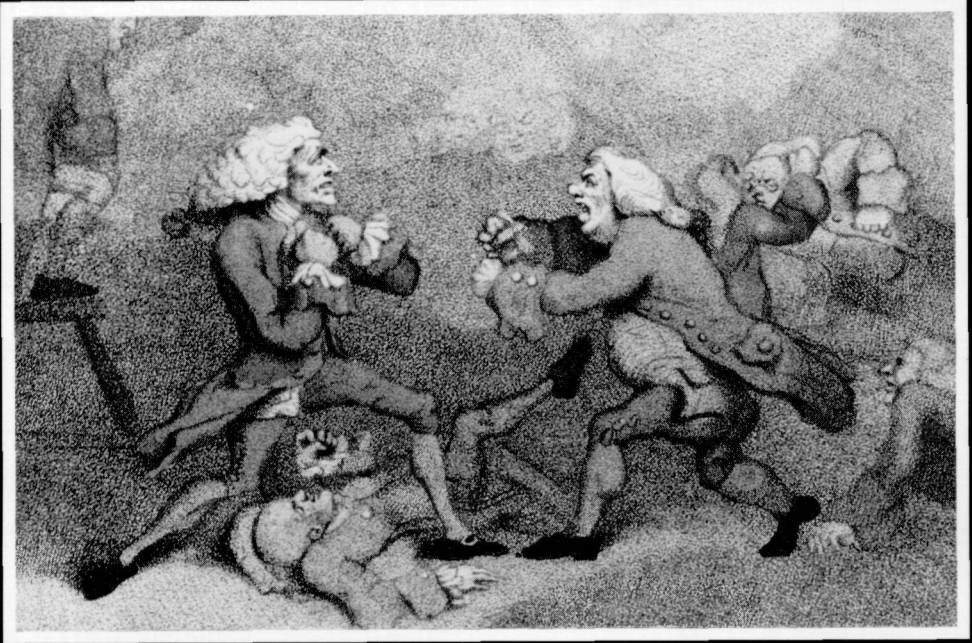


The History of Anesthesiology

Reprint Series: Part Eighteen



Doctors Differ; Published in London, November 28th, 1785 by S. W. Fores at the Caracature Warehouse No. 3 Piccadilly. Reproduced by courtesy of the Boston Medical Library in the Countway Library of Medicine.

CONTROVERSIES IN ANESTHESIA

In any human endeavor whether it be in the realm of religion, metaphysics or science, history shows that new ideas are rarely accepted without controversy. The reception of several innovations in anesthesia surely falls into this pattern. Consequently, for the current reprint series on the History of Anesthesiology, the Trustees of the Wood Library-Museum have elected to address the subject of Controversies in Anesthesia.

Leroy D. Vandam, M.D.

HISTORY OF ANESTHESIOLOGY REPRINT SERIES

Part Eighteen
1988

CONTROVERSIES IN ANESTHESIA

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Controversies in Anesthesia

In any human endeavor whether it be in the realm of religion, metaphysics or science, history shows that new ideas are rarely accepted without controversy. The reception of several innovations in anesthesia surely falls into this pattern. Consequently, for the current reprint series on the History of Anesthesiology, the Trustees of the Wood Library-Museum have elected to address the subject of Controversies in Anesthesia.

While we refrain from tilling the old ground over who should be given credit for the discovery, two items merit further comment. The first pertains to Horace Wells' 1847 tract on A History of the Discovery of Nitrous Oxide Gas, Ether and Other Vapors, to Surgical Operations. Wells, who is usually given little credit, eloquently displays some remarkable insight. "Reasoning from analogy, I was led to believe that surgical operations might be performed without pain, by the fact, that an individual, when much excited from ordinary causes, may receive wounds without manifesting the least pain". This indeed is a thoroughly modern conception.

Second, amidst the priority controversy, one should not disregard the medical opposition to the employment of anesthesia, particularly in obstetrics. This kind of reservation is revealed in Charles D. Meigs' turgid and obfuscatory letter of April 26, 1848, to Walter Channing, as reprinted in the Introduction to, "A Treatise on Etherization in Childbirth". The objection is quite modern in that anesthesia might adversely affect the forces of labor and harm the foetus as well.

From time to time the statement is still made that Dr. J. Leonard Corning, neurologist, was the first to give a spinal anesthetic, in 1885. Little problem exists in discarding this claim in that Corning never once mentions the cerebrospinal fluid (CSF), that it was merely his intention to inject cocaine into the vicinity of the spinal cord, and further, that CSF was not recovered on lumbar insertion of the needle.

For well over 50 years, controversy raged over the reason for the sudden patient collapse experienced during chloroform anesthesia, whether it related to respiration or circulation. Typically, as a result of advances in the collateral sciences, A. Goodman Levy, utilizing the electrocardiogram, showed in the cat that ventricular fibrillation was the cause. Furthermore, this occurred during the lighter planes of anesthesia and was readily induced by the injection of recently discovered epinephrine. Thus was born the hydrocarbon-epinephrine experiment which concerns anesthesiologists to this day.

Until the 1950s, spinal anesthesia was given with relatively little opposition under the most crude technical circumstances. Cumulative reports of neurological sequelae led S. Foster Kennedy to exclaim, "That paralysis below the waist is too large a price for a patient to pay in order that the surgeon should have a fine relaxed field of operation." The clamor was great but corrections were made and spinal anesthesia now enjoys a good reputation.

Lastly, while overlooking the fact that chloroform anesthesia might cause delayed poisoning or acute yellow atrophy of the liver, halothane, a halogenated hydrocarbon, was introduced to practice in the 1950s. Although preliminary testing in surgical patients allayed any fears that might have existed, a number of suspicious incidents occurred several years after widespread use of this new, nonflammable agent. Thus, an inquiry was begun by the National Research Council which resulted in a comprehensive report of the National Halothane Study. Although it seemed fairly certain that acute hepatic necrosis might rarely develop after anesthesia, a long time elapsed before clinicians would accept the idea that halothane was responsible.

Leroy D. Vandam, M.D.

A

HISTORY OF THE DISCOVERY

OF THE APPLICATION OF

NITROUS OXIDE GAS,

ETHER, AND OTHER VAPORS,

TO

SURGICAL OPERATIONS.

BY HORACE WELLS.

HARTFORD:
J. GAYLORD WELLS,
CORNER MAIN AND ASYLUM STS.
1847.

P R E F A C E .

IN answer to a request, made by several scientific and medical societies of Europe, who have desired me to furnish them with the evidence of my priority of discovery of the application of gas, or vapor, for the performance of surgical operations, I have obtained testimonials and affidavits sufficiently numerous and satisfactory, as I believe, to establish the fact beyond a doubt.

I have forwarded the original papers to Dr. C. S. Brewster, of Paris, (No. 11 Rue de la Paix,) who will have charge of them until this question is settled.

The following pages contain a correct copy of those papers, which prove, conclusively, that I made known this discovery in November, 1844, which date is nearly two years prior to that given by Drs. Jackson and Morton.

HORACE WELLS.

Hartford, March 30, 1847.

HISTORY, &c.

TO THE EUROPEAN AND AMERICAN PUBLIC:

I propose, in the briefest manner possible, to give, in the following pages, a true and faithful history of the discovery which is at present causing an unparalleled excitement throughout the whole medical world. I refer to the administering of exhilarating gas, or vapor, to prevent pain in surgical operations. It is very unfortunate that there should be more than one claimant for the honor of the discovery; but so it is: and the only alternative now is, for the man who considers himself entitled to this honor to present his proofs, that a discriminating and impartial public may "give credit to whom credit is due."

Reasoning from analogy, I was led to believe that surgical operations might be performed without pain, by the fact, that an individual, when much excited from ordinary causes, may receive severe wounds without manifesting the least pain; as, for instance, the man who is engaged in combat may have a limb severed from his body, after which he testifies, that it was attended with no pain at the time: and so the man who is intoxicated with spirituous liquor may be severely beaten without his manifesting pain, and his frame, in this state, seems to be more tenacious of life than under ordinary circumstances. By these facts I was led to enquire if the same result would not

follow by the inhalation of exhilarating gas, the effects of which would pass off immediately, leaving the system none the worse for its use. I accordingly procured some nitrous oxide gas, resolving to make the first experiment on myself, by having a tooth extracted, which was done without any painful sensations. I then performed the same operation for twelve or fifteen others, with the like results.

This was in the fall of 1844. Being a resident of Hartford, Connecticut, I proceeded to Boston, in December of the same year, in order to present my discovery to the medical faculty; first making it known to Drs. Warren, Hayward, Jackson, and Morton: the last two of whom expressed themselves in the disbelief that surgical operations could be performed without pain,—both admitting that this *modus operandi* was entirely new to them; and these are the individuals who now claim to be the discoverers!

