

PREGNANCY AND CHLOROFORM ANESTHESIA.

A STUDY OF THE MATERNAL, PLACENTAL, AND FETAL TISSUES.*

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The question of pregnancy and the use of anesthetics is a most important one and has called forth numerous contributions and a large amount of speculation and controversy. The opinion seems to be gaining ground that chloroform is an unsatisfactory anesthetic because of danger during the time of anesthesia, and, perhaps, more because of the possibility of the so-called effects of "late chloroform poisoning." It is claimed by obstetricians that during pregnancy the maternal organism is fortunately immune to the dangers of chloroform anesthesia and that the fetus is not injured by chloroform, as may be the case when ether is used as an anesthetic. We have made no attempt to study the resistance of pregnant animals to acute chloroform poisoning, but have studied them carefully with the idea of comparing the degree of late chloroform poisoning with that of non-pregnant animals. In dogs, the liver offers a good index of the extent of late chloroform poisoning, as the amount of central hyaline necrosis can be readily estimated.

In previous publications,¹ we have reported our observations on chloroform poisoning in dogs in which a careful study of the necrosis and repair of the liver was made. Since we have studied in detail these effects in one hundred or more animals, we believe that it is possible to define the average condition that is produced. Chloroform anesthesia continued for two hours will invariably bring about central hyaline liver necrosis in normal dogs, that is best studied after an interval of forty-eight hours, when the necrotic

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¹ Whipple, G. H., and Sperry, J. A., *Bull. Johns Hopkins Hosp.*, 1909, xx, 278; Whipple, G. H., and Hurwitz, S. H., *Jour. Exper. Med.*, 1911, xiii, 136.

areas are sharply outlined. The extent of the necrosis depends on unknown factors and includes from one fifth to four fifths of every lobule. Young animals, as a rule, are more susceptible, but the average amount of central necrosis is from two fifths to one half of each liver lobule. It is rare for an animal to be fatally poisoned after a single anesthesia; when this happens, almost complete destruction of the liver parenchyma has been produced.

It is obvious that with this wide individual variation in susceptibility to chloroform we must be cautious in drawing any conclusions as to the relative susceptibility of pregnant animals. A study of the examples given below indicates that, speaking conservatively, the normal and pregnant dog are equally susceptible to chloroform poisoning, whether in the latter case the anesthetic is administered during labor, shortly before it, or immediately following delivery. The pregnant animals show the same amount of liver necrosis as do normal animals, or even perhaps a somewhat greater amount. These observations apply not to the effects of acute poisoning, but only to those of the late chloroform poisoning, as indicated by the liver necrosis. Clinical observations on these animals indicate that a rough estimate of the liver necrosis can be made by careful observations concerning the icterus, vomiting, bleeding from small wounds, muscular tremors, stupor, etc. These symptoms may be very slight or severe, depending upon the amount of liver injury.

It may be of interest to take up the further observations in their order of study. After establishing the point, to our own satisfaction, that the liver of a pregnant dog was as easily injured by chloroform as that of a normal dog, we studied the fetal tissues. Much to our surprise, it was found that the fetal tissues, while still *in utero* were absolutely normal and uninfluenced by anesthesia of two hours' duration. This point having been secured by repeated tests, the placental tissues were studied with the hope of clearing up this question. It was found that normally some areas of hyaline-like degeneration or necrosis may be present in the border zone between the maternal and fetal halves of the placenta. After chloroform anesthesia, these areas of necrosis may be quite conspicuous and lead to placental separation, hemorrhage, and premature delivery. The possibility then suggested was that the placenta per-

formed some of the hepatic functions of the fetal liver and, perhaps, for this reason was susceptible to injury by chloroform.

At this point, it was thought best to test the placental and fetal tissues for chloroform. It was found that the placenta contained about one half as much of the drug as did the maternal blood, and the fetus, about one eighth as much by weight as is present in the maternal blood. This indicated about the same concentration in maternal, placental, and fetal blood, so that the absence of fetal liver injury could not be explained by lack of the drug in the circulating medium. Observations given in a following report² show that pups, for some days after birth, are insusceptible to chloroform poisoning by anesthesia, which supports the above conclusion that the fetal tissues as well are not readily subject to injury by chloroform. The reasons for this peculiar resistance of the fetal liver will be discussed later.

