THE PATHOGENESIS OF THE HEMORRHAGIC DISEASES OF THE NEW-BORN.*

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PLATES 46 AND 47.

INTRODUCTION.

Because of insufficient knowledge of the causes that underlie the hemorrhagic diseases, it has been impossible to classify them with satisfactory precision. Our present classifications are, for the most part, based upon clinical or morbid anatomical differences, although occasionally other well recognized characteristics are concerned, such as heredity and epidemicity; therefore, a confused state of the literature prevails. This confusion is particularly marked in connection with those diseases of the new-born that are characterized by a hemorrhagic tendency, icterus, and fatty infiltration of the viscera. This latter group has been from time to time split up into various subdivisions, and although these are based almost entirely upon symptomatic and morbid anatomical features, there is still a tendency on the part of clinicians to preserve their distinctive names as if these different conditions were worthy of being regarded as distinct diseases; thus, Buhl's disease, Winckel's disease, melena neonatorum, icterus gravis neonatorum, etc.

The present study was undertaken to learn whether, by the experimental use of a single agent, the clinical and pathological picture of more than one of these diseases could be produced; in other words, whether the differences between such conditions as Buhl's disease, Winckel's disease, etc., are sufficient to warrant the belief that they are separate entities, or whether all may not represent

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merely different expressions of the same general process. Chloroform was the experimental agent used because of the close resemblance noted at autopsy between a case of late chloroform poisoning in the adult and a typical case of Buhl's disease in an infant, the diagnosis of each having been made by Dr. E. R. LeCount.

When pregnant animals were chloroformed, their offspring showed changes characteristic of the pathological and clinical pictures of the various hemorrhagic diseases of the new-born; thus the experiments seem to show that the differences between the various members of this group are not such as to indicate fundamentally separate etiologies. On the contrary, there is evidence strongly suggestive that primarily all are manifestations of an insufficient supply of available oxygen in the tissues with the train of consequences that this implies. The same ultimate result can be accomplished in a variety of ways and by a variety of chemical substances, of which chloroform represents one.

HISTORICAL.

Before recording our own experiments in detail, it may be well briefly to review the extensive literature on this subject, in order (1) to emphasize the characteristic features of the various syndromes under discussion, and (2) to record the dominant ideas which have been expressed to explain their etiology.

(a) Description of Syndromes.—The association of congenital syphilis and navel sepsis of the new-born, with a pathological picture of which hemorrhages, fatty changes, and icterus are prominent features, has long been recognized. But in 1861 von Hecker and Buhl (1) described a series of cases under the title of "Acute Fettdegeneration der Neugeborenen," that presented a somewhat similar picture without evidence of either syphilis or navel sepsis. Since that time this condition has been commonly called Buhl's disease. In the original article, it is noted that most of the children suffering from this disease have been born in asphyxia. They show bloody diarrhea or vomitus, become icteric after three to six days, and usually on the fifth day there begins an active, irrepressible hemorrhage from the cord. There are also extravasations in the conjunctive, the various mucous membranes, and purpuric lesions in the skin, with or without anasarca. Many die in a cyanotic condition within an hour after birth; most do not live beyond the early part of the second week, and the longer they live the more anemic and icteric they become. At autopsy in all the viscera the principal lesions are multiple hemorrhages, as large as pin-heads, or larger, together with fatty changes that may be extensive.

Von Hecker and Buhl do not attempt to explain the etiology, but they think that the condition is not due to navel inflammation, and that it is not hemophilia,
because the ratio of males to females is not maintained as in hemophilia. In commenting upon the condition, they say: "It is hardly necessary to state that one here has to do with a disturbance of metabolism manifested over the whole body, in which the changes in single organs are only a partial expression of the whole disease. This disturbance is evidently inborn, acquired in the last days before birth."

It is noteworthy, however, that as early as 1813 John Cheyne (2) called attention to what seems to have been an identical condition; and in this country, in 1852, Francis Minot (3), in an analysis of forty-six cases of hemorrhages in the new-born, associated with jaundice, recorded numerous instances of the condition later described by von Hecker and Buhl.

In 1879, Winckel (4) attempted to establish an entity distinct from the so-called Buhl's disease by describing a series of cases that manifested slightly different clinical and pathological findings. In his disease, also, the onset occurred in the first few days after birth. The principal features were cyanosis, icterus of varying intensity, hemorrhages, hemoglobinuria, and visceral fatty changes. Edema was frequently present but was not emphasized as a prominent characteristic. In some of his cases he found "hemoglobin infarcts" in the papillae of the kidney; and the stomach was usually dilated and showed many ecchymoses. In certain cases, also, the mesenteric glands and Peyer's patches were swollen. He considered this condition distinct from Buhl's disease, chiefly because it seemed to be epidemic in character, and because the hemorrhages were more, and the fatty changes less prominent than in the disorder described by Buhl. As in Buhl's disease, also, the umbilical vessels showed no suppuration. Winckel recognized the similarity of this condition to that of intoxication by phosphorus, arsenic, and potassium chlorate; and he ruled out, by careful histories and by chemical examination of the viscera, any possible participation of these drugs in the etiology of his cases. He suggested as a name for the condition, cyanosis afebrilis icterica perniciosa cum hemoglobinuria.

In more recent times, the Germans, in particular, have come to regard as Buhl's disease any condition affecting the new-born that manifests a severe icterus and fatty infiltration without evidence of infection, whereas any similar condition, of which the chief features are icterus and hemoglobinuria without omphalitis, has been looked upon as Winckel's disease.

Probably others antedated Winckel in describing the condition that bears his name. Thus Parrot (5), in 1873, described a series of similar cases under the title of "tubulhématie rénale"; Laroyenne and Charrin (6), in the following year, reported additional cases; and in 1875, Bigelow (7) recorded ten fatal cases in new-born infants, all of whom showed hematuria.