By invitation of Dr. Warren, I addressed his medical class upon the subject. I embraced the opportunity, and endeavored to establish the principle that the system, when wrought up to a certain degree of nervous excitement, by any means whatever, would thus be rendered insensible to pain, and would admit of surgical operations being performed without any disagreeable sensations. In proof of this theory, I related my experience in extracting teeth under the influence of nitrous oxide gas, stating that, with one or two exceptions, all on whom I had operated (numbering twelve or fifteen) assured me that they experienced no pain whatever; and, in further proof of the truth of this principle, I cited analogous cases, as, the man

who is excited by passion, or he who is much intoxicated by liquor; stating, that individuals under these circumstances uniformly testify, when wounded, that such injuries were inflicted without pain. I stated, also, that I was making use of nitrous oxide gas simply because I considered it more harmless than any thing else which could be used for this purpose; assuring them that the same result would follow, let the nervous system be excited sufficiently in any manner whatever. I remained several days in Boston in order to have an opportunity of administering the gas to a man who was expecting to have a limb amputated, but the operation was postponed. I was then invited to extract a tooth for a patient in presence of the medical class, which operation was performed, but not with entire success, as the gas-bag was removed too soon; and as the man said he experienced some pain, the whole was denounced as an imposition, and no one was inclined to assist me in further experiments.

The excitement of this adventure immediately brought on an illness, from which I did not recover for many months; being thus obliged to relinquish, entirely, my professional business. I will now, in a few words, state how the names of Jackson and Morton came into notice, as being connected with this discovery.

Dr. Morton, who is a dentist in Boston, was instructed in his profession by myself, about five years since, and I subsequently assisted in establishing him in the city of Boston, and after I had made the above discovery, I had frequent interviews with him; and he, being aware that I had relinquished my professional business in consequence of a protracted indisposition, requested me to instruct him

how to prepare the gas which I had been giving so successfully in Hartford, stating that he wished to make a trial of it in Boston. As this interview was in Hartford, I told him to request Dr. Charles T. Jackson (with whom we were both acquainted) to prepare him some of it, as he was a chemist. Accordingly, Dr. Morton went to Dr. Jackson for the gas, who gave him the ether, as being attended with the least trouble. After one or two teeth were extracted, it was then introduced into the Massachusetts General Hospital, where a capital operation was performed under its influence with perfect success; which fact was immediately published in the principal newspapers of the day, with the names of Jackson and Morton (who had, by a written contract, entered into a sort of co-partnership business in this matter) as the discoverers; and Dr. Jackson, as I have since been informed, immediately sent letters to London and Paris, to be read to the several Academies, where he takes all the credit to himself, not even mentioning the name of Morton, his partner by written contract, which contract was signed and executed on the 27th of October, 1846. In this agreement, Dr. Jackson acknowledges that Dr. Morton made the discovery "*in conjunction*" with himself, as the following extract from the paper signed by Jackson fully proves :

"To all persons to whom these presents shall come: Whereas, I, Charles T. Jackson, of Boston, in the State of Massachusetts, chemist, have, *in conjunction* with William T. G. Morton, of said city, dentist, invented, or discovered, a new and useful improvement in surgical operations on animals, whereby *we are enabled* to accomplish many, if not all operations, such as are usually attended with more or less pain and suffering, without any, or with very little, pain or muscular action, to persons who undergo the same," &c., &c.

After the fact came to the knowledge of Morton that Jackson had sent privately to Paris, he, as a natural consequence, became very indignant; and each of these individuals now deny that the other has had anything to do with the discovery which was at first claimed by both, "acting in conjunction." I will here make a quotation from the Boston Advertiser, of March 6th, 1847, which contains Dr. Morton's reply to Dr. Jackson. Dr. Morton proceeds as follows:

"In the letter to M. Beaumont, of Paris, from which I have already made extracts, Dr. Jackson says:

" 'Five or six years ago, I remarked the peculiar state of insensibility into which the nervous system was plunged by the inhalation of the vapor of pure sulphuric ether,' &c.

"Previously to this, he had already stated, under oath, in the preamble to the specifications, which bear date the 27th of October, 1846, that the same hath not, to the best of his knowledge and belief, *been previously known*. Now, Dr. Jackson either did know, previous to this time, that sulphuric ether would produce insensibility to pain; or he did not. If he did, as stated in his letter to M. Beaumont, then I have to remind him of his oath, under the solemnity of which he states that, according to the best of his knowledge and belief, *'the fact had not been before known.'* But if he did not, then I remind him of his statement to M. Beaumont, in which he says that he *had known it for 'five or six years.'* And the learned Doctor may take either horn of the dilemma he may prefer.

"It is not known that Dr. Jackson ever made more than one experiment in inhaling ether; and then he used it as an antidote to the vapor of chlorine, which he had accidentally breathed, but from his own statement, in the Advertiser, it did not answer the purpose — the deleterious effects returning with the return of consciousness. But, supposing he had known of it six years or six months before Dr. Morton applied it in practice, is it not inexcusable in him to

have withheld from suffering humanity this inestimable boon so long—a boon by the gift of which such an incalculable amount of misery might have been saved? Or is it within the limits of probability, that if he had been so long in possession of a discovery which, if made known, would in four months call down blessings on his head from ten thousand hearts, and from all civilized lands, and which, from present prospects, would make him to be remembered and cherished by the side of Jenner by all coming generations, and to all coming time—I say, is it probable, had he known of this noble gift, that he would not have been more zealous in publishing it to the world? If he did make this discovery, is it not a remarkable coincidence that Dr. Morton should have made it at the same time, and still more remarkable, that Dr. J. should leave to another the honor to make his discovery known? But to settle this whole matter, and it might have been done in the outset, to the satisfaction of any candid mind:—After Dr. Morton began to use the ether in his practice, and for some weeks, it is well known to a large number of our most respectable citizens, that Dr. Jackson clearly and distinctly repudiated and washed his hands of the whole thing. He, on many occasions, as it is well known to his friends, disclaimed all connection with the discovery or use of ether in surgery. A gentleman of high standing, asked Dr. J., in presence of several others, if he ‘knew that, by the inhalation of ether, such a state of insensibility could be produced as that the knife could be applied, and the patient feel no pain?’ Dr. J. replied:

“‘No; nor Morton either, nor any one else. *It is a humbug*, and it is reckless in Morton to use it as he does.’

“In speaking to two other persons, at different times, on this subject, he said:

“‘I don’t care what he [Morton] does with it, [the discovery,] if he does not drag my name in with it.’

“At another time, he said, he ‘did not know how it would work in pulling teeth, but he knew its effects at college upon the students, when the faculty had to get a certificate from a physician that it was injurious, to prevent them

from using it.' Many other statements, on this point, can be given, but it is deemed wholly unnecessary. The above, and other statements even stronger, can be verified by affidavits."

When it was announced in the Boston papers that Drs. Jackson and Morton claimed this discovery, the citizens of Hartford were taken by surprise, for it was well known here that I had put in practice the same more than two years before, and not only this, but it was generally known that I had long since made a journey to Boston exclusively on this business, in order to present it to the medical faculty. Dr. P. W. Ellsworth, a son of the Hon. W. W. Ellsworth, Ex-Governor of Connecticut, who was acquainted with the circumstances above mentioned, immediately published an article in the Boston Medical and Surgical Journal, stating those facts that came under his personal observation—which accord perfectly with what I have already stated. Dr. E. E. Marcy, of this city, also published an article in the Journal of Commerce about the same time, stating that he was knowing to my making the discovery, and going to Boston in 1844, when I had an interview with Dr. Jackson, who said that he did not believe that surgical operations could be performed without pain, when I informed him of the discovery I had made. Dr. Marcy quoted Dr. Jackson's language to me, and in his (Jackson's) reply, he does not deny that I had this interview with him, but simply says that he did not use the *words* which are credited to him in the quotation marks. He does not deny but that the substance of those words were said by him!; and, furthermore, he cannot deny this.

This letter of Dr. Jackson, in reply to Dr. Marcy, requires still further notice. He says that he had merely

heard that I had tried some experiments with nitrous oxide gas, but had never heard that they were successful. Now I am fully persuaded that Dr. Jackson does not remember the circumstance of his being informed and assured in November, 1844, that my operations were uniformly successful, with but one or two exceptions; but such was the case, and the individual who informed him of this fact will make the statement under oath, if necessary. Dr. Jackson was then informed that I had operated on twelve or fifteen patients by the use of nitrous oxide gas, without causing the least pain, in but two instances.

Dr. Jackson claims that the nitrous oxide gas and the vapor of ether are essentially different in their effects when inhaled. He asserts, in this letter, that sulphuric ether, as it is used in Boston, does not act as a stimulant, but has the reverse effect. In reply to this statement, Dr. Marcy quotes an article from the Boston Medical and Surgical Journal, where Dr. J. C. Warren, of the Hospital, in his report, proves that ether, as given in Boston, acts as a stimulant; but in order to prove, even to the satisfaction of Dr. Jackson himself, that he was mistaken, I will quote his own language, from an article published in the Boston Advertiser, of March 3, 1847. He says:

“We are aware that ether ranks in the pharmaceutic books and dispensaries, as a diffusible stimulant, and that its fumes or vapor produce intoxication of short duration.”

The fact is, that nitrous oxide gas and the vapor of ether, are identical in their effects; first exhilarating, then, when continued to excess, the reverse effect follows, acting as a sedative, throwing the person into a deep sleep or stupor.