Opie,³ in a recent publication, has shown that chloroform liver necrosis plus bacterial infection may start a progressive inflammation of the liver resulting in more or less cirrhosis, a condition that never happens in the case of a simple chloroform necrosis, following which repair is perfect. Since the dangers of infection at time of delivery are conceded, we suggest that after more or less liver necrosis is caused by chloroform anesthesia of some duration, the possibility of a progressive liver injury is thus afforded.

These considerations cannot be rejected by pointing to numerous cases of pregnancy and operation where chloroform has been employed for one or two hours, and a favorable outcome has resulted. The great majority of dogs submitted to chloroform for two hours will recover after a few days with no apparent ill effects; and yet we have been able to show that liver necrosis affecting perhaps one half of every lobule will be produced that may be completely repaired in a few days by multiplication of the normal liver cells. No one can deny that it is a dangerous experiment to damage a liver so severely and trust that the injury may not be serious because the repair will be rapidly effected. There is no known method of estimating the susceptibility of persons or animals to this drug, so one can never tell when the limits of safety have been passed.

² Whipple, G. H., *Jour. Exper. Med.*, 1912, xv, 259.

³ Opie, E. L., *Jour. Exper. Med.*, 1910, xii, 367.

Experiments have been performed in this laboratory to ascertain whether liver necrosis following chloroform anesthesia can be prevented or lessened by bleeding and infusion at varying intervals during or after anesthesia, from which it appears that bleeding and infusion may indeed slightly lessen the resultant liver injury, but yet the variation is too small to estimate in view of individual variations in the animals. There is no evidence from these experiments that hemorrhage during delivery could have any protective influence.

EXPERIMENTAL PART.

PREGNANCY, DELIVERY (PARTIAL), UTERINE RUPTURE, CHLOROFORM, AND LIVER NECROSIS.

Dog B-17.—Large mongrel, weight 30 lbs.

November 18. Breasts very prominent; animal probably near term.

November 22. Delivery of two pups during the preceding night; one dead, the other strong.

10:30 A. M. Chloroform anesthesia for one and a half hours; 2/5 oz. given. Anesthetic well taken, and the dog came out of it two minutes after its removal. The pup nursed normally during and after the anesthesia.

4 P. M. One dead pup born. A little later an active pup born; nursing normally at 5 o'clock.

7 P. M. Dog very quiet and drowsy. Eyes appeared dull. Large amounts of water ingested, but there was no vomiting. Abdomen definitely tender.

November 23. Found dead. Rigor mortis present.

Autopsy performed at once. Abdomen, on incision, contained fluid of a turbid brownish color with a good deal of fibrin. A rupture in the left uterine horn was found with part of a fetus protruding into the abdominal cavity. Peritoneal surfaces greatly injected and coated with a granular, fibrinous exudate. Mediastinal glands greatly enlarged and moist. Heart dilated and contained firm clots. Right lung normal; left lung showed areas of atelectasis. Spleen normal. Intestines and stomach showed normal mucosa.

Liver enlarged, rather friable, and hyperemic. Lobulation conspicuous, but no indication of marked fatty degeneration.

Microscopical sections show a characteristic picture of early central hyaline necrosis involving about one half to three fifths of every liver lobule. The necrotic cells are sharply differentiated from the normal cells and show beginning pyknosis of their nuclei and eosin staining of their protoplasm. There is very little fat except just in the middle zone and very few wandering cells. The extent of the necrosis, however, is very sharply outlined, indicating the usual amount of injury following chloroform anesthesia of two hours' duration.

In the uterus there has been some softening and discoloration of the placental site at the point of rupture. The rupture measured 3 cm. in diameter. Its edges were rounded and coated with fibrin. Another fetus found *in utero* showed considerable post-mortem change, evidently due to placental separation before the death of the mother.

Microscopical sections show the usual appearances in the placental site, with complete separation of the fetal tissues. On the peritoneal surface is an acute exudate of fibrin and leucocytes. One section of the lung shows a small patch of bronchopneumonia with a few leucocytes and some fibrin, but considerable blood in the exudate.