These two classifications, however, have failed to suffice for all the hemorrhagic-icteric conditions of the new-born infant. Various other names have sprung into rather general use, and have served to complicate the nomenclature by adding terms based solely on clinical and morbid anatomical differences. Thus one often finds these conditions discussed in text-books under some such classification as icterus gravis neonatorum, Buhl's disease, Winckel's disease, melena neonatorum, etc. Indeed, in recent years, there has even been a tendency
to set apart by themselves those cases that are associated with hemorrhage into
the adrenal glands.¹

As already implied, the boundary lines between these various conditions are
indistinct. It is difficult to discern any differences between the conditions of
icterus gravis neonatorum and Buhl's disease, as these terms are used by vari-
ous authors. Melâna neonatorum is a term that has been applied to conditions
in which hemorrhage has occurred from the gastro-intestinal tract, without
necessarily any clinical evidence of hemorrhage elsewhere. Since 1829, when
Cruveilhier (8) found ulcers in the stomach of an infant who had presented
evidence of a true melâna, many others have recorded their presence in this
condition with the result, that a gastric or intestinal ulcer is usually considered
to be the source of the hemorrhage in these conditions. For a more complete
discussion of the occurrence of these ulcers, reference may be made to the
articles of Vassmer (9) and of Helmholz (10).

Another group of these conditions, which probably has correctly been con-
sidered as distinct from the others, concerns those cases of true (hereditary)
hemophilia neonatorum. But this term has been improperly used by many
clinical writers with the result that the great majority of those cases described
as hemophilia neonatorum have in reality been other conditions. In fact, in
Grandidier's (11) series of 220 cases, only twelve were found in the families of
"bleeders," and the females were affected about as often as the males. Recently,
Larrabee (12) has reported, with the family history, a case of apparently true
hemophilia of the new-born.

The generally unsatisfactory classification of these conditions has doubtless
been due to the obscurity of their fundamental cause. For, up to the present,
no one idea that has been advanced seems sufficient to explain all the cases of
any one of these various groups.

(b) Various Ideas of Etiology.—The causes that have been chiefly con-
sidered are as follows: (1) syphilis, (2) bacterial infections, (3) mechanical
factors, (4) heredity, (5) intoxications by known chemical agents.

1. Syphilis.—As has been already stated, congenital syphilis has repeatedly
been found associated with conditions of the new-born, characterized by hemor-
rhages, cyanosis, edema, icterus, etc.² But in many cases, evidence of syphilis,
and even of sclerosis of the vessels, is absent. Indeed, cases presenting the
typical features of Buhl's disease have been described by Fürstenburg (14) and
Roloff (15) as occurring spontaneously even in the offspring of domestic animals,
where presumably the presence of syphilis may be safely excluded.

2. Bacterial Infections.—The rôle of bacteria has received the greatest con-
sideration for several reasons: (1) the close similarity between these condi-
tions and the picture produced by navel sepsis; (2) the recognized epidemicity
of at least one of these groups (Winckel's disease); (3) the finding of micro-

¹For a discussion of this subject see C. Riviere, Tr. Path. Soc., London,
Hektoen, Tr. Chicago Path. Soc., 1910, viii, 87; Simmonds, Virchows Arch.

²For a discussion of this subject together with a report of six cases, see
organisms at autopsy; (4) the experimental production in animals of certain of these conditions by inoculation with bacteria; (5) the autopsy findings, in many instances, of lesions suggesting infection. At the present time there is practically unanimous consent to regard infection, either evident or obscure, as the cause of all of these hemorrhagic diseases except in certain special instances, as in true hemophilia, etc. (Knöpfelmacher (16), Heubner (17), Runge (13), Bendix (18), Hutinel and Merklen (19), Holt (20), Cautley (21)).

But the conception, which has been occasionally expressed, that certain ones are specific infectious diseases, is not now generally held; and the suggestion, made by Lubarsch (22), to regard the Gärtner bacillus as the specific cause of Winckel's disease has found no general support. On the contrary, the belief is now almost universally held that many different bacteria may produce these diseases, because of the variety of microorganisms that has been found at autopsy. Such an opinion is expressed in the articles by Finkelstein (23), Knöpfelmacher (16), Thomson (24), Hamill and Nicholson (25), and others. Klebs (26) found a micrococcus in the urine of an infant that died of hemorrhage; and by inoculating rabbits with the organism, he produced experimental hemorrhages. Later, Weigert (27), Eppinger (28), and others reported practically the same finding in other cases. Streptococci have been found by Baginski (29), Babes (30), and Bar (31); Bacillus pyocyaneus and staphylococci of various kinds, by Neumann (32), Bar (31), and Finkelstein (23); pneumococcus, by Babes (30); Friedländer's pneumobacillus, by von Dungern (33); a short unidentified bacillus, by Gärtner (34); the colon bacillus and several types of cocci, by Hamill and Nicholson (25); the colon bacillus, by Wolżynski (35) and by Kamen (36); a streptococcus and a bacillus, by Strötz (37); staphylococci and streptococci, by Tavel and de Quervain (38); staphylococci, by Röthler (39), etc.

The inoculation of animals by many of these organisms has frequently been followed by the production of diseases similar to those in human beings. The epidemicity so strongly emphasized by Winckel in describing his original cases has been noted also by later writers. For example, Ljwow (40) has reported an epidemic of seven cases. But there have been reported also many sporadic cases of Winckel's disease.

Comment has already been made on the finding at autopsy, in certain cases, of lesions indicative of an infectious process, as, for example, the hyperplasia of intestinal lymphatic tissue, etc. But such findings are frequently absent. Indeed, it is striking that in many cases there seems to be very insufficient evidence that infection has played an important rôle. Runge (13), after a careful review of the literature, states, with reference to Winckel's disease, that "the search for bacteria in the tissues has usually been negative," even in the tissues of the intestines. Councilman in one of Townsend's (41) cases found the blood to be sterile.