This discovery does not consist in the use of any one specific gas or vapor, for anything which will cause a certain degree of nervous excitement, is all that is required to render the system insensible to pain; consequently, the only question to be settled is, which exhilarating agent is least likely to do harm? I have confined myself to the use of nitrous oxide gas, because I became fully satisfied, from the first, that it is less injurious to the system than ether. In the fall of 1844, after I had tried several experiments with nitrous oxide gas with perfect success,—then wishing to use a substitute which would be attended with less trouble in its preparation,—I advised with Dr. E. E. Marcy, of this city, at which time we discussed the comparative merits of nitrous oxide gas and rectified sulphuric ether. Knowing that both had the same effects upon the system, so far as causing insensibility to pain was concerned, the object of the discussion was to ascertain which would do least harm. I had, previous to this, inhaled ether, as well as nitrous oxide gas, and found their effects upon the nervous system to be precisely the same; but I found it very difficult to inhale the vapor of ether in consequence of the choking sensation. For this reason, and for the reason that Dr. Marcy and myself came to the conclusion that nitrous oxide gas was not so liable to do injury, I resolved to adhere to this alone. Let it be observed, however, that at this time, (November, 1844,) while we had the subject under consideration, a surgical operation was performed at Dr. Marcy's office, under the influence of sulphuric ether, as is proved by affidavit. The Doctor then advised me, by all means, to continue the use of nitrous oxide gas.

If the question is asked, why so much time has elapsed since its first discovery, without its coming into more

general use, I can only say, that I have used my utmost endeavors, from the first, to influence physicians and surgeons to make a trial of it, assuring them that my operations were numerous, and perfectly successful. But all were fearful of doing some serious injury with it; and not wishing to incur the responsibility of administering this powerful agent without the co-operation of the medical faculty, and also for the reason that I was obliged to relinquish my professional business in consequence of ill health, my operations have been somewhat limited.

On making the discovery, I was so much elated respecting it, that I expended my money freely, and devoted my whole time for several weeks, in order to present it to those who were best qualified to investigate and decide upon its merits, not asking or expecting any thing for my services, well assured that it was a valuable discovery. I was desirous that it should be as free as the air we breathe; but judge of my surprise, after the lapse of many months, when I was informed that two individuals (Drs. Jackson and Morton) had claimed the discovery, and had made application for a patent in their own names.

After making the above statement, and submitting the following testimonials and affidavits, I leave it for the public to decide to whom belongs the credit of this discovery.

Respectfully,

HORACE WELLS.

TESTIMONY.

Boston, March 23, 1847.

We, the undersigned, residents of Boston, Mass., testify, that in the fall of the year 1844, while attending lectures given by Dr. J. C. Warren, of the Massachusetts General Hospital, the students were informed by Dr. Warren, at the close of his lecture, that Mr. Wells, of Connecticut, was present, and would address them upon the subject of rendering the system insensible to pain, during the performance of surgical operations, by the inhalation of exhilarating gas. The students accordingly retired to an adjoining room, where we were addressed upon this subject by Mr. Horace Wells, of Hartford, Conn., who invited us to meet in the evening to witness an operation, which operation was performed in our presence, while the patient was under the influence of the gas.

THOMAS WM. KENNEDY, M. D.,

Office corner of North Charles and Livingston Streets, Boston.

P. B. MIGNAULT, M. D.

City of Boston: On this 23d day of March, A. D. 1847, the above-named Thomas J. W. Kennnedy, M. D., and P. B. Mignault, M. D., personally appeared before me, the subscriber, Mayor of the city of Boston, and made oath that the above certificate, by them subscribed, is true.

XXXX
L.S.
XXXX

In testimony whereof I subscribed the same and caused the city seal to be hereunto affixed, the day and year last within written.

JOSIAH QUINCY,

Mayor of the city of Boston, Justice of the Peace.

Hartford, March 26th, 1847.

I, the undersigned, resident of Hartford, Connecticut, testify, that, in the fall of the year 1844, while attending medical lectures, given by Dr. John C. Warren, of the Massachusetts General Hospital, the students were informed by Dr. Warren, at the close of his lecture, that Mr. Wells, of Connecticut, was present, and would address them upon the subject of rendering the system insensible to pain during the performance of surgical operations, by the inhalation of exhilarating gas. The students accordingly retired to an adjoining room, where we were addressed upon this subject by Mr. Horace Wells, of Hartford, Connecticut, who invited us to meet in the evening to witness an operation, which operation was performed in our presence, while the patient was under the influence of the gas.

CINCINNATUS A. TAFT, M. D.

STATE OF CONNECTICUT,

Hartford County, ss :

City of Hartford, March 27, 1847.

Then personally appeared before me, Cincinnatus A. Taft, who signed the foregoing affidavit, and made solemn oath that the same was true.

XXXXX
L.S.
XXXXX

Given under my hand and the seal of said city.

A. M. COLLINS, Mayor.

Boston, March 23, 1847.

I hereby certify, that the following gentlemen attended my Lectures on Anatomy and Surgery in the season of 1844-45, viz : Thomas Wm. Kennedy, P. B. Mignault, and Cincinnatus A. Taft.

JOHN C. WARREN,

Professor of Anatomy and Surgery.





Boston, March 23d, 1847.

I do hereby testify that Horace Wells, of Hartford, Connecticut, with whom I have been acquainted for several years, came to Boston in the year 1844, (I think in November or December,) and informed me that he had made a valuable discovery, which enabled him and others to perform surgical operations without pain. He then informed me of the result of his experiments, which he assured me were numerous, and perfectly successful. I accompanied him to a hall in Washington street, where a large number of medical students had assembled, as I understood, to witness an operation to be performed by Dr. H. Wells, upon a patient while under the influence of exhilarating gas, which was the discovery above referred to. The gas was administered, and the tooth extracted under its influence by the said Wells, in presence of myself and many others. I am not able to say whether the patient experienced any pain or not. There was certainly no manifestation of it, yet some present expressed themselves in the belief that it was an imposition.

I was subsequently informed that his operations in Hartford, prior to 1845, were uniformly successful under the influence of gas.

DANIEL T. CURTIS,
No. 23 Bedford street.

City of Boston: On the twenty-third day of March, A. D. 1847, the above-named Daniel T. Curtis, personally appeared before me, the subscriber, Mayor of Boston, and made oath, that the foregoing certificate, by him subscribed, is true.

 In testimony whereof I have subscribed the same,
 L.S.  and caused the city seal to be hereunto
 affixed, the day and year last above written.

JOSIAH QUINCY,

Mayor of the city of Boston, Justice of the Peace.

I hereby certify, that Horace Wells, dentist, has, for more than two years, had the reputation, in this city, of

having made a discovery which enabled him, and others, to extract teeth without pain, by the use of exhilarating gas. I have conversed with several gentlemen, whose reputation for honor and veracity places them above suspicion, who have had these operations performed by the said Wells, in the fall of 1844; and they assure me that the operation was attended with no pain whatever. There is no doubt in my mind that said Wells discovered and made the first practical application of this principle in surgical operations. By comparing dates of the several claimants, there can remain no doubt of this fact.

S. FULLER, M. D.

Hartford, March 25th, 1847.

Hartford, March 25, 1847.

As attempts have been made to deprive Mr. Horace Wells, dentist, of the honor of discovering the effects produced by certain gases in allaying pain, I feel it my duty to state the facts in the case. Dr. Jackson does not claim an earlier discovery than the latter part of 1846, and even then only suggested to Mr. Morton that ether might answer the purpose, and says that the first trials of Morton were successful, "proving exactly as I had predicted." The first trial of Morton, according to his own (Morton's) statement, was on the 30th Sept., 1846. Now, I hereby declare, that to my full knowledge, nitrous oxide gas was administered two years earlier than this, viz., in 1844, by Mr. Wells, and that many teeth were extracted without pain under its influence; and that Mr. Wells went to Boston at that time, as I was then informed, for the purpose of introducing the gas to the attention of surgeons in that city. Moreover, in an article published June 18th, 1845, in the Boston Medical and Surgical Journal, I referred to it as a thing well known and established—the article being headed, "On the Modus Operandi of Medicine," written to show that many, if not all, local diseases, are cured by specific stimulants. Now, when it is known that Mr. Morton was instructed in his profession by Mr. Wells, and introduced into business by him, we can easily

trace the manner in which Mr. M. *might* have derived his information. It is to be borne in mind, also, that Jackson and Morton have, through the public prints, each denied the other his claim—a thing easily settled, one would think, if it in justice belonged to either. In my own mind, there is not a shadow of doubt that the whole merit of the discovery of this thing rests with Wells, and with him alone, although others may have experimented with ether before him. The idea and its practical application *are his*, and let the public concede that to him which his generosity, unrestricted with patents, demands and which has been, as far as possible, wrested from him. The claimants in Boston I do not know, and should be unwilling, in any manner, to injure their feelings, but I must say that they are laboring under an hallucination at least; though I cannot but hope they may be able to establish some claim to originality—a task somewhat difficult, as the case appears to stand. These statements are given, not from any personal considerations, but simply as an act of justice; and I hope that the profession, after due deliberation, will give a righteous award.

