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Special Article

Obstetric Anesthesia and Concepts of Placental Transport:

A Historical Review of the Nineteenth Century

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THE ENTHUSIASM with which physicians accepted Morton's demonstration of anesthesia for surgery was not accorded James Young Simpson when he suggested that anesthesia also could be used for obstetrics. Opposition came from various segments of society, but especially from physicians, who questioned its safety.[1]

Obstetricians were concerned in part with the effect on the newborn of anesthetic gases given to the mother. It was a practical problem that had not confronted them before and one with which they grappled for the next half century. Reviewing the development of concepts concerning transplacental movement of drugs is warranted for general interest; it occurred early in the movement in which science entered the practice of medicine. But the concepts themselves are important, as they form the basis for our current practice.

Early Reaction to Obstetric Anesthesia

In 1847, opinion regarding the effect of anesthesia on the unborn child was sharply divided. Walter Channing, professor of obstetrics at Harvard and dean of the School of Medicine, thought it was negligible, inasmuch as he had been unable to detect the odor of ether at the cut ends of the umbilical cord.[2] From this he inferred that ether did not cross the placenta. Both observation and inference were important, for they implied that physicians could use anesthesia liberally in obstetrics without concern for the newborn. In fact, it suggested that close examination of the child would be superfluous. Channing's opinions on this and other facets of anesthesia were quoted widely and gave tremendous impetus to early acceptance of anesthesia into obstetric practice.

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It was odd that anyone was satisfied with the conclusion that ether did not cross the placenta. It ran contrary to thought that had prevailed in biology and medicine for several thousand years. For example, physicians had long assumed that foodstuffs crossed the placenta. In his book on embryology, Aristotle[3] said the placenta took nutrients from the mother's blood as the roots of a tree take sustenance from the soil. The great English physician-physiologist William Harvey repeated the analogy in his book on embryology.[4] And, of course, in the mid-seventeenth century the Oxford physiologist John Mayow suggested that the placenta served the fetus as a lung, permitting the transfer of "nitro-aerial" particles from the mother's blood.[5] In the nineteenth century Carpenter elaborated on the idea in his popular textbook on physiology.[6] Though he had no experimental evidence, he suggested that nutrients move between maternal and fetal bloods just as they move from the lumen of the gut across the mucosa to the veins and lacteals, a process that had been studied thoroughly.

One may argue that physicians saw no similarity between transplacental movement of food stuffs and that of drugs or other foreign materials. But again, evidence was to the contrary. Physicians knew of infants infected with smallpox or syphilis after their mothers had contracted the disease during pregnancy. There were instances in which phosphorus, mercury, lead, potassium iodide and saffron had been detected in organs or in body fluids of infants whose mothers had been given the chemicals while pregnant.[7] Physicians had observed bile-stained organs of fetuses whose mothers died of acute yellow atrophy of the liver. Should there be questions of the ability of drugs to cross an intact membrane such as the placenta, they had only to consider the phenomena of drug absorption from the gastrointestinal tract and excretion in the urine that were discussed extensively in early textbooks on pharmacology.[8] In fact, the great French physiologist Magendie specifically tested and found evidence for placental transport when he injected camphor into the circulation of dogs, subsequently detecting its odor in the blood of the fetuses. This experiment was described in the English translation of his

book published in 1834[9]—a volume that probably was available to Channing at Harvard.

Indeed, in 1850 there was enough evidence to support the idea of placental transport to stimulate a Scottish physician, Alexander Harvey, to publish a three-part article in the *Edinburgh Journal of Medical Sciences* entitled "On the Foetus in Utero, as Innoculating the Maternal with the Pecularities of the Paternal Organism; and on Mental States in Either Parent, as Influencing Nutrition and Development of the Offspring."[10] Despite the whimsical title, Harvey cited many examples to support the idea of placental transport and was quoted often in England and on the Continent.