Pup B-17-a.—November 22. Born during the preceding night; dead and cold.

Autopsy at once. In the thymus, many ecchymoses. Heart and lungs negative. Liver rather soft and blood-stained. Kidneys congested. Other organs normal.

Pup B-17-b.—November 22. Born during the night; active and strong.

November 23. Pup not well; had not been properly nursed. Died 3 p. m.

Autopsy showed marked congestion everywhere. Intestines distended with gas and curds, and spotted with purple areas. Thymus pale. Heart greatly dilated. The lungs showed a few purplish areas. The spleen presented a mottled reddish purple appearance. Liver normal in gross. Kidneys congested. Blood clots of normal toughness.

Microscopical sections of the liver show normal parenchyma. The liver was evidently actively concerned in forming red blood cells. Fat stains show only a few tiny fat droplets here and there. Spleen and kidney sections normal. The small intestine shows extensive hemorrhage into the submucosa, as well as less extensive hemorrhages into the subserous tissue.

Pup B-17-c.—November 22, 4 p. m. Born four hours after chloroform anesthesia of mother.

November 23. Pup cold and did not look well. This pup had been subjected to chloroform anesthesia for one and one half hours while in the uterus and was born shortly afterwards. The findings in this pup's liver are of particular interest when contrasted with the mother's liver. Pup died 2 p. m.

Autopsy at once. Intestines greatly distended with gas and mottled with purple patches, as in the preceding case. Blood clots quite normal. The lungs showed large purplish areas of bronchopneumonia. Spleen, pancreas, and kidneys negative. The liver showed normal lobulation and an indefinite purplish mottling.

Microscopical sections of the liver show no evidence of cell necrosis. Great numbers of blood-forming cells everywhere in the sections. Fat stains show scattered, small droplets of fat in the cell protoplasm, as is normally present in control animals. Lung sections show an extensive bronchopneumonia with considerable hemorrhage. The small intestine shows rather extensive submucous hemorrhages with some edema of the mesentery. Pancreas and kidney sections normal.

It is of particular interest to compare the findings in the maternal and pup livers. The maternal liver showed the usual susceptibility to chloroform poisoning, although the anesthetic was given during delivery. The pup that was born before anesthesia presented normal tissues in gross and under the microscope. The pup that had been subjected to chloroform anesthesia *in utero*, with birth a few hours later, died later than the mother, but the liver tissue showed

not the slightest evidence of necrosis due to the action of chloroform which must have been circulated in the fetal blood. The tissues in all respects were similar to those of the control animal born before administration of the anesthetic.

PREGNANCY, CHLOROFORM, PARTIAL UTERINE RESECTION (REPEATED). MATERNAL LIVER NECROSIS AND NORMAL FETAL LIVER.

Dog 88.—Large, fat, long haired mongrel, weight 47 lbs.

January 28. Operation for removal of fetuses (control). Ether began at 10:50 A. M.; changed to chloroform at 11:30. The left uterine horn including one fetus was removed and the end of the uterus closed by mattress sutures. Chloroform anesthesia was continued for two hours, 1 oz. being given. During the latter part of the anesthesia, muscular tremors were very striking, indicative of intoxication. The resected uterine horn containing one fetus was injected and placed in formalin.

January 29-30. Dog quiet. No bleeding and no vomiting.

January 31. Animal well. Urine contained bile pigment.

Second operation, with chloroform anesthesia, beginning at 10:35 A. M. Chloroform anesthesia continued for two hours; 1¼ oz. given. Anesthesia not well taken, and muscular tremors very conspicuous. Operative incision through the right rectus with removal of a part of the right uterine horn including two fetuses. It is found that there has been some intra-uterine hemorrhage associated with placental separation. The blood in the uterus was black and unclotted. The uterus and two fetuses were preserved in formalin. There was a good deal of bleeding during the operation and oozing from all severed vessels, indicating a low fibrinogen content in the blood. There had been a good deal of hemorrhage into the uterus, as indicated by its color.

February 1. Dog weak, but no vomiting in the morning.

2:30 P. M. Vomiting frequent, and animal obviously much poisoned. Under anesthesia, animal bled to death from the carotid artery. This blood contained only a trace of fibrinogen.