P. W. ELLSWORTH, M. D.

I take pleasure in certifying, that more than two years since, at the request of Horace Wells, Esq., of this city, I visited his rooms for the purpose of witnessing the extraction of a tooth from a man, while under the influence of the nitrous oxide gas. The idea was novel to me, and I took occasion to be present during the operation. The gas was administered by Mr. Wells, and the operation performed without any apparent suffering on the part of the individual operated upon. I afterwards questioned him in regard to his sensations during the extraction, and he assured me that he had not experienced the slightest degree of pain. At this time, the comparative merits of the gas and of rectified sulphuric ether vapor, were discussed, and I gave it as my opinion, that the nitrous oxide gas was the safest, inasmuch as the after-effects of this gas are not so

unpleasant as from the ether vapor. I also take this occasion to assert, from my positive knowledge, that the ether vapor was administered very soon after this period (and prior to 1845,) for the performance of a surgical operation.

In conclusion, I beg leave to offer it as my opinion, *that the man who first discovered the fact that the inhalation of a gaseous substance would render the body insensible to pain, during surgical operations, should be entitled to all the credit or emolument which may accrue from the use of any substances of this nature.* This is the *principle*—this is the *fact*—this is the *discovery*. The mere substitution of ether vapor, or any other article, for the gas, no more entitles one to the claim of a *discovery* than the substitution of coal for wood in generating steam, would entitle one to be called the discoverer of the powers of steam.

E. E. MARCY, M. D.

Hartford, March 27th, 1847.

STATE OF CONNECTICUT,
Hartford County, ss :

City of Hartford, March 27, 1847.

Personally appeared E. E. Marcy, Physician and Surgeon, resident in this city, and made solemn oath to the truth of the foregoing affidavit by him subscribed before me.



Given under my hand and the seal of said city,
the day and year aforesaid.

A. M. COLLINS, Mayor.

THIS IS TO CERTIFY, That during the last two or three years, I have been familiar with the successful operations of Mr. Horace Wells, and other dentists of this city, in extracting teeth, without pain, by the aid of nitrous oxide gas, and he, alone, was regarded as the author of this discovery.

G. B. HAWLEY, M. D.

Hartford, March 27th, 1847.

I, John M. Riggs, surgeon dentist, of the city and county of Hartford, State of Connecticut, in the United States of America, being of lawful age, and duly sworn, do depose and say :

That on or about the first of November, Anno Domini one thousand eight hundred and forty-four, I was consulted by Horace Wells, surgeon dentist, of the city, county and state as aforesaid, as to the practicability of administering nitrous oxide gas prior to the performance of dental or surgical operations.

Thinking favorably of the suggestion, it was decided to make trial of the gas in question ; and on the day following, per agreement, the protoxide of nitrogen was administered to Horace Wells, aforesaid, at his request, and I extracted one of his superior molar teeth : he manifesting no signs of suffering, and stating that he felt no pain during the operation.

Encouraged, and gratified with the success of the first experiment, the aforesaid Wells and myself continued to administer to various individuals the said gas, and to extract teeth while under its influence, in the presence of several gentlemen, until fully satisfied of its usefulness and applicability in surgical operations. I further affirm that the said Wells avowed his intention to communicate the discovery to the dental and medical faculty, and, in pursuance of that intention, proceeded to the city of Boston, State of Massachusetts, for that purpose ; whilst I continued to use the said gas with great success—the patients assuring me they felt no pain.

JOHN M. RIGGS.

STATE OF CONNECTICUT,
Hartford County, ss :

City of Hartford, March 27, 1847.

Personally appeared John M. Riggs, and made solemn oath to the truth of the foregoing affidavit, by him subscribed before me. Given under my hand, and the seal of said city, the day and year above written.

XXXX
L S
XXXX

Given under my hand and the seal of said city.
A. M. COLLINS, Mayor.

I, the undersigned, resident of Hartford, Connecticut, do hereby testify, that, more than two years since, I submitted to the operation of having a tooth extracted while under the influence of nitrous oxide gas. According to the best of my recollection, this was in the month of November, 1844. The gas was given, and the tooth extracted by Horace Wells, dentist, of Hartford; and I do further testify that the operation was attended with no pain whatever.

MYLO LEE.

STATE OF CONNECTICUT,
Hartford County, ss

City of Hartford, March 26, 1847.

Then personally appeared before me, Mylo Lee, signer of the foregoing affidavit, and made solemn oath that the same was true.

⌘⌘⌘⌘
⌘I.S.⌘
⌘⌘⌘⌘

Given under my hand, and the seal of said city.
A. M. COLLINS, Mayor.

—

During the winter of 1844, I learned that Dr. H. Wells, dentist, Hartford, Conn., had discovered the mode of extracting teeth *without pain*. This was accomplished by administering to the persons operated upon exhilarating gas or vapor, which, it was asserted, rendered the human system insensible to pain. At first I was incredulous of the fact, and received the assertions of individuals familiar with the operation with a degree of distrust. Being, however, by invitation, a personal witness of the process of extracting teeth without pain, under this new mode, discovered and practiced by Dr. Wells with so much apparent success, I was induced to submit to a personal operation, that I might test its utility. The Dr. was most successful—extracting for me a large, firmly-set bicuspid tooth, without the slightest sensation of pain.

I also witnessed, soon after, a repetition of the same

process, by Dr. Wells, upon several individuals, accompanied, in every instance, with perfect success.

F. C. GOODRICH.

Hartford, March 27, 1847.

STATE OF CONNECTICUT,

Hartford County, ss :

City of Hartford, March 27, 1847.

Then personally appeared before me, F. C. Goodrich, of this city, who signed the foregoing affidavit, and made solemn oath that the same was true.

⊗⊗⊗⊗
⊗L.S.⊗
⊗⊗⊗⊗

Given under my hand and the seal of said City.

A. M. COLLINS, Mayor.

Hartford, March 26, 1847.

I hereby testify, that, more than two years prior to this date, on being informed that Horace Wells, dentist, of this city, had made a valuable discovery, by which means he could extract teeth without pain to the patient, which consisted in the use of stimulating gas, or vapor, I inhaled the exhilarating gas, and, under its influence, had six extracted without the least pain. I would further state, that for more than eighteen months from the time I first submitted to this operation by the application of gas, I heard no other name mentioned as the discoverer, except that of the above-named Horace Wells.

J. GAYLORD WELLS,

184½ Main street.

STATE OF CONNECTICUT,

Hartford County, ss :

City of Hartford, March 26, 1847.

Then personally appeared before me J. Gaylord Wells, of this city, who signed the within deposition, and made solemn oath that the same was true.

⊗⊗⊗⊗
⊗L.S.⊗
⊗⊗⊗⊗

Given under my hand, and the seal of said city.

A. M. COLLINS, Mayor.

A little more than two years since, I learned that Dr. H. Wells, dentist, of this city, had made the discovery that by the use of an exhilarating gas or vapor, he could render

the nervous system insensible to pain under severe surgical operations, and that he was using it in his practice with success. Having an opportunity to witness its effect upon several persons, during the operation of extracting teeth, I was so delighted and surprised with its manifest success, that I desired a trial of it upon myself. The gas was accordingly administered, and two carious teeth were extracted from my lower jaw, without the *least suffering* on my part; though ordinarily, owing to the firmness with which my teeth are fixed in my jaw, I suffer extreme pain from their extraction.

WM. H. BURLEIGH,
Editor of the "Charter Oak."

Hartford, March 25, 1847.

STATE OF CONNECTICUT,
Hartford County, ss :

City of Hartford, March 26, 1847.

Then personally appeared before me, William H. Burleigh, signer of the foregoing affidavit, and made solemn affirmation that the same is true.

XXXX
XLS.X
XXXX

Given under my hand and the seal of said city.
A. M. COLLINS, Mayor.

TO WHOMSOEVER IT MAY CONCERN :

We, the undersigned, physicians of the city of Hartford State of Connecticut, U. S. A., do hereby certify, that we know, and have conversed with the persons whose names are appended to the above affidavits, viz., Wm. H. Burleigh, J. G. Wells, F. C. Goodrich, Mylo Lee, and place implicit reliance upon the statements made therein, by each of them, to wit: that the operation of extracting one or more teeth without producing any pain, whatever, was performed upon each of them, by Horace Wells, surgeon dentist, of this city, at or about the time specified by them respectively, in their several affidavits above referred to.

We take pleasure, also, in expressing our entire confidence in the integrity of the said Horace Wells, than whom

no person in our city is more favorably known, as a gentleman of honor and integrity. We know, moreover, that he has for several years past successfully devoted himself to subjects pertaining to invention and discovery.

S. FULLER, M. D.	DAVID S. DODGE, M. D.
GEORGE SUMNER, M. D.	P. W. ELLSWORTH, M. D.
BENJ. ROGERS, M. D.	GURDON W. RUSSELL, M. D.
J. B. BERESFORD, M. D.	G. B. HAWLEY, M. D.
H. ALLEN GRANT, M. D.	E. K. HUNT, M. D.
WM. JAMES BARRY, M. D.	DAVID CRARY, M. D.
E. E. MARCY, M. D.	JOHN SCHUE, M. D.
C. A. TAFT, M. D.	HENRY LEE, M. D.

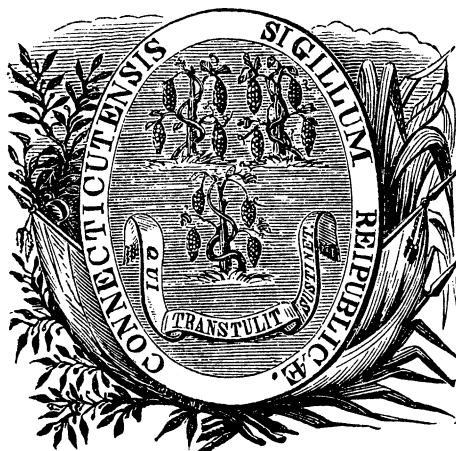
I certify that the foregoing document is subscribed by the principal surgeons and physicians of the city of Hartford, in the State of Connecticut, U. S. A.