It is interesting that Thomson (42), evidently impressed by the general belief that all these hemorrhagic-icteric diseases are infectious, divides those cases of icterus of the new-born other than the simple icterus neonatorum, into infective jaundice of umbilical origin, and infective jaundice of intestinal origin. Then, however, in discussing the second group, and in view of the usual absence
of fever and from the normal size of the spleen in most cases, he is forced to
the conclusion that "the general infection shows itself by drowsiness, slight
fever, and emaciation," all of which symptoms might occur in any intoxication,
whether of bacterial nature or otherwise. We may conclude, therefore, that
although there is very strong evidence favoring the idea that many cases of these
conditions were caused by infections, there is, on the contrary, very insufficient
evidence for assuming that all were infectious.

3. Mechanical Factors.—Mechanical factors as the causes of any of these
conditions have not been generally considered important. Mention should be
made, however, of the idea of Pomorski (43) and von Preuschen (44), who
considered cerebral hemorrhage, caused by trauma during birth, as a factor of
prime importance in causing later hemorrhages elsewhere. To a certain extent
these authors substantiated their idea experimentally by obtaining multiple
hemorrhages in rabbits after first producing cerebral hemorrhages through
trauma. They considered the condition to be due to vasomotor interference
brought about by hemorrhage into the brain. In human beings, however, in
many cases there has been no evidence, either of cerebral hemorrhage, or of
excessive trauma to the head. Moreover, it is unnecessary to remark that
trauma, capable of producing hemorrhage into the brain, carries with it altera-
tions in the nervous system capable of producing a series of profound metabolic
disturbances, alteration of respiration, etc. The idea of Landau (45), who
considers traumatic thrombosis and subsequent embolism, particularly in the
alimentary tract, important causative factors, should also be mentioned in this
group. But, as Thomson states, such factors have been found only occasionally.

4. Heredity.—The possible importance of hereditary influences was con-
sidered by von Hecker and Buhl when they stated that their disease was evidently
inborn and acquired during the last few days of pregnancy. The relation of
heredity to the true hemophilia neonatorum needs no comment.

Occasionally other hemorrhagic syndromes have been described as having
been transmitted from the mother to the fetus. For example, Diehl (46) has
reported a case in which at autopsy both mother and fetus showed marked pur-
puric lesions.

There are also certain other affections of the adult, at present of unknown
etiology, which, if transmitted to the fetus, might cause these various syndromes
in the new-born. Reference is made particularly to the closely related condi-
tions of acute yellow atrophy, of eclampsia, and of certain septicemic infec-
tions. Numerous observations are on record describing the pathological changes
in the offspring of eclamptic mothers. It is particularly interesting that in
general they correspond closely with the icteric and hemorrhagic syndromes of
the new-born already described. Esch (47) summarizes them as thrombosis
and parenchymatous degeneration, fatty degeneration or necrosis, especially,
in the liver and kidneys, hemorrhages in the organs, and subpleural, subepicardial,
and subendocardial extravasations of blood. He also makes the important
observation that of 234 children born of eclamptic mothers, 22.7 per cent. died.
Welch (48) records similar findings in the fetuses of three eclamptic women.

5. Intoxication by Known Chemical Agents.—Closely related to the question
of hereditary influences is that of intoxication by known chemical agents. As
noted above, Winckel recognized the close similarity between his disease and intoxication by phosphorus, arsenic, and potassium chlorate. The possibility of the transmission of phosphorus poisoning from the mother to the fetus is well known. Friedländer (49) has reported a typical case; and it has been produced experimentally by Miura (50) in the fetus of a pregnant animal.

A COMMON PROCESS PROBABLY UNDERLIES ALL.

From all this, it becomes clear that the same general symptoms or symptom groups may result from the action of a considerable variety of agencies, and it would seem equally clear, in view of the virtual identity of their final results, that all these agents, directly or indirectly, interfere ultimately with the same fundamental physiological processes. The questions that now present themselves are as follows: What are the simple physiological functions, interference with which will induce the various pictures, and by what general means are they really accomplished?

If instead of dwelling on the differences between these various conditions, we give our attention to their points of similarity, the following facts stand out conspicuously: (1) Cyanosis, edema, icterus, more or less pronounced fatty changes in the viscera, a hemorrhagic tendency, and gastro-intestinal symptoms are constant in all. (2) The onset in all is usually within the first week after birth.

That there are many features of these conditions that suggest a common general process has already been emphasized by Runge (13), Knöpfelmacher (16), Baginsky (51), Brandenberg (52), and others. The symptoms and gross pathological findings are at once suggestive of those that follow the administration of phosphorus, chloroform, arsenic, hydrazin, and a long line of chemical agents, but occur also in the conditions of obscure etiology known clinically as acute yellow atrophy of the liver, eclampsia, and cyclic vomiting of children. Furthermore, they occur in the severest forms of diabetes, both experimental and idiopathic; and, finally, in connection with certain severe infections. Winckel himself remarks on the resemblance between phosphorus effects and the changes in the organs found in the disease that bears his name.
SIMILARITY TO THE CONDITION INDUCED BY LACK OF OXYGEN.

