysis; (g) chronic diseases involving both liver and kidney, such as cirrhosis and nephritis.

6. As a result of this fatty degeneration and necrosis of the liver cells, toxins are produced either from the liver cells themselves or as a result of the failure of these cells to eliminate substances which, under normal conditions, they eliminate, but which under these abnormal conditions they fail to do, and these substances, therefore, may accumulate and produce toxic effects.

7. These toxins produce a definite symptom-complex which makes its appearance from 10 to 150 hours after the anesthesia. This symptom-complex consists of vomiting, restlessness, delirium, convulsions, coma, Cheyne-Stokes respiration, cyanosis, icterus in varying degree, and usually terminates in death.

8. It is probable that milder degrees of this poisoning are recovered from, and that the transient icterus noticed after chloroform anesthesia without other evident cause is due to such poisoning, and many cases which exhibit restlessness, fright, mild delirium, drowsiness, etc., after anesthesia may be due to the same cause.

9. This disease is an hepatic toxemia; the toxins producing it hepatic toxins; and possibly the previous condition making its development easily possible should be described as liver insufficiency. Just as we have for a long time recognized a condition, uremia, in which we find arising from a variety of noxious agents, anesthetics, poisons, infections, pregnancy, etc., affecting the secreting cells of the kidney and preventing their normal function, a pathologic condition, accompanied with a certain definite symptom-complex; so we must now, we believe, recognize a condition involving the liver in which we find from a variety of noxious agents (anesthetics, poisons, infections, pregnancy, etc.), affecting the secreting cells of the liver and preventing their normal function, a pathologic condition which we must describe as hepatic toxemia, accompanied with a certain symptom-complex, and showing certain changes postmortem.

We believe that the condition of acute fatty degeneration of the liver with resulting hepatic toxemia is as definite a pathologic entity as is acute pancreatitis with fat necrosis.

10. As by-products in this toxemia, but not as the essential poisons, are found acetone, diacetic acid and betaoxybutyric acid in the blood and urine.

11. Postmortem reveals fatty degeneration of the liver, fatty degeneration and mild degree of inflammation of the kidneys, and, in extreme cases, fatty degeneration of heart and other muscles. The lesion of the liver, we believe, to be the overshadowing and important one, and the one which is responsible for the symptoms and fatal result. The injury to the liver, in some cases, is so great as to result in practically a total destruction of the organ.

12. Somewhat similar hepatic toxemias resulting from fatty degeneration of the liver cells occur in other conditions, and are accompanied with very similar symptoms. In such conditions as phosphorus poisoning, diabetes, puerperal eclampsia, acute yellow atrophy of the liver.

13. This fatty degeneration of the liver with hepatic toxemia following anesthesia is almost invariably due to chloroform in the fatal cases. Ether is seldom the cause of a death of this kind.

14. This serious and even fatal late effect of chloroform which has heretofore not been generally recognized must still further limit the use of this powerful and dangerous agent.

15. The possibility of the development of hepatic toxemia makes chloroform distinctly contraindicated in those cases in which there exist the conditions which seem to favor its development, i. e., diabetes, sepsis, starvation, hemorrhage; the presence of intoxication from dead material; the presence of fatty degenerations, as already cited, after infantile paralysis, and lesions of the liver. The susceptibility of children to this hepatic

toxemia must be recognized. That chloroform is capable of producing these serious late poisonous effects is a strong argument against its employment, and an argument in favor of the more general use of ether; and yet we are confronted at times with the Charybdis of ether pneumonia, on the one hand, and the Scylla of chloroform hepatic toxemia, on the other.

16. The recognition of this danger of hepatic toxemia is a strong argument against the employment of chloroform for long anesthesia, as it can be shown that a two-hour chloroform anesthesia is almost invariably fatal to rabbits and guinea-pigs, from fatty degeneration and necrosis of the liver cells; and a two-hour chloroform anesthesia in man is an exceedingly dangerous thing.