ISAAC TOUCEY.

Hartford, March 29th, 1847.

STATE OF CONNECTICUT, ss:

Office of Secretary of State.



I hereby certify, that his Excellency Isaac Toucey, (whose name, in his own handwriting, is subscribed to the foregoing certificate,) is Governor in and over the State aforesaid.

In testimony whereof, I have hereunto set my hand and affixed the seal of said State, at Hartford, this 29th day

of March, A. D. 1847, and in the 71st year of the Independence of the United States of America.

CHARLES WM. BRADLEY,

Secretary of State.

A TREATISE
ON
ETHERIZATION IN CHILDREN

Property of



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FIVE HUNDRED AND EIGHTY-ONE CASES.

BY WALTER CHANNING, M.D.

PROFESSOR OF MIDWIFERY AND MEDICAL JURISPRUDENCE IN THE UNIVERSITY
AT CAMBRIDGE.

“Give me the facts, said my Lord Judge: your reasonings are the mere guess-
work of the imagination.” — OLD PLAY.



BOSTON:
WILLIAM D. TICKNOR AND COMPANY,
CORNER OF WASHINGTON AND SCHOOL STREETS.
M.DCCC.XLVIII.

It will be seen, in my first extract from Professor Meigs's reply to Professor Simpson, that reference is made to a work by Professor Warren, of Boston, on "Etherization," which speaks of his reserve as to its employment in midwifery, and of the freer use made of it by Dr. Homans and Dr. Channing, of Boston. In my very first effort to obtain facts from my professional brethren respecting etherization in childbirth, and I believe before Professor Warren's book was published, I addressed a copy of my circular to him; feeling particularly anxious to obtain a precise statement both of facts and opinions concerning the employment of etherization, in this application of it, derived directly from his own observations of its effects in midwifery. I was the more desirous to obtain this information from this source, as Professor Warren was among the first to use etherization in important operations in surgery, of which midwifery is a department, and because of the weight of his opinions with the community in which he lives, and abroad. I have not received his reply; but my impression is, that his remarks were intended as a lesson of caution, and not as the results of actual experience.

From Professor Meigs, almost by return of mail, I received the following reply to my letter. It is written in a spirit of so much kindness, so much courtesy, — is expressive of an interest so deep in the important and the true, — of so hearty a love of science, that I cannot withhold this public expression of my thanks to its honored author. As a mere matter of taste, it may be questioned if somewhat of that which is especially personal to myself might not have been left out of the print. But I prefer to publish the letter just as it is, and to take the chances with my reader concerning other and purely inferential matters.

"Philadelphia, April 26, 1848.

"Dear Sir, — I feel much honored by your letter of the 21st instant, covering certain interrogatories relative to the use of anæsthetic agents

in midwifery; and I beg you to accept my sincere thanks for the attention.

"I believe I have read all the articles, within my reach, that have appeared upon the anæsthetic practice; and I misconceive of my own motives, if the hesitation which hitherto has prevented me from employing either chloroform or ether arises from any other than a conscientious scruple as to the administration of remedial agents, that I do not deem it indispensably necessary to employ. I have as yet met with no such case, and have therefore remained an interested observer of what my brethren have deemed it expedient, and certain of them indispensable, to do in the matter. I am therefore incapable of answering your interrogatories; being without any clinical experience in the case.

"Seeing that so many thousands of persons have taken, and do daily take, advantage of the insensibility produced by etherization, to avoid the pain of surgical operations, one might well charge me with being cautious overmuch in so long refraining from adopting the remedy in my own practice; but it seemed to me, that the motives set forth for my recusancy, in a published letter to Professor Simpson, ought to be of weight sufficient to determine my action in the premises. The results thus far attained, although they are doubtless beneficent in most cases, are nevertheless mixed up with elements of distrust, as to the permanency of present opinions and indications of practice, so considerable, that I am most anxious to have a candid exposition of the motive for or against it; comprising an amount of intelligence, drawn from different sources, sufficient to lead the body of the profession to clear views of duty upon the point.

"I hold myself in readiness to yield to conviction upon sufficient evidence of the necessity and propriety of etherization in midwifery; but I beg leave to say, that this is a case in which I should hardly yield my opinions to the force of statistical returns, because I have no doubt of some physiological and therefore needful and useful connection of the pain and the powers of parturition, the inconveniences of which are really less considerable than has by some been supposed. If I am not here in error, I submit that no statistics ought to have a real power to convince. There are a few of my brethren here who have exhibited chloroform or ether in their obstetric cases. The instances are not numerous. Dr. Hodge and Dr. Huston, who enjoy a large share of the public confidence as obstetricians, tell me they have not yet resorted to the anæsthesia, nor do they at present feel inclined to do so. Perhaps, sir, when the volume you are preparing for the press shall have appeared, and we shall have become masters of the results obtained and collected by you, we may all give our adhesion to the recommendation. I shall take great pleasure in studying your work with care, as soon as I can get it from the booksellers.

"I have to-day received Ed. Wm. Murphy's pamphlet, which he was so good as to send me by the 'Acadia.' Dr. Murphy gives us accounts of *seven* cases, five of which were under his own observation. I cannot say, that any influence has been produced upon my mind, to change my purpose, by reading Dr. Murphy's cases and observations. In the seventh case particularly, I do not perceive any good fruits of the administration. The success was extraordinary, but can by no means be attributed to the chloroform.

"It is obviously, my dear sir, so much more agreeable to say yes than to say no to any honorable invitation, and it is so clear that you have many distinguished names to sustain the practice now common in Boston, that I could almost feel ashamed not to be on your side also; but if, after reading your forthcoming work, I shall find all my objections swept away by the power of truth, I shall hasten to confess my conversion, and my obligation to you. It is certain, that those who establish great practical truths, that are efficient in meliorating man's condition, are deserving of all honor and commendation.

"The motives that govern me thus far are connected with, or rather dependent upon, my views of the nature and offices of different parts of the brain. If you will do me the favor to look over Mons. Flourens's pamphlet, a copy of which I beg you to accept, you will perhaps see the course of my reasoning against etherization in obstetrics.

"We both seek the truth. I hope that you may find and establish it. In the meantime, I rest, with the greatest respect and esteem, your most obliged and very faithful servant,

"CH. D. MEIGS."

"Professor Channing."

It will be perceived, that the objection of Professor Meigs is wholly and purely physiological. Etherization being given, this objection demands for its removal the law of succession of its action on the several portions of the brain, from the hemispheres to the medulla oblongata, should it happen to reach so far; while it is at the same time obvious, that no such law as this can be ascertained. It is hence an impossible objection, and the true question is whether it should for a moment influence practice. We know not what is the succession of events from the slightest impression made by ether or chloroform on the hemispheres, or upon any intervening point between them and the medulla oblongata. We know not, and cannot know, where safety ends, and danger begins, by any known action of the agent,

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FRANK P. FOSTER, M.D.

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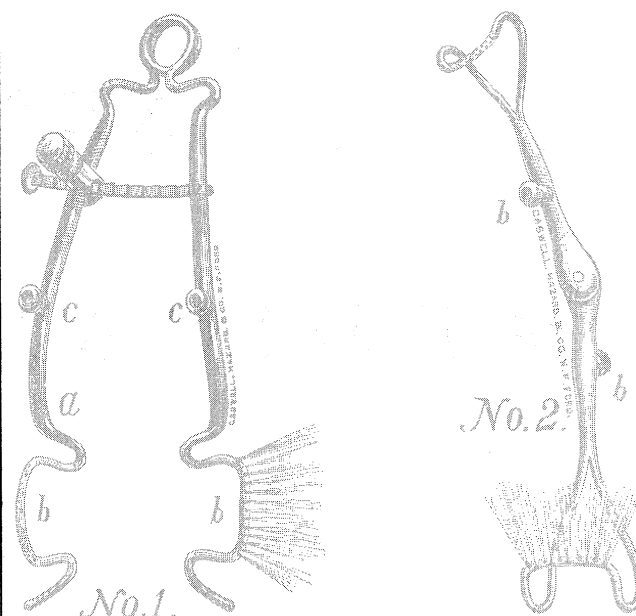
NEW YORK:
D. APPLETON AND COMPANY,
1, 3, AND 5 BOND STREET,
1885.

it to their use. The irrigation will have to be repeated as often as may be indicated by the quantity and quality of the discharge. If there is much swelling of the eyelids, the outer canthus should be cut. The application of cold should not be made with ice-bags. Pledgets of linen—to be burned after use—should be laid on a piece of ice at the bedside, and this application of cold requires care and a constant attendant.