All the cardinal features that characterize this latter group, including certain common metabolic phenomena, such as appearance of lactic acid and sugar in the urine, not to mention others, are known to occur also after respiration of rarified air, or after asphyxia from any cause, that is to say, from lack of oxygen. The similarity has been clearly portrayed by Araki (53) and Lewinstein (54), also by Bauer (55), the former seeing in all such chemicals as phosphorus, etc., the power to cause directly or indirectly an actual deficiency of available oxygen. Edema, a common manifestation in this group, has been brought into relationship with deficient oxygen supply and the incidental formation of acid by Jacques Loeb (85), and more recently the importance of the action of acid on the tissue colloids has been emphasized by the work of M. H. Fischer (56). Although Lusk (57) has effectively set at rest the idea that phosphorus poisoning and the like are marked by any general deficiency of oxidation in the sense in which this expression is employed by numerous medical writers, we may, nevertheless, speak in these instances of local or selective impairments of oxidation. In connection with fatty changes, for example, interference with the sugar oxidation, however caused, appears to be highly important. Until our knowledge of the mechanism of the action of these agents is more complete, they may be classified most conveniently as agents, the effects of which resemble those caused by the lack of oxygen. Such agents fall into three groups: (1) known chemical substances (phosphorus, chloroform, arsenic, etc.); (2) certain products of microorganisms (streptococcus, Spirocheta pallida, plasmodium malariae, etc.); (3) poisons of obscure origin and composition (as in eclampsia, acute yellow atrophy, etc.).

SIMILARITIES TO "LATE CHLOROFORM POISONING" IN ADULTS.

Chloroform is one of the drugs in the category just mentioned that produces a morphological picture suggesting that of deficient oxygen. Moreover, chloroform is administered almost as a rou-

*Wells (58) also states that in chloroform poisoning "probably it is the oxidizing enzymes that are particularly involved." Vernon (59) has recently found that chloroform depresses respiratory powers in a perfused kidney.
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The idea of chloroform administration to women in labor, the idea having become prevalent that it may be administered practically with impunity (Jardine (60), Wright (61), Williams (62)). The fact that the onset of the various conditions under discussion is usually on the fourth or fifth day after birth is in harmony with the clinical and experimental experience concerning the condition of so-called "late chloroform poisoning" in the adult, which has been described by Bandler (63), Bevan and Favill (64), Wells (65), Whipple and Sperry (66), and others. Therefore, it would seem a priori that there was some evidence to suggest the existence of a causal relationship between chloroform used at labor and the occurrence of some of these various conditions in the new-born. In order to investigate further this possibility, experiments were devised with the object of answering the following questions: (1) Will chloroform when given in an amount small enough to be comparable with that ordinarily used at labor, produce any anatomical lesions in the young? (2) When given at or near the time of labor, can conditions be produced resembling clinically any or all of the affections of the new-born under discussion?

**EXPERIMENTAL PRODUCTION BY CHLOROFORM OF EACH OF THE SYNDROMES.**

The experimental results may be summarized briefly as follows:

1. When chloroform was administered to pregnant animals near term in two or three overwhelming doses, at intervals of only a day or two, it was followed by intra-uterine death of the fetuses with pathological pictures characterized chiefly by visceral fatty changes and slight icterus. In most of the experiments, also, the mother died showing a similar picture.

2. When given in an amount small enough to produce anesthesia for only ten to fifteen minutes in the pregnant animal, which is comparable with the amount frequently given to women in labor, it was followed by intra-uterine death of the young and abortion with very definite fatty changes in the livers of the offspring.

3. With a very light anesthesia for a few minutes, the young have been born apparently in good health, have remained so for a
few days, but have generally succumbed during the first week with pictures sometimes resembling Buhl's, sometimes Winckel's disease, and at other times, some of the previously mentioned conditions.

(a) The Results May Be Those of Direct Asphyxia.—From these experiments, the conclusions have been reached that chloroform, when administered in the manner and at the time mentioned, is capable of inducing conditions in the offspring entirely comparable to those conditions in human beings known as Buhl's disease, Winckel's disease, etc. It should be borne in mind, however, that the giving of the drug in these experiments always preceded the spontaneous onset of labor. Should any inferences be made as to the dangers attending the use of chloroform during labor or the likelihood of thereby inducing a hemorrhagic disease in the offspring, they should be limited, as far as these experiments are concerned, to those cases in which the conditions of administration are the same, i.e., to cases of induced labor, or other procedures carried out under chloroform some hours or days prior to the onset of labor. Whipple and Sperry (66), and Whipple and Hurwitz (67), working on the action of chloroform given to pregnant dogs, found at times that necrosis and a separation of the placenta occurred, but that the young never showed marked visceral changes of any sort. They were unable, furthermore, to produce the picture of chloroform poisoning in newly born pups by administering to them a large amount of chloroform during the first few days after birth. In view of this work and of the fact that the organs of the offspring in our cases fail, in their lack of certain morphologic features (central necrosis in the liver lobule, etc.), to agree entirely with what has been regarded by Whipple and Sperry (66), and later by Opie (68), as essential for typical chloroform poisoning, some reserve should be exercised in interpreting the changes we have noted as due to a direct action of chloroform on the fetal organs.

In this connection, however, it may be stated that Wells (65), after reviewing the literature, found numerous cases of chloroform poisoning in children in which presumably there was no liver necrosis, although excessive fat infiltration had occurred.

*A preliminary report of our experiments was published in 1910 under the title of “Chloroform Poisoning in the New-Born” (69).*
It is not essential to discuss here how the chloroform has acted, whether directly on the cells of the young, or indirectly by causing injury to the placenta, or otherwise. The final result has been a picture like that caused by deficient oxygen. Possibly, owing to differences in the composition or circulation of the fetal liver, the typical distribution of lesions, as seen in adult chloroform poisoning with its central lobular liver necrosis, may be impossible to obtain; and the picture seen by us may be due to a more generalized, but nevertheless direct action of chloroform on the organs. For this view we have no preference or direct evidence, although parallels come easily to mind (congenital syphilitic pneumonia alba, the absence of characteristic gingivitis in infantile scurvy, etc.).

More interesting is the question as to why Whipple and Hurwitz (67) were unable to cause changes of any sort in the offspring from dogs poisoned with chloroform. Most of our experiments have been carried out with guinea pigs, rabbits, and cats, only two dogs having been used. The question as to the composition of the chloroform used might be considered, since Müller (70) has found that phosgene is capable of causing fatty visceral changes. But in our work a high grade of chloroform was used (Squibb’s anesthetic chloroform, protected in brown bottles). Another important consideration is the state of nutrition of the animals, since, as is well known, this may account for marked variations in the susceptibility to a great variety of poisons, including those of the group with which we are concerned. The “detoxicating influence” of liver glycogen has long been known.