Autopsy performed at once. Heart normal except for a slight increase in pallor. Lungs normal. The subcutaneous and fat tissues everywhere showed marked jaundice. Spleen, pancreas, stomach, and intestine normal. The kidneys showed opaque medullary rays, but otherwise were negative.

Liver large, pale, and friable, with conspicuous lobulation. The centers of the lobules were depressed and of a bright pinkish color, while the edges were yellow, opaque, and swollen.

In the uterus, operation wounds had healed well and there was no exudate in these areas. The left horn contained two fetuses which were preserved in formalin. The right horn contained one fetus. The lower part of the uterus contained four fetuses, two of which were macerated and associated with a good deal of dark, fluid, unclotted blood. One fetus had a normal placenta and appeared normal in every respect. An incision was made into the thoracic cavity and the heart was found beating vigorously. This fetus also was preserved in formalin.

Control fetal tissues were removed before chloroform anesthesia. Microscopical sections of fetal liver perfectly normal, but of rather immature type. The blood-forming elements are very conspicuous. The placenta shows normal tissues everywhere. Small, indefinite areas of hyaline degeneration or necrosis involving some of the tissue at the junction of the maternal and fetal tissues. Some sections show marginal hemorrhage with a little thrombus formation, but there is no hemorrhage into the placental tissues. Glycogen is conspicuous in many of the fetal cells which were intimately associated with the maternal glandular epithelium.

Tissues removed three days after chloroform anesthesia of two hours. The fetal liver sections are quite normal in every respect and exactly similar to the control. There is no indication of any liver necrosis. The placental tissue shows evidence of considerable hemorrhage in the border zone between fetal and maternal tissues. Hemorrhage is present also in the depths of the uterine mucosa. Some parts of the fetal placenta show necrosis suggesting infarct formation. Edema was marked in some areas. The areas of hyaline necrosis in the border zone are much more conspicuous than in the control sections.

The tissues obtained at autopsy had been submitted to chloroform anesthesia of four hours' duration; the first period of two hours, four days previously, the second period of two hours, one day previously. The maternal liver sections show the usual central hyaline necrosis involving about one half of each lobule. Fatty degeneration of an extreme grade is present in addition, involving the greater part of the liver cells which are not completely necrotic. Very little normal liver tissue present. Perhaps one or two rows of liver cells about the portal spaces are relatively normal. Numbers of wandering cells are present and mitotic figures are seen, indicating a beginning hepatic regeneration. Fat stains show an extreme grade of fat deposit in the peripheral zone of every lobule. Kidney sections show numerous fat droplets in collecting tubules, more numerous than normally, but probably having no significance. Sections of the other organs are normal. Placental sections show practically the same picture described above. Some of the placental sites show a good many polymorphonuclear leucocytes in the villi of the uterine mucosa, but this picture is not unusual in animals that have not been operated upon. The fetal portion of the placenta shows some areas of hemorrhage.

Fetal tissues were examined in considerable detail and presented a uniform picture in every case. The liver was practically identical in every respect with the control liver. There is not the slightest indication of any injury or necrosis in sections taken from the various fetuses. The heart, thymus, intestine, and lung sections are all normal. One kidney section shows a few small hemorrhages into the cortex, but the other sections are normal. Fat stains show some fine droplets in the collecting tubules of the kidney.

To summarize: Dog 88, about one week before term, was poisoned by chloroform anesthesia and presented liver necrosis of the usual type and extent. Control fetal and placental tissues removed before anesthesia were normal. Fetuses removed three days after the first anesthesia were normal, as was one fetus at autopsy one day after

the second chloroform anesthesia. The fetal liver tissues showed no evidence of necrosis and injury. The placentæ showed some necrosis in the border zone between the maternal and fetal halves with more or less hemorrhage and separation. The blood of the mother showed the usual drop in fibrinogen, which is an important predisposing factor in hemorrhage.

PREGNANCY, CHLOROFORM, LIVER NECROSIS, AND FATAL UTERINE HEMORRHAGE.

Dog 31.—Large bull terrier, weight 38 lbs.

May 2. Chloroform anesthesia for two hours; 1¼ oz. given. Anesthetic poorly taken. Muscular twitchings conspicuous.