In the severe forms of gonorrhœal conjunctivitis—and this disease is nearly always very severe—when not seen very early and treated at once, the cornea runs great risk. The eyelids are intensely swollen, and when the ocular conjunctiva is much infiltrated the cornea is in great danger of suppuration, and the treatment should be directed to the reduction of the pressure on the eyeball and diminution of the secretion already formed. The pressure caused by the chemosis and swollen lids compresses the vessels which supply the margin of the cornea, causing an insufficient circulation. In order to remove this factor, the outer commissure should be divided to its fullest extent, together with the canthal ligament. The late Mr. Critchett, of London, proposed to divide the upper lid vertically to the orbital margin in severe cases, evert the flap and fix it to the skin above, and he says the cornea does not suppurate when this is done. Fuchs* has modified this operation. He divides the outer commissure to such an extent as to relieve also the symptoms of pressure. He then puts a suture through the lower lid and attaches it on the cheek, ectropionizing it entirely. He detached the suture, in the case he reports, at the end of the fifth day, and the healing was good. If the cornea is involved, it requires special attention in addition to the use of atropine. A thorough removal of the secretion from the upper *cul-de-sac* is not possible by the ordinary means; this may, however, be done by means of a simple instrument which I have devised for the purpose. The instrument is an eye-speculum, the arms of which are hollow and the claw deeper than in the ordinary eye-speculum; it has a number of perforations for the passage of the fluid, which is supplied by a fountain syringe. It is inserted between the lids with great gentleness, and care should be taken not to injure the cornea with it. The lids should be gently lifted from the eyeball by means of the speculum, and the spray of fluid allowed to play upon the upper *cul-de-sac*. Even when the lids are extremely painful, it is a relief to have them gently lifted from the eyeball and the stream of fluid allowed to play upon the upper conjunctival *cul-de-sac*.

Of course the use of this instrument should not be intrusted to an ordinary nurse, but the physician can at least perform the operation twice daily, and keep up the irrigation for from ten to fifteen minutes. The solution of carbolic acid in the case of adults, when the inflammation is intense, may be as strong as three per cent.—to be diluted as the disease improves; this is astringent as well as antiseptic. And the silver I would apply, according to the exigency of the case, in four-per-cent. or twelve-per-cent. solutions, and neutralize with salt and water, and then apply the medicated vaseline to the conjunctiva, and over the lids the iced

cloths. Iodoform has not met with much favor in this disease. Quinine in solution has also been used, but it has no



The instrument shown in Fig. 1 may be used for either eye, the tube with the water-supply being attached at *a*, and to the upper branch only in case it is desired to irrigate the upper *cul-de-sac* alone. Fig. 2 represents a folding lid-elevator (of large and small size) designed for the same purpose as the spring-speculum. The tube of the fountain syringe is attached at *b*.*

advantage over the carbolic acid. Dr. H. Linds Ferguson (Dublin) reports cases of gonorrhœal conjunctivitis in which he has had good results from the use of finely powdered boric acid. The bichloride of mercury has no claim to advantage over the boric acid.

DIPHTHERITIC CONJUNCTIVITIS.—Measures of prophylaxis based upon bacteriology must lie in the future. We must be content with the enforcement of general hygienic laws. Mr. Tweedy† used one-per-cent. solutions of quinine in this disease, and did not see any serious damage to the cornea when it was used. Iodoform does not seem to be of much use in diphtheritic conjunctivitis. Vossius‡ recommends a four-per-cent. solution of salicylic acid in glycerin.

40 WEST TWENTY-FOURTH STREET, NEW YORK.

SPINAL ANÆSTHESIA AND LOCAL MEDICATION OF THE CORD.

By J. LEONARD CORNING, M. D.

It is my desire on this occasion to draw attention to a procedure in therapy which, so far as I am aware, possesses the merit of novelty. The arguments which I shall advance in its favor are twofold in kind: First, I shall cite certain physiological facts with which the procedure in question stands in immediate relationship; and, secondly, I shall endeavor to record conscientiously the actual phenomena evoked by the use of the method itself.

To take up the argument in this order, I would remark, then, that, when a certain quantity of a remedy, say strychnine,

* These instruments are made by Mr. W. F. Ford, of Messrs. Caswell, Hazard & Co.

† London "Lancet," 1882, No. 1.

‡ "Klin. Monatsbl. f. Augenheilk.," Bd. xix, p. 423.

* "Centralblatt f. prakt. Augenheilkunde," 1881, p. 198.

nine, is thrown under the skin of a frog, certain phenomena make their appearance which show indubitably that the functions of the spinal cord are profoundly affected. The animal is thrown into violent convulsions, and assumes a rigid attitude, and we have presented the picture of an artificial tetanus. This is a spectacle of the physiological laboratory, and one with which we are all familiar.

If, now, we remove the posterior arches of three or four of the vertebræ of the animal, and, seizing the membranous coverings of the cord, insert the end of a hypodermic needle so that we are able to inject a small quantity of a solution of strychnine, we shall find, first, that not only are the convulsive phenomena immediately produced, but, secondly, that a smaller quantity of the fluid is required to evoke them than when the drug is placed under the skin at a point remote from the spinal cord.

It was formerly supposed that this phenomenon was due to the direct contact of the strychnine with the nervous elements of the cord, but Harley* has shown that the poison can act only through the intermediation of the blood-vessels, since, when the latter are separated from the cord, the solution remains entirely inert, the convulsions failing to appear.

From the foregoing considerations, it is clear that, in order to obtain the most immediate, direct, and powerful effects upon the cord with a minimum quantity of a medicinal substance, it is by no means necessary to bring the substance into direct contact with the cord; it is not necessary to inject the same beneath the membranes, as in the case of the frog, since the effects are entirely due to the absorption of the fluid by the minute vessels. On the other hand, in order to obtain these local effects, it is first necessary to inject the solution in the vicinity of the cord, and, secondly, to select such a spot as will insure the most direct possible entry of the fluid into the circulation about the cord. Is there in man a locality which fulfills these conditions? Instead of answering this question at once, I will rather detail some recent experiments performed by myself, by means of which, I trust, all doubts on the subject will be effectually set at rest.

PROTOCOL OF EXPERIMENTS.—Some time since I began a series of experiments with a view to determining whether the local medication (anæsthetization) of the spinal cord was within the range of practical achievement. The drug made use of was the hydrochlorate of cocaine. As the introduction of a hypodermic needle beneath the membranes of the medulla spinalis is not practicable without removal of the arches of the vertebræ (on account of the danger of wounding the cord), I decided to inject the anæsthetic between the spinous processes of the lower dorsal vertebræ. I was led to resort to this expedient from a knowledge of the fact that in the human subject numerous small veins (*venæ spinosæ*) run down between the spinous processes of the vertebræ, and, entering the spinal canal, join the more considerable vessels of the plexus spinalis interna. From these theoretical considerations I reasoned that it was highly probable that, if the anæsthetic was placed between the

spinous processes of the vertebræ, it (the anæsthetic) would be rapidly absorbed by the minute ramifications of the veins referred to, and, being transported by the blood to the substance of the cord, would give rise to anæsthesia of the sensory and perhaps also of the motor tracts of the same. To be more explicit, I hoped to produce artificially a temporary condition of things analogous in its physiological consequences to the effects observed in transverse myelitis or after total section of the cord. I therefore anticipated a more or less local action of the drug upon the cord. My hopes in this regard were based somewhat upon the well-known lethargy of the circulation in the cord, particularly at its lower portion—a condition of things highly promotive of the local action of the drug.

Experiment I.—This was performed on a young dog. At ten o'clock, A. M., I injected twenty minims of a two-per-cent. solution of the hydrochlorate of cocaine into the space situated between the spinous processes of two of the inferior dorsal vertebræ. Five minutes after the injection there were evidences of marked inco-ordination in the posterior extremities; the dog threw his hind-legs about aimlessly, holding them far apart, much after the manner of some ataxic patients. A few minutes later there was marked evidence of weakness in the hind-legs, but there were no signs whatever of feebleness in the anterior extremities. I now tested the condition of sensibility by means of a powerful faradaic battery, one of the conducting cords of which was attached to a fine wire brush. When the wire brush was applied to the hind-legs, there was no reflex action whatever on the part of the latter, at least such was the case except when the most powerful currents were employed. But, on the other hand, when I applied the wire brush to either of the anterior extremities, the limb was drawn away violently, and the animal set up the most dismal howls. Similar effects were observed on pinching and pricking the limbs.

These phenomena persisted for a considerable length of time, and traces of inco-ordination were observed two hours after the injection had been made. After the lapse of about four hours, however, the dog seemed to have recovered his usual health, and walked about without difficulty.

During the duration of the experiment nothing of an abnormal nature was observed in the fore-legs. I infer from this fact that the action of the anæsthetic was practically local, being confined, for the most part, to that portion of the cord situated immediately beneath the point of injection. It is conceivable, however, that, had the quantity of anæsthetic fluid injected been greater, the anterior limbs might also have been affected. An *absolute* localization of the anæsthesia is indeed hardly within the range of possibilities, on account of the numerous blood-vessels. It is true, nevertheless, as we have seen, that the local action of the drug is greatly favored, at least so far as the inferior segment of the cord is concerned, by reason of the lethargy of the circulation at this point.

Experiment II.—This was performed on a man who had long been a sufferer from spinal weakness and seminal incontinence, and who for many years had been addicted to masturbation and other forms of sexual abuse. Without entering into the details of the case, which are devoid of any special interest, I will proceed at once to give an account of the experimental observation which constitutes its only claim to attention.