Our results harmonize better with those of Raysky (71), who has recently found that chloroform, when given to pregnant rabbits, may produce parenchymatous and fatty changes in the fetuses, but to a much less degree than in the mothers. He makes no mention of the presence of definite areas of necrosis in the liver lobules of the young. Here, again, the fetal lesions may be those of asphyxia produced by the slipping of the placenta, etc. Pertinent to the discussion also is the work of Nicloux (72) who, in experiments on pregnant guinea pigs, has found that the quantity of chloroform fixed by the fetal liver is proportionately greater than that fixed by the maternal liver.
(b) Details of Experiments.—The chloroform experiments have been carried out with guinea pigs, rabbits, cats, and dogs. In all, 80 animals have been studied, of which number 18 were the mothers, and the remaining 62 constituted the young of the various litters. In all but three of the experiments the whole litters were affected. Once a pregnant guinea pig after being anesthetized for thirty minutes gave birth, two days later, to a litter of four, of which two remained healthy and lived to be adults, and two died during the first three days, showing rather high grade visceral fatty changes, but no hemorrhage or icterus. In another experiment, the administration of chloroform to a guinea pig for fifteen minutes was not followed by sufficient changes in the young (a litter of three) to result in the death of any one of them. Finally, a cat that was anesthetized for twenty-five minutes, gave birth two days later to a single kitten, apparently not premature, which lived for only twenty-four hours, but which showed no pronounced visceral changes of any sort at autopsy. The experiments were controlled by the examination of the tissues of at least two newly born normal animals from each species. Of the animals used as controls, the dogs and guinea pigs were obtained from the same source as those used in the experiments, but the control rabbits and cats were obtained from a source different from that of the experimental animals.

It is worthy of mention that a pregnant street dog brought to the laboratory three days before labor showed a high grade icterus and other evidence of a severe intoxication of some sort, such as drowsiness, lack of appetite, and scanty urine. Three pups that lived for only a few minutes after birth, although apparently at full term, showed pronounced jaundice, very extensive visceral fatty changes, and a few ecchymoses on the various membranes. The mother dog, after being killed, showed practically the same changes. Cultures from the blood were sterile. These findings warn against undue certainty that in experimental animals the chloroform is the only cause of the lesions produced. The chloroform has always been given by inhalation.

Cultures on blood agar have been made in practically every instance, but, with three exceptions, they have remained sterile. The positive cultures were obtained in two young guinea pigs and a kitten. All three showed a general invasion by an organism, that was morphologically, culturally, and in staining characteristics, identical with the ordinary colon bacillus. Also, when tested on young animals of the same species and approximately of the same age, all three strains were non-pathogenic, except when injected intraperitoneally in overwhelming doses of 2 c.c. of dense twenty-four hour bouillon cultures. Following the injection of these cultures, death occurred only after the lapse of two to three days, and post-mortem examination failed to reveal the same lesions as those seen in the animals from which the growths were obtained. Both pigs that gave positive cultures showed extensive fatty changes in the liver and other viscera, with a few ecchymoses, but no icterus and no large hemorrhages. One of the pigs died on the third, and the other on the sixth day after birth. The kitten that gave the growth died on the third day, and at autopsy showed moderate icterus and fatty changes in the viscera, but no hemorrhages. Control cultures were made from fifteen animals by Dr. D. J. Davis to serve as a check upon a duplicate set of cultures made by myself. In each set, all the cultures were sterile.
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For microscopical examination, pieces of tissue from the different organs were fixed in Zenker's fluid and in 10 per cent. formalin. Both paraffin and frozen sections were made, the former of which were stained with hematoxylin and eosin, the latter with fat stains, such as Sudan III and osmic acid. Several pieces were also examined for fat by the Marchi method. For the sake of brevity, only certain of the more interesting experiments will be recorded in detail.

Experiment 1.—A pregnant guinea pig, known to be within a few days of term, was deeply anesthetized with chloroform on three successive days for fifteen minutes. On the morning of the third day after the last anesthesia, the animal was found dead; the body was still warm. At autopsy, a slight icteric tinge was noted in the sclerae and subcutaneous tissues. The liver was large, soft, and yellowish gray in color. The lobular markings could be made out distinctly as pin-point sized, dark central areas surrounded by pale peripheries. The kidneys were large, pale, and slightly granular. The heart was large, soft, and pale. The uterus contained five dead fetuses, all of which appeared to be near term. They all presented the same slightly icteric tinge, and on examination they all showed practically identical changes:—large, pale, soft livers, enlarged granular pale kidneys, and soft pale hearts. Microscopically the most important finding was the presence of extensive fatty infiltration of the viscera of both the mother and the fetuses. This, of course, was most marked in the livers. Hardly a single normal cell in any of the livers could be made out, and when sections were stained with osmic acid they gave a striking appearance (figure 1). Cultures from the fetuses and the mother remained sterile.

Experiment 2.—A pregnant guinea pig was kept under anesthesia for one hour and forty minutes. Two days later, apparently within a few days of term, it gave birth to three dead fetuses. The labor occurred under observation. Examination of the viscera of all, microscopically and with the naked eye, revealed essentially the same picture as that described in experiment 1, except that no icterus was noted. The mother showed no marked ill effects and was not killed. This experiment seems to show that the administration of chloroform prior to labor may result in abortion and death of the fetus without causing the death of the mother.