May 3. Animal appeared well. Fetal movements felt. Slight bleeding noticed from vagina.

May 4. There had been bleeding from the vagina during the night, but the animal seemed bright. There was some vomiting and no appetite. Chloroform anesthesia for one and one half hours in forenoon; ¾ oz. given. Death 3:30 P. M.

Autopsy at once. Liver large, swollen, friable, and presented the usual appearance in chloroform poisoning. Every lobule showed a red center and yellow margin. Microscopical sections suggest acute yellow atrophy. Only a few intact liver cells remain about the portal structures, and these cells contain great numbers of fat droplets. The central portions show extreme hyaline necrosis with numbers of wandering cells.

This necrosis obviously was due to the first chloroform anesthesia, as death occurred four hours after the second anesthesia, which would permit of no histological change as the result of the second anesthesia.

The uterus was very large and there has been considerable intra-uterine hemorrhage with fluid and clotted blood together with eight fetuses. The placentæ showed partial separation from the uterine wall. Microscopical sections show a certain amount of necrosis in the border zone between maternal and fetal tissues in the placenta. Fetuses normal. Sections from the different organs are normal. Liver sections were studied with particular care and show no signs of necrosis nor of cell injury. Blood formation going on actively in the liver sinuses.

PREGNANCY, CHLOROFORM, LIVER NECROSIS WITH HEMORRHAGE, AND NORMAL FETAL TISSUES.

Dog B-15.—Large white bull dog, weight 38 lbs. Breasts quite prominent, and dog undoubtedly close to term.

January 8. Chloroform anesthesia for two hours; 1½ oz. given. Muscular tremors well marked during anesthesia, and recovery rapid after anesthesia.

January 9. Dog seemed pretty well.

January 10, 10 A. M. Operation under ether anesthesia with complete removal of uterus in the usual way. There was very free bleeding during the entire operation with continuous oozing from every cut tissue. At the close of the operation, the abdomen contained about 30 c.c. of fluid blood in which nothing

but the most delicate filmy clots could be found on mopping out with gauze. It was evident that the animal would bleed to death because the clots were not sufficient to close the severed vessels, and the animal was bled to death at the end of the operation. Blood (200 c.c.) collected in a large cylinder was allowed to clot, but the clots were so delicate that the blood could readily be poured into another receptacle. A few filmy, flabby clots formed on the sides of the cylinder, and after settling amounted to 15 c.c. by volume. They could be easily broken up by passing a glass rod through the coagulum. The fibrinogen, as determined by heat coagulation, was scarcely more than a trace. The other elements of blood coagulation were normal.

Autopsy performed at once. The heart contained fluid blood. Lungs normal except for a few tiny purplish areas not over 5 mm. in diameter. Spleen, pancreas, stomach, and intestines perfectly normal.

Liver.—The liver was large, friable, and fatty, and presented the typical picture of chloroform necrosis. The lobules showed conspicuous red centers and swollen, opaque, yellow margins. The kidneys presented the normal architecture, but the cortex was rather more opaque than normally, and a little swollen.

Uterus.—The uterus, after operative removal, put at once into formalin, and at this time violent movements were noted, indicating viability of the majority of the fetuses. After four hours' fixation, two of the fetuses were cut out of the uterus and fixed more carefully for histological study, part of the tissues being placed in Zenker's fluid, and part in fresh formalin. The fetuses were obviously well developed and very near term. After twenty-four hours, the uterus was dissected, and eight well developed fetuses were found. Particular care was taken to preserve the placenta without disturbing their attachment to the uterine wall. Some of them showed small hemorrhages with extravasation at the edges of the placental sites, but there was no complete separation of any placenta from the uterine wall.

Microscopical sections (maternal tissues) show the usual type of central hyaline necrosis involving about one half of each liver lobule. The remaining liver tissue shows an advanced grade of fatty degeneration, only a few normal liver cells remaining about the portal spaces. Wandering cells are numerous, especially polymorphonuclear leucocytes. Fat stains show great numbers of fat droplets in the marginal and central zones of every lobule. Other tissues normal. The fetal tissues present no evidence of cell necrosis. Liver sections show a pretty mature parenchyma with, however, quite a good many blood-forming elements present. The liver cells show a pale protoplasm, but fat stains show only small, uniformly distributed fat droplets present in normal controls. The placental sections show rather extensive hemorrhages into the marginal zone between the maternal and the fetal tissues. In places, laminated thrombus masses had been formed in such areas. There are extensive areas of hyaline necrosis in the boundary zone, perhaps accounting for a part of the placental separation. A part of the fetal placenta shows beginning infarct formation with numbers of polymorphonuclear leucocytes particularly in the margins of such areas.