Contemporary physicians also disagreed with Channing regarding placental transfer of ether. Sir John Snow, the first anesthesiologist and one of the discipline's greatest founders, detected the odor of ether on exhalations of infants whose mothers had received the drug during labor. This was a simple extension of the test Channing applied unsuccessfully.[11] Francis Ramsbotham,[12] a prominent London obstetrician, cited two cases in which fetal heart rate increased when mothers were given ether and decreased when ether was discontinued. He assumed this was a direct effect of the drug on the infant's heart. Therefore, both men believed placental transmission of ether occurred, and that the infant was affected by the exposure. Ramsbotham said that ether might be "detrimental to the tender organization of the newborn," although he didn't say how; Snow suggested that such infants tended to be less active and responsive in the first moments of life.

C. C. Hüter, professor of obstetrics at the University of Marburg in Germany, gave a most explicit warning about chloroform. He was concerned about the effects of anesthetic gases on the mother and child—particularly their vascular and nervous systems.[13] Hüter questioned whether the use of anesthetic gases might increase the risk of neonatal depression or death. In a long article, he described his experience with patients to whom chloroform had been given. The outcome had not always been good. During one autopsy he smelled chloroform in the infant's liver. Subsequently he tried two chemical methods to identify chloroform in umbilical blood. The second, adapted from a method described by von Ragsky, was successful: In August 1849, he observed a color reaction in a specially prepared indicator paper when it was exposed to blood taken from the umbilical cord of a child whose mother had received chloroform during childbirth.

It is important to note, however, that observations by Snow, Ramsbotham and Hüter appeared to have had no impact on medical practice. In medical literature of the succeeding 25 years there is nothing to suggest that the growth in popularity of anesthesia for obstetrics was in any way impeded because of consideration for its effect on the newborn. For example, clinical reports stated only that the child was born alive or dead. Virtually none gave even a modest description of the infant's behavior, certainly not in relation to drugs that the mother had received during pregnancy or labor.[14–16]

That concepts of placental transport failed to influence clinical practice illustrates an important point: the difference between those facts that physicians know and those they understand. There certainly was sufficient evidence by 1850 to establish that drugs crossed the placenta. It appears, however, that physicians failed to comprehend the implications of that information. Almost a quarter of a century passed before they did.

Experimental Evidence, 1850–1875

Between 1850 and 1875 several experiments were undertaken specifically to study aspects of placental transport. In 1858, Savory,[17] an Englishman, injected strychnine into the circulation of fetal dogs to see whether the mothers would convulse. Because they did, he concluded that drugs could cross the placenta in both directions. In 1865, Reitz,[18] a German, described experiments in which he injected particles of mercuric sulfite into the circulation of pregnant rabbits. At autopsy he observed particles wedged in the small vessels of the cerebral circulation of the fetuses. Four years later, Hoffmann and Langerhans repeated the experiment but were unable to duplicate the results.[19] More interesting, perhaps, are two papers, one published in 1874 and the other in 1877, in which the authors considered the feasibility of treating fetal disease by administering drugs to the mother.[20,21] The suggestions were never implemented, possibly because the diagnosis of fetal disease was more elusive than its treatment.

These experiments, however, appeared to have no more impact on medical practice than the earlier clinical observations by Snow, Ramsbotham and Hüter. In fact, the concept of placental transport of drugs appears to have been established as a consequence of two quite different developments in medicine: a change in the clinical use of narcotics and a growth of interest in fetal physiology.

Clinical Use of Narcotics in Obstetrics

Narcotics had been used medically for centuries. The manner and extent to which they were used in obstetrics, however, are difficult to ascertain. In many obstetric textbooks from the nineteenth century, particularly those from the first half of that century, narcotics are not mentioned at all. Curiously enough, even books of *materia medica*

FIG. 1. Adolph Gusserow (1836–1906). Arch Gynaekol, vol. 78, 1906 (courtesy of J. F. Bergmann-Verlag, München).

do not describe childbirth as a medical condition requiring narcotics.