Experiment 3.—A pregnant dog, near term, was anesthetized for twenty minutes with chloroform, during which time the reflexes were never entirely abolished. Two days later five pups were born, all normal in appearance and action and of about the same size. One pup died when twenty-four hours old. An autopsy showed no evidence of infection about the navel or elsewhere. There was no icterus, but moderate fatty changes were evident in the liver. The microscopical examination further showed moderate fatty changes in the kidneys and heart, but nothing else of importance.

Another pup died when forty-eight hours old, and a third when about sixty hours old. The other two died during the next twenty-four hours. At autopsy each showed essentially the same conditions:—no evidence of infection, slight icterus, rather marked fatty changes in the viscera, most pronounced in the liver, and multiple ecchymoses in the subcutaneous tissues, stomach, and small intestines. In addition, the kidneys were soft, and very dark red in color, this color
extending into the renal pelvis. Microscopically, the fatty deposits in the liver lobules were diffuse. The areas of central hyaline necrosis found by Whipple and Sperry (66) in adult dogs with experimental late chloroform intoxication were not demonstrable. There were occasional foci of round cell infiltration, usually at the periphery of the lobule, but no increase in connective tissue. The bile ducts were normal. The epithelial cells of the kidney were swollen, granular, and contained numerous small fat droplets. These changes were most conspicuous in the convoluted tubules. The lumina of the tubules contained no blood. In the myocardium, the muscle cells contained a moderate amount of fat. The stomachs of the third and fifth pups showed microscopically several small hemorrhages in the mucosa, but no ulceration. The other viscera showed no changes of importance.

The mother dog, on the fifth day after the birth of the litter, was killed by a sudden overwhelming inhalation of ether. Ether administered in this manner is incapable of causing fatty changes in the liver. At autopsy, immediately after death, the liver was large and slightly paler than normally, and the lobular markings were a little more distinct than usual in the dog. No changes were noted in the other viscera. Microscopically, sections of the liver showed a moderate increase of fat in the parenchymatous cells, which was most marked at the peripheries of the lobules. Otherwise the liver was normal.

In this experiment, a condition has been produced by means of chloroform, which in its essential characteristics is identical with that described by Buhl. The pups have lived for variable times after birth, and after death have shown a picture of which the principal features are slight icterus, high grade fatty changes in the viscera, numerous hemorrhages, and absence of infection.

Experiment 4.—A pregnant guinea pig, thought to be near term, was anesthetized for thirty minutes. Two days later it gave birth to a litter of two, both of which died on the second day after birth. At autopsy, performed while the bodies were still warm, very striking changes were found (figures 2 and 3).

Guinea pig 1 was slightly icteric. The skin and subcutaneous tissues were the site of many pin-head sized hemorrhages. The liver was large, yellow, and soft, and evidently contained a large amount of fat. Both kidneys were almost uniformly brownish black in color, slightly larger than normally, and very soft. The heart muscle was pale and flabby. The stomach and duodenum contained dark brown material, and the mucosa of each showed numerous ecchymoses. At one place in the pylorus, as well as in the duodenum, the mucosa was absent over the area of hemorrhage, so that a superficial ulceration had resulted.

The microscopic findings are as follows:

The liver presents a striking appearance by virtue of the extensive fatty infiltration. Practically every parenchymatous cell contains several fat droplets. In general, this process is most marked in the central portion of the lobule. In the mid-zonal region of each lobule there is an area which under high magnification is seen to consist of finely granular cells. Only a few nuclei of the parenchymatous cells are evident, most of them being stained fairly well. There are, however, small mid-zonal or peripheral collections of round cells, many of these being also about the bile ducts. A number of small hemorrhages are
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present, which have occurred in the mid-zonal areas. The blood in most of the central veins and other vessels is much disorganized so that it is difficult to distinguish the corpuscles. The bile ducts show no important changes.

Sections of the kidney strongly recall the picture of a hemorrhagic infarct or that of a kidney that has been experimentally asphyxiated by clamping the renal artery. The whole structure appears more or less melted together, and stains poorly; it is difficult in the cortex to differentiate the separate anatomical parts. In the medulla, where the process is less marked, the straight tubules and the renal pelvis are filled with blood, most of which is completely disorganized. Kidney cells, blood cells, and supporting structures, all tend toward solution.

In the adrenals are moderate fatty changes and occasional hemorrhages, particularly in the fascicular zone. The heart muscle is the seat of marked fatty infiltration. The other organs show no important changes.

Guinea pig 2 shows practically the same findings as guinea pig 1, except that its kidneys, instead of being dark brown in color, are pale, soft, granular, and slightly yellowish. Microscopically, they show an extensive parenchymatous degeneration with many fat vacuoles in the epithelium of the tubules, especially in the convoluted tubules. The veins and capillaries are considerably distended with blood, but no hemorrhages have occurred into the lumina of the tubules.

The mother of the guinea pigs, on the third day after the birth of the litter, showed numerous small hemorrhages in the skin of the abdomen, and had lost sixty grams in weight during the first two days after delivery. Simultaneously also, its hair was shed in abundant quantities, so that in several places the animal became practically bald, and by its drowsiness, apathy, and loss of appetite gave evidence of a severe disturbance. However, after ten days it had apparently entirely recovered from the condition and was not killed.

In this experiment, guinea pig 1 presents clinical and pathological features corresponding to the description of the so-called Winckel's disease; and guinea pig 2 shows the characteristics of Buhl's disease. These facts are particularly interesting when it is considered that the two guinea pigs were of the same litter, and hence were subjected to the same general conditions, because proof is hereby brought that one and the same cause may be responsible for pictures that are so different as to have been regarded as separate diseases. Moreover, it indicates that it is not necessary for chloroform to be administered to a pregnant animal over a long period of time in order to induce labor and to produce extensive visceral changes in the young. Further comment on this experiment is given below.