This dog (B-15) was possibly more susceptible than normally to chloroform poisoning. Anesthesia of two hours' duration caused extreme and probably fatal liver injury with almost complete disappearance of the blood fibrinogen and uncontrollable hemorrhage at operation. Such dogs often die from spontaneous gastric, intestinal, or peritoneal hemorrhage. The fetal tissues nevertheless were quite normal. The placental tissues showed some necrosis and hemorrhage with beginning placental separation.

PREGNANCY, CHLOROFORM, UTERINE RESECTION, AND LIVER NECROSIS.

Dog 89.—Old black and tan, weight 20 lbs.

February 17. Chloroform anesthesia for two hours, beginning at 11:20 A. M.; $\frac{3}{8}$ oz. given.

February 18. Dog quiet but seemed normal.

February 19. 11 A. M. Operation (ether anesthesia) with total resection of uterus. Liver seen at operation was large and tense with conspicuous markings. The lobules had a bright red center and a conspicuous yellow margin, the characteristic picture of chloroform poisoning at this stage. There was a good deal of bleeding everywhere from the severed vessels, with oozing from the edges of the wound. Clots were inconspicuous and flabby.

February 23–March 1. Animal made an uneventful recovery.

The uterus was placed in formalin, the ends being secured by clamps to prevent escape of the fetuses. The specimen was dissected after twenty-four hours, and it was found that the right horn contained three partly macerated fetuses associated with soft placenta, in which there had been a certain amount of hemorrhage, but only slight hemorrhage beyond the sites of the placenta. The left horn showed one partially macerated fetus with considerable hemorrhage into the placenta. There are two normal, well preserved fetuses with normal placenta in this horn.

No tissue was removed from the maternal liver at the time of operation, but the gross appearance made it certain that the usual hyaline central necrosis was present. This is supported too by the evidence of lowered fibrinogen in the blood. On microscopical section, the uterus shows the usual picture, described previously. The areas of hyaline necrosis in the boundary zone between the fetal and maternal tissues are quite conspicuous, apparently more so than normally, and there are hemorrhages into this same tissue. There are some areas of hyaline necrosis in the placental portion involving numbers of villi here and there, associated with a good many polymorphonuclear leucocytes. Sections through some of the placental sites show nothing unusual. Polymorphonuclear leucocytes are quite numerous in the large villi of the uterine mucosa. Liver tissue removed from different fetuses is normal. Liver sections show rather immature parenchyma with great numbers of blood-forming cells. The liver cells everywhere are normal and show no indication of necrosis. Fat stains show a few scattered fat droplets of small size. Sections of lungs and kidneys normal.

PREGNANCY, CHLOROFORM, AND LIVER NECROSIS. CHLOROFORM DEMONSTRATED IN FETUS AND PLACENTA.

Dog 106.—Small black and tan dog, weight 17½ lbs.

May 12. Chloroform anesthesia for two hours; ¾ oz. given. Operation done through the right rectus with amputation of the left uterine horn. This portion of the uterus contained three pups. The largest one (weight 170 grams) was used to test for the presence of chloroform. Chloroform was demonstrated to be present (Ragsky process).