During the mid-nineteenth century the use of narcotics for childbirth changed. In 1803, Sertürner isolated morphine from the crude extract of opium. In 1853 (by coincidence, the year Queen Victoria was anesthetized for childbirth), practical techniques had been developed for hypodermic administration of drugs.[22] Wood developed the hollow metal needle and Pravaz the syringe.[23] In 1860, Kormann of Germany published a widely quoted paper recommending hypodermic administration of morphine to control the pain of labor.[24] About the same time, Isaac Taylor, professor of obstetrics at the College of Physicians and Surgeons in New York, appears to have introduced hypodermic administration of morphine to the United States, although his innovation was not described in writing.

During this time, physicians began to recognize problems associated with the use of narcotics during pregnancy. In 1834, Francis Ramsbotham observed that children born to an addicted patient were "dull and sleepy in the first few hours of life."[25] In 1847, Pereira[8] warned against giving narcotics to pregnant or nursing women because of their effect on the child. However, neither man cited specific dangers of giving narcotics during labor or gave a detailed description of their effect on the infant.

The full impact of the dangers of narcotics came between 1875 and 1880 and was related in part to the tremendous increase in drug addiction among the general populace. At that time, physicians treating addicted women described situations in which their children appeared to undergo withdrawal symptoms *in utero* or in the first few days of life.[26] Others described instances in which fetuses died shortly after, and supposedly because of, a hypodermic injection of morphine given to the mother.[27] (Similar observations had been made with chloral, which also was used widely in obstetrics at that time.[28]) These problems rekindled interest in the question of transplacental movement of drugs and gave it a poignancy not present a quarter of a century earlier. The problem was debated extensively in meetings of obstetrical societies in Leipzig[29] and New York.[30]

Development of Medical Science

Perhaps the most important factor that led to incorporation into clinical practice of the concept of transplacental movement of drugs was a fundamental change in medical thought. By 1850 there was still very little science in medicine. Nowhere was this more evident than in the United States. Channing, for example, graduated from the University of Pennsylvania in 1809, a year in which Benjamin Rush and Hahnemann dominated medicine with ideas of bloodletting and homeopathy.[31] Men like Channing, who trained in this atmosphere, were at the peak of their power and influence in 1847, the year Simpson introduced anesthesia to obstetrics. It was natural their ideas would prevail.

One must also remember the high infant and maternal mortality rates at that time. A successful delivery was one in which both mother and child survived. It was still accepted that on occasion the obstetrician would have to sacrifice the infant to save the mother. Deaths from anesthetics had been reported, but few occurred in obstetrical patients. In view of all this, subtle changes in the behavior of newborns, such as those described by Snow and Ramsbotham, may have seemed trifling, particularly to men unschooled in science and in the critical interpretation of clinical observation.

By 1870, however, particularly in Europe, the field of medicine had changed. In fact, some of the greatest contributors to biology and physiology were men who originally trained as physicians. Johannes Müller and Claude Bernard laid the

foundations of physiology. Rokitansky and Virchow began studies of organ and cellular pathology. Koch showed relationships between microorganisms and clinical disease. In short, the practice of medicine expanded to embrace the study of disease, and basic science became an implement to shape progress in medicine.

In obstetrics Adolph Gusserow epitomized the new direction. Born and educated in Berlin, he held academic posts in Utrecht and Zurich.[32] In 1872, after the defeat of Napoleon III by the Prussian army, Gusserow was appointed to the chair of obstetrics at the University of Strasbourg, in the province of Alsace. The appointment was part of a program in which top academic posts were transferred to men of German descent to hasten the cultural assimilation of the local populace. Whatever opinion one may have of the politics of the program, it had one practical effect. It brought together some of the brightest young men of German academia. Those who joined Gusserow on the faculty of medicine included von Recklinghausen and Felix Hoppe-Seyler.