Experiment 5.—A pregnant dog, considered to be within a day or two of labor, was chloroformed for one hour. Three days later two pups that had been born during the night were found in the cage. One, which was probably dead at birth, had been chewed and macerated to such an extent that a satisfactory examination was impossible. The other was normal in appearance but had little desire to suck. It was found dead on the morning of the third day after birth. Post-mortem examination showed no icterus, but a few subcutaneous ecchymoses. The chief visceral abnormalities were in the liver and the kidneys. The former was large, soft, and almost cream colored, due evidently to the accumulation of fat. The kidneys also were large and flabby. The most
striking change was in the renal pelvis, which was deeply injected, and contained a small amount of loosely clotted blood. The medulla was much lighter in color, but presented numerous dark red streaks. The cortex was brown (figure 4).

Microscopically, the changes in the liver were such as have been described in connection with other experiments. The kidneys showed extensive hemorrhages into the renal tubules and the mucosa of the pelvis. In addition, the parenchymatous cells, particularly those of the convoluted tubules, were swollen, granular, and infiltrated with droplets of fat.

In this experiment, also, we are dealing with a condition of acute parenchymatous degeneration and fatty infiltration of the liver, with hemorrhage into the renal tubules, in a pup that died on the third day after birth; in other words, with a condition which, except for the absence of icterus, would commonly be called Winckel's disease.

Summarizing the experimental results up to this point, it may be said that administration of chloroform to pregnant animals a short time before term has been followed within a few hours or days by labor. The regularity with which labor follows the anesthesia seems to indicate that it is induced thereby. The mothers may give no external evidences of injury or they may die with icterus, hemorrhages, and acute parenchymatous degeneration of the viscera, accompanied by fatty infiltration which is most marked in the liver. The offspring may be born dead, or may die soon after birth, or live for a few days in apparent health and then develop symptoms ending in death, or they may show only mild symptoms and go on to a normal development. The changes shown by the offspring are always much the same, except as regards intensity and distribution. The general changes and those in the different viscera are, we believe, hardly distinguishable from those that may be experimentally produced by general or local protracted asphyxia; namely, cyanosis, hemorrhages, acute parenchymatous degeneration with marked fatty infiltration of the liver, or acute parenchymatous degeneration and some fatty infiltration in the other viscera, edema, and icterus. According to the degree, relative proportion, or site of these changes, we have the picture of Buhl's disease, Winckel's disease, etc., as the case may be.
DIRECT ASPHYXIA OF THE FETUS PRODUCES ESSENTIALLY THE SAME CHANGES.

In order to portray more clearly the similarity of these conditions to those following a lack of oxygen, another set of experiments was devised which had as their object the production of direct asphyxia of the fetus. These experiments will be reported more completely at a later time. Only three typical experiments are summarized here.

Experiment e1.—A pregnant guinea pig was put into a glass jar with just enough air admitted to maintain life. After four hours, marked dyspnea and cyanosis developed which continued during the whole experiment. The animal, however, in spite of the conditions, consumed daily about half its customary allowance of carrots. On the morning of the third day (at the end of forty hours), two dead fetuses, apparently fully developed, were found in the jar, the mother being still alive. At autopsy both fetuses showed essentially the same changes. The livers were moderately infiltrated with fat. The kidneys were large, fatty, and showed several subcapsular ecchymoses. No icterus was present. The other viscera showed no changes of note. The mother guinea pig remained healthy for ten days.

Experiment e2.—A pregnant guinea pig was anesthetized with ether. Under aseptic precautions three branches of the uterine artery at the fundus of the uterus were ligated, and the abdomen was closed. The duration of the operation was ten minutes. Twenty-four hours later three dead guinea pigs, apparently at term, were found in the cage. At autopsy, guinea pig 1 showed slight fatty infiltration of the liver, and marked hyperemia and ecchymoses of the kidneys. The stomach was distended with blood and its walls were hemorrhagic. Icterus was not present; and there were no important changes in the other viscera. Guinea pigs 2 and 3 showed much more fat in their livers than guinea pig 1, and no blood in the stomach, but otherwise the findings were the same.

Experiment e3.—Under ether anesthesia, branches of the uterine artery of a pregnant guinea pig were ligated aseptically as in the preceding experiment, and the abdomen was closed. Three days later the animal died, and an autopsy was made while the body was still warm. There were recent adhesions about the laparotomy incision but no evidence of extensive peritonitis. A small amount of clear fluid was present in the abdomen. The mesenteric glands were not enlarged. The uterus was markedly hemorrhagic and contained two dead fetuses which seemed to be fully developed. Both young guinea pigs showed substantially the same condition. The tissues of each were intensely hemorrhagic, and the abdominal cavities contained much free blood, almost completely laked. The livers were greatly enlarged and showed excessive fatty infiltration. The kidneys were large and fatty, and were diffused throughout with laked blood. The stomachs were filled with blood-stained fluid, and their walls were hemorrhagic. There was no icterus. The mother showed no fatty changes or hemorrhages, except in the uterus.
Hemorrhagic Diseases of the New-Born.

Cultures were made on agar from the heart's blood of one fetus and of the mother. The former was sterile, but the latter, in 3 c.c. of blood examined, showed eight colonies of the colon bacillus.

In these experiments, hemorrhages into the kidneys, alimentary tract, and elsewhere, in addition to pronounced visceral fatty changes, have been produced by direct asphyxia of the fetus.

Through the courtesy of Dr. E. R. LeCount and Dr. H. F. Helmholz, I have had the opportunity of studying three cases of this general condition in new-born infants, all of which had been delivered under chloroform and were born in asphyxia. Clinically and pathologically, two agreed with Buhl's syndrome; the third was associated with evidence of intestinal infection. The close agreement between these clinical cases and our experimental results was striking. Here again it is interesting that although the gross pathological picture presented by these infants closely resembled the condition of "late chloroform poisoning" in the adult, nevertheless microscopically the central areas of necrosis in the liver were not found.

GENERAL DISCUSSION OF THE RESULTS.