As in the case of the dog previously referred to, I was bent upon abolishing reflex action and annulling sensory conduction

* "A Hand-book of Therapeutics," by Sydney Ringer, M. D., New York, 1870, p. 387.

in the cord. To this end I injected thirty minims of a three-per-cent. solution of the hydrochlorate of cocaine into the space situated between the spinous processes of the eleventh and twelfth dorsal vertebra. As there was no numbness, tingling, or other evidence of modified sensibility after the lapse of six or eight minutes, I again injected thirty minims of the solution at the same spot and in the same manner. About ten minutes later the patient complained that his legs "felt sleepy"; and, on making a careful examination with the wire brush, I found that sensibility was greatly impaired. Currents which caused lively sensations of pain and reflex contractions in the upper extremities were disregarded and barely perceived in the lower limbs. The same was true of the prick of a needle. Fifteen or twenty minutes later the anæsthesia had increased in intensity, and, although there were some evidences of diffusion on the part of the anæsthetic, the impairment of sensibility was principally limited to the lower extremities, the lumbar regions, the penis, and the scrotum. About this time I applied the wire brush to the soles of the feet and to the toes, using about the maximum strength of a powerful faradaic battery, without causing either pain or reflex contractions, while a current of half the strength evoked intense pain and reflex contractions in the upper limbs. Some time later I fancied that I could discern some obtuseness of sensibility in the upper limbs; but on this point I feel compelled to speak with reserve. When the patient closed his eyes he experienced some dizziness while standing, but there was no inco-ordination or motor impairment discernible in the gait. The power of distinguishing differences in pressure seemed also to be preserved; but I regret to say that I did not test the sensibility to variations of temperature. The passage of a sound, though usually accompanied by considerable pain, remained almost unperceived, and an urethral electrode caused no inconvenience, even when strong currents were used. The sensibility of the scrotum and glans penis was also impaired to a marked degree, as proved by repeated tests with the electric brush. The pupils were but slightly dilated.

When the patient left my office, an hour or more after the injections, sensibility was still impaired to a marked degree, but otherwise he seemed none the worse for his experience. The patellar tendon reflexes were, however, abolished.

The therapeutic advantages afforded by such local medication would seem to be great in a large number of morbid conditions of the cord. There is, indeed, no reason why strychnine and other remedies should not be employed in this local manner as well as cocaine. In strychnine poisoning, tetanus, and hydrophobia, it should also render good service. I will merely add that on the morning succeeding the injections the patient informed me that he had experienced tingling sensations and numbness in the lower limbs until nightfall. There was also dryness of the throat and mouth, accompanied by mental exhilaration. I could hear nothing of any cardiac disturbances.

On making an examination with the electric brush, sensibility was found to be normal in the lower limbs, scrotum, and glans penis. The passage of the sound was, as formerly, accompanied by some pain, and the urethral electrode provoked unpleasant sensations, even when mild currents were employed.

The only constitutional symptoms complained of were headache and slight vertigo, already referred to. At no time was there nausea.

Whether the method will ever find an application as a

substitute for etherization in genito-urinary or other branches of surgery, further experience alone can show. Be the destiny of the observation what it may, it has seemed to me, on the whole, worth recording.

26 WEST FORTY-SEVENTH STREET, October 27, 1885.

SEASICKNESS AND ITS TREATMENT.

By ADOLPH KESSLER, M. D.,

NEW YORK.

In the "New York Medical Journal" of September 20th I find a therapeutical note, taken from the "Berlin. klin. Wochenschrift" and "Lancet," in which Manassein recommends the use of cocaine in seasickness, and speaks of the gratifying results obtained in several cases. Unaware of the fact that it had been recommended and used in seasickness, I gave it a pretty extensive trial this summer, merely prompted by its general physiological and anæsthetic effects, but with results far from gratifying. It does not act as a palliative, much less as a curative; on the contrary, its use does actual harm. The effect of cocaine upon seasickness, as a combination of the most varied bodily and mental sensations, is purely negative, except for a decided increase and aggravation of certain symptoms. The most striking effect of the medicine is an intense and persistent nausea, which becomes the more distressing as all efforts, mechanical or otherwise, of obtaining relief by vomiting prove unavailing. Now, any one that has ever suffered the pangs of seasickness will agree with me that this very nausea, *unrelieved by vomiting*, forms the most distressing and depressing feature of the mysterious disorder, and that the act of vomiting is the only efficacious means by which temporary relief is afforded and comparative physical and mental comfort restored to the sufferer.

The cocaine seems to exercise a paralyzing influence upon the motor-nerve apparatus of the stomach, thereby hindering vomition and preventing the display of the only function which is apt to give any relief, and which nature itself has beneficently instituted as a *vis medicatrix*. This characteristic and uncomfortable condition is further aggravated by a total loss of appetite and an invincible repugnance to food in every form and shape—an inertia of the digestive organs, in fact, that is very rarely experienced in ordinary and even severe yet uncomplicated cases of seasickness. But the influence of the drug does not stop here; it reaches further yet and extends to the whole length of the alimentary tract, giving rise to great torpidity of the intestines; defecation becomes almost impossible without artificial measures, and is even then slow, difficult, and painful, and reacting unfavorably upon the entire system.

However favorably cocaine might affect the nervous system, intellect, and mind, under ordinary circumstances when taken on land, I have certainly failed to notice its brightening and inspiring effects during the reign of seasickness, except that it sharpened the pangs of the latter by keeping the suffering victims wide awake and unable to find rest and oblivion in sleep.

The bromides have enjoyed a certain reputation in the treatment of seasickness since the late and lamented

HEART IRREGULARITIES, RESULTING FROM THE INHALATION OF LOW PERCENTAGES OF CHLOROFORM VAPOUR, AND THEIR RELATIONSHIP TO VENTRICULAR FIBRILLATION.

BY A. GOODMAN LEVY AND THOMAS LEWIS.*

(From University College Hospital Medical School).

Introduction.

THE following research was undertaken with a view to the further elucidation of certain cardiac phenomena, originally observed by one of us in connection with the administration of low percentages of chloroform to cats, and described in the form of a preliminary communication to the Physiological Society.¹ In this paper a peculiar form of blood pressure curve was described, which is characterised by rapid heart action, high or medium blood pressure, and certain fluctuations and irregularities which are made evident by reason of the inertia of the mercury column in the Ludwig's manometer. This peculiar form of curve was found to occur quite commonly under chloroform administered at a lower percentage strength than 1 per cent., or thereabouts; and it is necessary to emphasise the point that it was obtained with great frequency in animals which had not had a large initial dose of the anæsthetic, and that it was not seen when the animals were under the full influence of the chloroform; it may be added, in confirmation of its frequent incidence, that it was readily obtained in the five experiments which form the basis of the present paper.

The significance of this irregularity was deduced from its uniform appearance immediately before the occurrence of heart failure as a result of fibrillation of the ventricles, a condition which was shown to occur in certain isolated instances in the course of a series of experiments carried out in another investigation upon cats under the influence of chloroform. Certain other irregularities, characterised by a regular intermission of the heart beat, were also frequently observed and appeared to be conditioned by the administration of a somewhat less rarified proportion of vapour.

It was further demonstrated that fibrillation of the ventricles could be induced in a large proportion of cases by the intravenous injection, under light chloroform anæsthesia, of small doses of adrenalin chloride, a drug which does not have a like effect under full chloroform anæsthesia or under any other ordinary experimental conditions; and that, when the cardiac

* Working under the tenure of a Beit Memorial Research Fellowship.

tracing was regular in the period preceding the injection, it assumed a form of irregularity before the onset of fibrillation, which was apparently similar to that described above as occurring spontaneously.

These observations appeared to us of sufficient importance to call for an investigation which would reveal the precise nature of the several heart mechanisms present under light chloroform anæsthesia.

Method.

Cats were employed exclusively. They were anæsthetised with chloroform regulated in percentage terms by means of an apparatus already fully described by one of us.⁵ A definite and known percentage of chloroform was conveyed by means of a Brodie's pump, through an elastic bag which served to convert the stream from an intermittent into a continuous one, to a funnel completely covering the face of the animal.

A blood pressure curve was taken on a kymograph drum, Hürthle's manometer being employed, with half saturated sodium sulphate solution in the connecting apparatus. Electrocardiographic curves were also obtained from time to time throughout the same experiments. The lead was in each instance from right shoulder to left groin. Two electromagnetic signals working in a single circuit (one writing upon the kymograph drum, the other upon the photographic paper) allowed simultaneous index marks to be recorded, and permitted the identification of the same beats in the Hürthle curve and electrocardiogram.

Intravenous injections of adrenalin chloride, as supplied by Parke, Davies & Co., were employed in the experiments. The dose administered was $\frac{1}{4}$ to 1 minim of the 1 in 1,000 commercial solution, (0.016 to 0.065 milligrammes), this being diluted with twenty times its bulk of normal saline solution previous to injection into the saphenous vein.

The irregularities produced by light chloroform anæsthesia alone.

The sole reference which we have found to irregularities of the heart, of the forms we describe and in experiments on chloroform, is in a paper by McWilliam.⁸ This writer incidentally mentions irregularities, which apparently correspond to the premature beats and bigeminal pulse which are fully discussed in the following paragraphs.