17. These facts in regard to the late poisonous effects of anesthetics and the fact that the dangers increase with the amount of the drug employed, and with the length of the anesthesia form a strong argument in favor of rapid operating and in favor of limiting in every way possible the length of the anesthesia and the dose of the anesthetic. For example, time-consuming preparations of the patient should be made before, not after, anesthesia. In the light of this present knowledge, no surgeon can claim, as some have in the past, that after the patient is once asleep, that it makes no difference whether it requires one hour or two hours for the doing of an operation. In the light of this knowledge, for instance, three-hour breast amputations with the unnecessary ligation of fifty vessels, becomes bad surgery.

18. This problem seems to us a very important one, and worthy of the most careful study and research. At present, we are practically limited to chloroform and ether as general anesthetics. Each has its danger; each has its special field in which one is safer than the other. We have, as a rule, heretofore, employed chloroform in cases in which there was a previous lung or kidney lesion, and in children, with the idea that it was less likely to produce nephritis and pneumonia, and have used ether in the bulk of our work and felt that it was specially to be selected in heart lesions. We must now add new limitations, and attempt to determine by previous examination whether there is what might be called hepatic insufficiency, the conditions present which favor the development of the late poisonous effect of chloroform on the liver. Another way of solving this problem would be the discovery of new anesthetic agents, which do not carry with them these poisonous effects, or the employment of the present anesthetic in such a way as to avoid these dangers.

For instance, it has been suggested that chloroform and oxygen combined would prevent the poisonous effects of chloroform alone, and there is some evidence to support this view. This should be determined by special research.

Again, nitrous oxid and oxygen combined can be employed for long anesthetics, and experience may show that this mixture may prove to be very much safer than chloroform and ether. Although at present there is not enough evidence on which to base such a claim, in this connection I would cite the fact that the anesthetist in Dr. Bevan's surgical clinic, Dr. F. B. Moorhead, has found that after prolonged anesthesia with gas there is a marked decrease in the amount of hemoglobin, apparently a rather serious destructive effect on the blood, which may limit the use if this mixture.

In conclusion, we believe that the dangers of late chloroform poisoning must be more generally recognized and understood; that the lessons from this study are the dangers of long chloroform anesthetics and chloroform anesthetics in patients suffering from the conditions which we cited favored its development; and, we must recognize the susceptibility of children to this form of poisoning. The problem of how to prevent these deaths confronts us unsolved. We have taken the first step in its solution, for we now recognize the cause of these deaths. We must work and find some way to prevent the occurrence of these serious and fatal accidents.

DISCUSSION.

DR. HERBERT C. MOFFITT, San Francisco, stated that during the last three years he has seen in consultation six cases similar to the one reported. In each instance there had been some previous affection that might render the liver insufficient. One man had gummata of the liver, with gallstones. A woman had gallstones with frequent attacks of cholecystitis. A child had an attack of catarrhal jaundice some months before an operation under chloroform for mastoid disease. A young woman had had malaria for years, with enlarged liver and spleen, before she was operated on for acute appendicitis. Another young woman had had catarrhal jaundice some weeks before an exploratory laparotomy was done under chloroform. In four of the cases there was the clinical picture described by Dr. Bevan. It has been Dr. Moffitt's rule of late, in view of such experience, to forbid the use of chloroform in any condition of suspected hepatic insufficiency.

DR. HARRY M. SHERMAN, San Francisco, said that Dr. Bevan has possibly explained something that puzzled him in a patient some time ago. A girl after an operation suffered from persistent vomiting and some jaundice with almost suppression of urine. One day the urine would contain casts with no albumin, and the next day albumin but no casts. Naturally Dr. Sherman thought there was some postoperative nephritis. To stimulate the kidney function he used salt solution under the skin, and the symptoms, including the vomiting, stopped and the patient began to take food, but the urine was not increased in quantity. Evidently it was not a case of nephritis and may not unlikely have been one that would fall into the class described by Dr. Bevan.