Gusserow may have been among the first to understand the importance of fetal metabolism in the practice of obstetrics. This interest probably began while he was a student at Virchow's Institute in Berlin. There he attended lectures on metabolism, nutrition and biochemistry given by Felix Hoppe-Seyler, one of the giants of German medical science in the last half of the nineteenth century. Hoppe-Seyler trained originally as a physician and qualified in obstetrics before he turned to physiologic chemistry.[33] He understood the significance of metabolism to medicine and to clinical obstetrics. In addition, he had the qualities found in all great teachers: infectious enthusiasm, a broad range of interests, tremendous energy, and the capacity to transmit all this to his students. It seems quite likely that contact with Hoppe-Seyler, first as a student and later as a colleague, was an important stimulus to the development of Gusserow's thought.

Gusserow asked whether the fetus carried out its own metabolic processes or whether those processes were performed for it by maternal tissues. The answer depended in part on the speed with which various materials traversed the placenta. In 1871 he published a long paper in which he reviewed the pertinent literature and described experiments in which he administered potassium iodide to women during the last weeks of pregnancy.[34] After delivery, he tested for potassium iodide in the fetal urine and amniotic fluid. The amounts he recovered were small, and he concluded that the rate of transfer was too slow to be of clinical significance. Gusserow returned to the problem in a second extensive paper published in 1878,[35] in which he sought to demonstrate the functional activity of the fetal kidney. He administered benzoic acid to pregnant

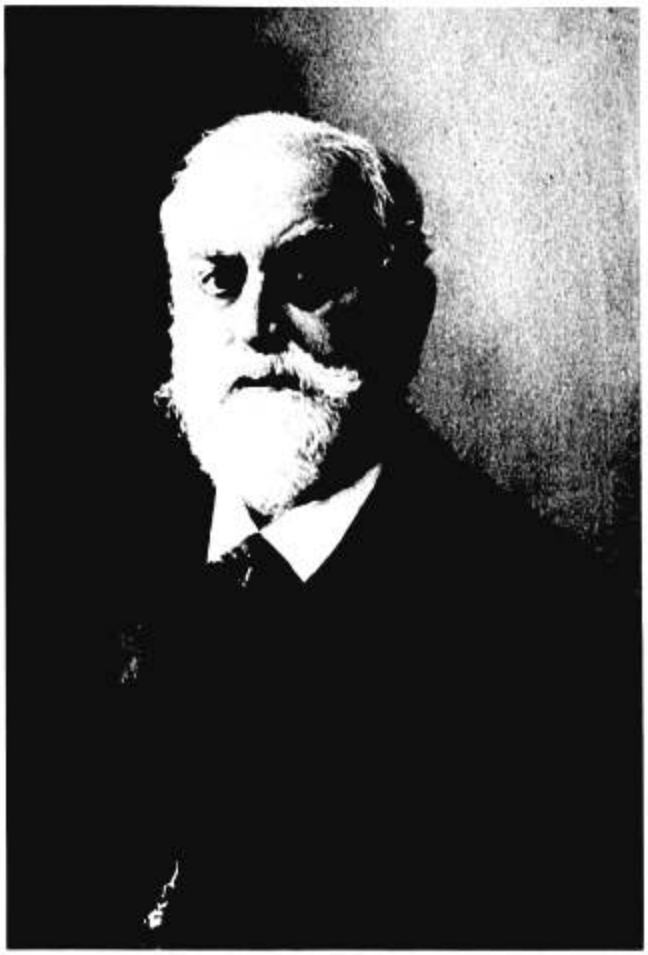

FIG. 2. Paul Zweifel (1848–1927). Arch Gynaekol, vol. 131, 1927 (courtesy of J. F. Bergmann-Verlag, München).

women, knowing that its biotransformation to hippuric acid took place only in the kidney. He found hippurate crystals but no benzoic acid in the urine of the newborn. From this he inferred that benzoic acid was transferred from mother to fetus and that it was metabolized by the fetal kidney.