Allusion has already been made to the similarities of these various conditions. They are so marked as to compel one to entertain the idea that all may be variations of one process. Further support is given to such an inference by experiment 4, in which two guinea pigs of the same litter developed conditions closely resembling Buhl's and Winckel's diseases respectively, although both animals had been subjected to identical conditions. Practically all the striking pathological changes described in these different conditions have been produced in various combinations by the use of one experimental procedure. Thus, fatty changes alone have predominated at times; at other times fatty changes with icterus; again fatty changes with ecchymoses, and sometimes a combination of all three changes with or without ulcerations of the gastric mucosa. Finally, in the experiments in which the kidneys were most involved, hemoglobinuria has occurred with the production of the typical picture of Winckel's disease. Is it not possible that simple, so-called physiological icterus of the new-born may be a
mild expression of the same process? It is interesting that Zweifel
(73) considered the possibility of a causal relationship between
chloroform intoxication and simple icterus neonatorum, but later
discarded it because, in a comparative series of births with and
without the use of the drug, he found the percentage of icterus
cases about the same in each series.

It is to be regretted that it has been impossible to formulate from
the literature any extensive series of statistics showing the fre-
quency with which any one of these various syndromes has fol-
lowed either the use of chloroform or a condition of extreme
asphyxia at labor.

The intimate association of icterus with a hemorrhagic tendency
has long been a question of great interest and has aroused much
discussion. In the earlier literature, much stress was laid upon the
influence that the bile in the blood exerts on its coagulability. Later
the observation was repeatedly made that those conditions
which were characterized by icterus and high grade fatty changes
in the liver were also likely to be associated with fatty changes in
the vessel walls. Thus the conception arose that the hemorrhage
was in a large measure due to a weakening of the vessel wall.
These observations have been made, particularly in connection with
phosphorus poisoning, by Klebs (74), Bollinger (75), Schultzen
and Riefes (76), Wegner (77), etc. In the last few years, much
valuable light has been thrown upon this question. In a series of
articles, Doyon (78), in conjunction with Gautier (79, 81), Kareff
(80), and Morel (82), has produced evidence which at first sight
strongly suggests that fibrinogen is formed chiefly in the liver, and
that interference with normal liver functioning interferes corre-
spondingly with the production of fibrinogen and therefore induces
a condition of diminished coagulability of the blood. Recently,
Whipple and Hurwitz (67), from experiments dealing chiefly with
chloroform intoxication, have arrived at the same general conclu-
sions. In the light of these facts, the temptation is strong to assume
that the hemorrhagic tendency in these affections of the newly born
is dependent primarily upon a process that interferes with normal
liver functioning, yet there are reasons for exercising some reserve
in accepting this hypothesis, and for preferring to ascribe the hemorrhagic tendency to a more fundamental and widespread change, as a result of which not only fibrinogen, but innumerable other proteins tend to remain in solution or to pass into solution, with the result that apart from diminished blood coagulability there is a great reduction in the firmness of the vessel walls.

The formation of ulcerations of the gastric and duodenal mucosa after the use of chloroform in these experiments is not surprising. Since 1866, when Nothnagel (83) described their occurrence in experimental chloroform intoxications in rabbits, numerous similar observations have been made in human beings as well as in animals. Whipple and Sperry (66), in six experiments on adult dogs, observed ulcerations of this kind in three of the dogs. They suggest as the cause of these formations the digestion of mucosa at the site of an ecchymosis or of a submucosal hematoma.

In considering the question of the fatty changes which, in general, are so conspicuous a feature of these various syndromes, it is interesting that one occasionally finds in the literature a report of one of these syndromes in which it is distinctly stated that no fatty changes were evident. In the light of Rosenfeld’s (84) important work this is not surprising; for this author has shown clearly that at least the greatest part of the fat found in the liver after phosphorus poisoning has been transferred to those viscera from the various fat depots of the body. Therefore, in emaciated infants whose fat has been used up, we should have no reason to expect marked fatty changes in the viscera; for sufficiently emaciated adults and animals fail to show fatty changes in the liver when poisoned with phosphorus.

SUMMARY.

Those conditions of the new-born characterized by a hemorrhagic tendency, icterus, and fatty changes, are probably all syndromes which may occur as the result of a number of toxic agents.

All of them, however, have been produced, in these experiments, by the action of a single experimental agent. Thus, a picture indistinguishable from that called Buhl’s disease has been obtained by
the use of chloroform, as have also the pictures known as Winckel's disease, melena neonatorum, etc.

Chloroform is not held to be the only substance that has this power. It stands rather as one member of a group of agents, the effects of which in general and in individual organs are similar to those caused by lack of oxygen.

The essential features of these conditions have also been produced by direct asphyxiation of the fetus. The suggestion is therefore made that underlying all these symptoms and pathological complexes, there is a deficiency of oxidation, general, local, or selective, thus bringing this group of diseases into the general category of acute yellow atrophy of the liver, eclampsia, pernicious vomiting, cyclic vomiting, phosphorus poisoning, etc.

In human beings, chloroform and asphyxia must, in many instances, be the determining causes.

There remain, however, other cases in which different factors are to be sought.

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EXPLANATION OF PLATES.

PLATE 46.

Fig. 1. Section of fetal guinea pig liver from experiment 1, stained with osmic acid to show the large amount of fat present. Death occurred in utero, following three administrations of chloroform to the mother.

PLATE 47.

Fig. 2. Kidney with extensive hemorrhage, from guinea pig 1 (experiment 4). Two days before birth, the mother of this guinea pig was given chloroform for thirty minutes. The young animal lived for a little over twenty-four hours, and presented the essential features of Winckel's disease.

Fig. 3. Kidney from guinea pig 2 of the same litter. This animal presented the characteristics of Buhl's disease.

Fig. 4. Kidney from the pup described in experiment 5, showing features of Winckel's disease.