DR. WOODS HUTCHINSON, Portland, Ore., declared that the greater frequency of the occurrence of this condition in children is probably due to the fact that physicians have always thought it perfectly safe to use chloroform in children. It also probably explains the unexpectedly bad results that sometimes follow operations for gallstones, the liver being already disabled and unable to resist the attack of the anesthetic. The liver, Dr. Hutchinson said, is a poison filter and reduces toxins in the blood both from the portal and general systems. These toxins are changed into the harmless excretion, bile. The liver certainly is the organ which first fails in puerperal eclampsia, probably in most cases of Bright's disease, and is beginning to attract suspicion even in acute infections like pneumonia. In chronic poisoning by alcohol, arsenic or phosphorus the liver acts as chief protector of the system and first shows the result of the attack in cloudy swelling and cirrhosis. No matter what the disease, our patients die with one familiar group of symptoms—headache, convulsions, blindness, coma, Cheyne-Stokes respiration, which is called "uremia"—because urea is precisely the one substance which the liver is unable to form and hence is present in the blood in less amounts than usual. Uremia is the syndrome of liver failure. Just as long as the liver can destroy the toxins just so long the system will be able to resist.

DR. OTTO S. BINSWANGER, Portland, Ore., agreed with Dr. Bevan that death in chloroform poisoning is due to degeneration or death of the liver cells. Dr. Binswanger said that considering the part played in diabetic coma by oxybutyric and diacetic acids, he is inclined to believe that these acids may be responsible to some extent for the fatal results in

these cases. In diabetes, he said, these acids cause an acidosis or a reduction in the alkalinity of the blood. They neutralize to some extent the carbonate of potassium or sodium. The carbonates are the chief agents for the removal of carbon dioxide. They are converted into bicarbonates, which in turn are broken up in the lungs into normal carbonates again and carbon dioxide, which latter substance is exhaled. If the quantity of carbonate of potash is reduced by the presence of oxybutyric and diacetic acid, naturally its functions as a carbon dioxide carrier will be reduced. The carbon dioxide will accumulate in the blood and give rise to carbon dioxide poisoning; exactly what happens is diabetic coma.

DR. D. A. K. STEELE, Chicago, reported one additional case of this comparatively rare condition. Two years ago he was called to see a girl aged 12, who was suffering from an acute attack of appendicitis. She had suffered an accident two weeks before by falling down stairs and fracturing both bones of her left forearm. The fracture was reduced under chloroform anesthesia. Dr. Steele had her removed to the Chicago Hospital and operated on her on the third day of her attack of appendicitis, finding an intensely inflamed and adherent appendix buried in a mass of lymph exudate, but not perforated. Chloroform was the anesthetic used during the operation. Everything went along normally for three days, when she began to be restless, delirious, and developed the classical symptoms referred to by Dr. Bevan. At the time of her death Dr. Steele attributed it to actonemia, but now he is convinced that it was a case precisely similar to the one described by Dr. Bevan.

DR. A. D. BEVAN said that Dr. Binswanger is quite correct in attributing certain results to acidosis. The primary cause is the destruction of the liver cells with the liberation in some way of a toxin which produces this symptom complex. Acetone and diacetic acid are to be regarded not as the essential cause, but as by-products in the pathologic process.

THE PRINCIPLE OF LIFE.*

MARSHALL LANGTON PRICE, M.D.

BALTIMORE.

"The days of our age are three score years and ten; and though men be so strong that they come to four score years, yet is their strength then but labor and sorrow, so soon it passeth away and we are gone."

To many of us who travel along the level, but somewhat narrow pathway of scientific research, there doubtless comes the desire, to leave its beaten surface and to stray in those bordering fields where fact and fancy are so delightfully intermingled; where the skies are always blue, the sunshine bright, and the flowers fresh and blooming; where substance appears as shadow and shadow substance and our pet hobbies, viewed with our indulgent paternal eyes, seem beautiful and spirited thoroughbreds. In this land, we can appropriately ask, in the words of the cynical Roman Governor of Judea (freed from the rigid limitations which science imposes), "What is truth?"

An excursion into these fields is not without benefit, even to the hard-headed man of science, and we have a precedent for invading the territory usually considered the exclusive possession of the poet, the artist, and the musician, from the highest possible source. M. Metchnikoff has recently made an excursion into this fascinating country and among the pebbles which he has gathered on its shores are a number of precious stones, which can not fail to add lustre to the crown of a man already a ruler in the field of scientific research.

I have chosen to-day (rather than to attempt the dif-

* Read in the Section on Hygiene and Sanitary Science of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.