The definitive experiments were done not by Gusserow, however, but by one of his students, Paul Zweifel. Zweifel,[36] a third-generation physician, was born near Zurich. He studied in Zurich with Gusserow and moved with him to Strasbourg after the Franco-Prussian War. Zweifel made two very important observations. First, he demonstrated a difference in oxygen contents of blood in the umbilical artery and that in the umbilical vein by using a spectral light-absorption technique developed by Hoppe-Seyler, thereby clarifying a long-debated point concerning the fetal metabolism of oxygen.[37] Second, he demonstrated unequivocably that chloroform crossed the placenta.

Zweifel's interest in chloroform developed from two clinical observations: He believed the incidence of neonatal jaundice was higher in the infants

whose mothers had received chloroform during labor, and he observed that the urines of such infants contained a reducing substance not present otherwise. It had been established from surgical patients that chloroform could cause jaundice and that it gave such a reaction in the urine. Zweifel therefore inferred that the infant's jaundice was secondary to the child's exposure to chloroform that had been transferred from the mother's circulation during labor.

Zweifel tested the assumption crucial to his argument. In 1874 he published work in which he demonstrated that chloroform could be detected chemically in the placentas of women exposed to its vapor during labor.[38] Critics[39] said the evidence was not conclusive, inasmuch as he could not eliminate the possibility that the chloroform was not in the parenchyma of the placenta but in maternal blood adherent to its surface. In rebuttal Zweifel published a second paper in 1877,[40] in which he demonstrated chloroform in umbilical blood and in the urines of newborns. He supported his argument by demonstrating that salicylic acid could also be detected in the urines of infants whose mothers had been given this drug during labor, an experiment first done by Benecke.[41] Within a short time his observations were confirmed by others.[42]

Although Zweifel discounted the role of chloroform as a cause of *icterus neonatorum*, the paper had great impact on medical thought. It was discussed at meetings and quoted in journals and textbooks. From that time on no one seriously questioned that clinically significant amounts of drugs could cross the placenta in short periods of time. They recognized that now they had only to define the factors that determined the rates of transfer of different drugs in different circumstances. Studies of this sort occupied physiologists and physicians for the next 50 years.

The impact of Zweifel's paper was greater on medical theory than on medical practice. Initially, anesthetic gases, narcotics and other drugs were used much as they had been before. As one obstetrician said, he had had 30 years' experience with anesthetics, most of which had been quite good, and he saw no reason to modify his practice just because he now knew that drugs crossed the placenta.[30] One might be more patient with such an attitude had the physician also conceded the need for close observation of the newborn for ill effects from drugs, even as he continued to use them. Only towards the end of the century did authors urge greater caution in the use of drugs. In fact, the full impact of Zweifel's observations may have been demonstrated only in the past few decades by the tragedies associated with "twilight sleep," thalidomide, and diethylstilbestrol.

In evaluating Zweifel's contribution, it is important to remember that his experiments were not the first to demonstrate transplacental movement of drugs. Zweifel succeeded where others failed because his experiments were not only good, but also timely. Physicians were prepared to examine the evidence in a new way, partially because of their experience with narcotics, but more important, because of their experience with science. The clinical question of placental transport was answered only after physicians considered the underlying physiologic mechanisms. For this, Gusserow may deserve the greatest credit. He became interested in fetal metabolism long before it was recognized as a part of clinical obstetrics, and he did much to establish it as part of the discipline. His papers summarized existing knowledge relating to placental transport and demonstrated ways in which the problem could be studied clinically. His use of pharmacologic properties of hippuric acid to study a problem of placental transport and fetal physiology was singularly imaginative, and is an approach whose potential has not been fully exploited by experimentalists today.

It has been said that fortune favors the prepared mind. In this case, it appears that Hoppe-Seyler prepared Gusserow to start this line of inquiry, and that Gusserow prepared physicians to recognize the significance of Zweifel's very important work.

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