The two smaller fetuses were examined for chloroform and shown to contain a definite amount of this drug (0.005 per cent.) in 194 grams of fetal tissue. Placental tissue from these same fetuses was examined and found to contain 0.020 per cent. of chloroform in 40 grams of tissue. These determinations were done after the Ragsky method.⁴ The method consists in a distillation of macerated tissue and decomposition of the distillate in a heated glass tube with a collection of the hydrochloric acid in a standard solution of silver nitrate. The circulating blood in an animal under chloroform anesthesia contains 0.03 per cent. to 0.05 per cent. of chloroform.⁵ It will be seen that the placental tissue which is very rich in blood contains about half the normal amount present in the circulating blood, and the fetal tissues about an eighth of the amount normally present in the maternal blood. This would indicate that the fetal blood contained relatively the same amount of chloroform as the maternal blood. The absence of liver necrosis in the fetal liver then must be explained not by absence of chloroform in the blood but by some insusceptibility of the liver parenchyma to this poison which acts so specifically upon the adult liver. It will be seen later that the liver of pups shortly after birth is likewise insusceptible to the toxic action of chloroform in the blood present in sufficient amount to bring about anesthesia.

May 13. Some vomiting. One pup (No. 106-A), born during night and given to dog 107 to nurse.

May 14. Dog found dead in cage.

Autopsy showed no peritonitis and no hemorrhages in the peritoneal cavity. Thorax negative. Heart contained small flabby clots. Lungs presented a few small, purplish patches. Spleen, pancreas, stomach, and intestines negative. The liver showed the characteristic picture of chloroform poisoning with central necrosis. The uterus showed a clean operation wound. One fetus was jammed transversely in the pelvis. The other two fetuses appeared relatively normal. They were preserved in formalin.

Microscopical sections show an extreme grade of central hyaline liver necrosis in the maternal organ. This central necrosis involves about four fifths of every liver lobule, and only one or two rows of relatively normal liver cells remain about the portal structures. Fat droplets are conspicuous in these intact liver cells. It is probable that this liver necrosis was largely responsible for the death of the mother, although the incomplete delivery with transverse presentation may have been a factor. The kidneys show a good many small fat droplets

⁴ Peterson and Haines, *Text-Book of Legal Medicine and Toxicology*, Philadelphia, 1904, ii.

⁵ Meyer and Gottlieb, *Die experimentelle Pharmakologie*, Berlin, 1911.

in the tubular epithelium, particularly the collecting tubules, and rarely the convoluted tubules. No evidence of cell necrosis.

Placental tissues show the usual picture. There are areas of infarction in the fetal portion of the placenta with complete necrosis of many of the villi, but some of the villi are quite normal. There is the usual zone of necrotic tissue between the maternal and fetal parts of the placenta, with more or less hemorrhage in this zone. There are no hemorrhages into the fetal portion of the placenta.

Sections of fetal tissue show normal parenchyma in the lungs, kidneys, pancreas, and duodenum. Liver sections show absolutely no liver necrosis. Fat stains show a good many fat droplets in the liver parenchyma, perhaps slightly more numerous than normally, but scattered diffusely throughout the parenchyma, perhaps more conspicuous about the portal spaces than in the centers of the lobules.

SUMMARY.

Pregnant dogs are susceptible to chloroform administered shortly before delivery or during labor, and show the same degree of liver injury as normal dogs, or even a somewhat greater one.

Chloroform anesthesia may cause more or less hyaline necrosis in the border zone between the maternal and fetal parts of the placenta that may lead to hemorrhage, placental separation, and premature delivery.

Chloroform anesthesia causes no injury to the liver of the fetus nor to any other fetal organ, in spite of the fact that it can be demonstrated to be present in these tissues.

These experiments raise objections to the use of chloroform in pregnant women where an anesthetic must be continued for half an hour or longer. Chloroform anesthesia may be admissible for the few minutes at the end of the delivery, but when operative measures are necessary, before or after delivery, it is a dangerous anesthetic and surely capable of producing injury to the liver in the manner recognized in the case of normal persons.

Objections may be raised to the application of conclusions derived from experiments on dogs to human cases; but the similarity of the effects of chloroform in man and dog surely affords a sound basis of comparison.

Two fundamental facts would seem to be now established: (1) Normal human adults may be fatally poisoned (late chloroform poisoning) by chloroform anesthesia of one half to one hour's

duration. (2) Normal and pregnant dogs are equally susceptible to late chloroform poisoning, and may be fatally poisoned by an anesthesia of two hours' duration.

Hence one may conclude that probably normal and pregnant human beings are equally susceptible to chloroform poisoning, that chloroform anesthesia during any part of the pregnant period is capable of causing liver necrosis, and, consequently, that chloroform is a dangerous anesthetic.