The irregularities of the heart, seen under light chloroform anæsthesia alone, were of varied form; a number of these will be described, and the description will be simplified if the irregularities observed in a single and typical experiment receive detailed attention. Emphasis should nevertheless be laid upon the fact that, from experiment to experiment, the types of irregularity encountered were very constant in form. Irregularity of the heart occurred when the tension of chloroform vapour in the inspired air

varied between .5 and 1.5 per cent. Repeated observation showed a definite relationship between the mechanism of the heart and the degree of anaesthesia. Thus, any animal which had inhaled 0.5 per cent. vapour for a few minutes, presented irregularity of the heart's action, and this was often marked in its degree. Similar irregularities were observed with higher percentages, for example 0.8 to 1 per cent., but as a general rule the degree of irregularity was less marked. Continued inhalation of percentages exceeding 1.5 per cent, usually abolished all irregularity. Short inhalations of 2 per cent. invariably abolished it.

The experiment chosen to exemplify the effects of chloroform upon the undamaged heart is illustrated by the electrocardiograms in Fig. 4. The animal was anaesthetised with 2 per cent. vapour, and during the succeeding ten minutes the strength was reduced in steps to 1 per cent.. The heart beat perfectly regularly on this percentage for five minutes, when the strength was reduced to 0.5 per cent.. A minute or so later the electrocardiogram and Hürthle curve showed marked irregularity. An electrocardiogram taken at this stage presented a tachycardia at the rate of 280 per minute and of the type seen in Fig. 4, VI; the actual curve is not published. The second electrocardiogram was taken approximately five minutes after the inhalation of 0.5 per cent. vapour commenced and is shown in Fig. 4, I. The curve demonstrates a regular bigeminy of the heart, due to premature contractions, such as are obtained on excitation of the apical or left portions of the ventricular musculature. The sequential beats are represented by the usual summits, *P*, *R* and *T*, and each cycle of this form is followed by an anomalous complex of which the first deviation is in the apex-negative, the second in the base-negative direction. The sequential auricular contraction, (*P*) to which there is no ventricular response, falls with the anomalous complex and is readily identified in the curve.

The animal was next placed upon 1 per cent. vapour and after five minutes had elapsed, Fig. 4, II was obtained. The curve shows the regular occurrence of a premature ventricular contraction after each second normal or sequential cycle. It is to be noted that the type of anomalous ventricular complex has changed, but that it is still complicated by the sequential *P* summit which falls at or near its commencement. Fig. 4, III was obtained some five to six minutes later and subsequent to the reduction of the strength of vapour to 0.5 per cent.. The simultaneous Hürthle curve is shown in Fig. 1, and the corresponding beats in the two curves are numbered. A bigeminy is present in that part of the tracing covered by the signal marks, and it is brought about by premature ventricular contractions. The normal cycles (*P*, *R* and *T*) are followed by anomalous complexes and these are alternately of the types seen in Fig. 4, I and II.

A few minutes elapsed and the percentage was changed to 0.8 per cent. ; a little later the heart showed a trigeminy (Fig. 4, IV). Premature contractions are shown in this figure after each second normal cycle. The corresponding ventricular complexes are of a third type, and consist of first

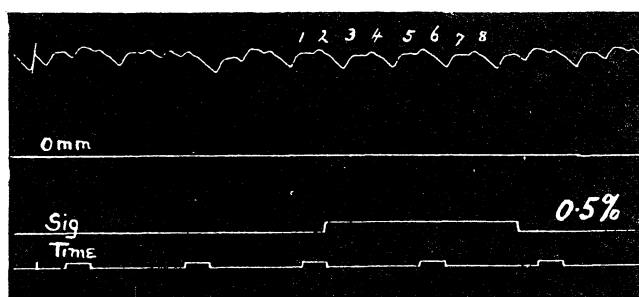


Fig. 1. A Hürthle manometer curve from the carotid of a cat under 0.5 per cent. chloroform vapour. The arterial curve shows an irregularity due to the presence of premature contractions. A portion of the curve, corresponding to the signal, has its beats numbered; the same beats are numbered in the simultaneous electrocardiogram shown in Fig. 4, *III*. The time is in 1.3 sec..

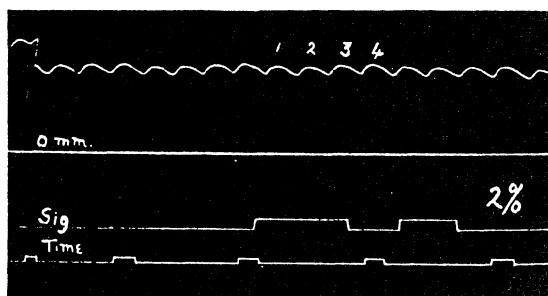


Fig. 2. A Hürthle manometer curve from the same animal, under 2 per cent. chloroform vapour. The arterial pulse curve is regular; the blood pressure has fallen. A portion of the curve corresponding to the signal has its beats numbered; the same beats are numbered in the simultaneous electrocardiogram shown in Fig. 4, *V*. The time is in 1.8 sec..

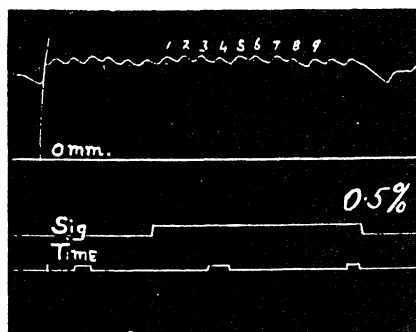


Fig. 3. A Hürthle manometer curve from the same animal, under 0.5 per cent. chloroform vapour. The arterial curve shows a number of rapid and almost regular beats, except towards the end where a pause occurs. Note the high blood pressure as compared to Fig. 2. A portion of the curve corresponding to the signal has its beats numbered; the same beats are numbered in the simultaneous electrocardiogram shown in Fig. 4, *VI*. The time is in 1.8 sec..

tall base-negative summits and secondly apex-negative summits; they conform in type to the anomalous complexes obtained upon stimulation of the basal or right portions of the ventricular musculature.

We need not concern ourselves with the accurate localisation of the origin of these beats; it is sufficient to emphasise the fact that each represents the origin of a ventricular contraction from a separate and fixed point or area, and that while in some curves the irregularity is due to new impulse formation from a single point or area (Fig. 4, *II*), in others two centres are active (Fig. 4, *III*).

The animal was placed upon 2 per cent. vapour and after the lapse of a few minutes the heart became perfectly and continuously regular. The mechanism is shown in Fig. 2 and 4, *V*, curves which were taken simultaneously. It is to be observed that the blood pressure had fallen somewhat with the rise in the percentage of vapour; the heart rate shown in the figure is 122 per minute. At the termination of this observation 0.5 per cent. was again administered and the simultaneous curves shown in Fig. 3 and 4, *VI* were obtained. The mechanism depicted in these figures, or a very similar mechanism, is extremely common upon the lighter percentages, and its analysis is aided by comparison with the other curves taken from the same animals. It consists of a rapid tachycardia of ventricular origin and is composed of beats which are placed at approximately regular intervals. The point of origin of the beats shown in Fig. 4, *VI* is variable and a comparison with Fig. 4, *I*, *II*, and *IV* shows that the new impulses are derived from areas which were previously active. Beats from three or more centres occur in haphazard sequence and follow each other at a rate of 232 per minute; no trace of auricular summits is to be found. It is probable that, with the establishment of the continuous tachycardia, the auricle is responding to ventricle and that the associated electric complexes approach the isoelectric state.

The Hürthle curve corresponding to this electrocardiogram is of peculiar interest, for it is, with the exception of the single long pause towards its termination, a regular and rapid pulse curve, in which the excursion of the several beats is approximately constant. Certainly the slight fluctuations seen are exaggerated when recorded by the mercury manometer, but the tracing as it appears in Fig. 3 might be readily mistaken, in the absence of other evidence, for that of a rapid and regular heart action of normal origin. The electrocardiogram, however, reveals the true nature of the condition; no single beat of sinus origin is present, but the mechanism is constituted by an ectopic rhythm generated in a number of ventricular foci. The importance of this conclusion is more evident when it is remembered that no *a priori* conclusions can be drawn in regard to the innervation of these new centres of impulse production. The approximate regularity of the tachycardia seems to be due to the appearance of a new contraction almost immediately at the cessation of the refractory period of the contraction which precedes it

Transitions between the simpler forms of irregularity shown in Fig. 4, *I-IV* and the tachycardia of Fig. 4, *VI* are common, and a single example which is taken from a separate experiment is shown in Fig. 5, the corresponding Hürthle curves as before being approximately regular. The auricular representatives are easily distinguished throughout the whole of this strip, but only a solitary normal cycle (*P*, *R* and *T*) is present. The premature contractions are coming from a number of separate ventricular foci.

A very curious type of tachycardia has been seen on several occasions and is illustrated by Fig. 6. It is a perfectly regular tachycardia generated from two separate ventricular foci, and the beats from one and the other focus occur alternately and follow each other at a rate of 312 per minute. In the corresponding Hürthle curves, the presence of two types of beat is recognisable only upon the very closest examination. The ventricular complexes of the beats follow each other so rapidly that each appears to start before the completion of the preceding one, and as a result the quick opening phases, some of which are directed upwards and some of which are directed downwards, do not start from the same abscissa. The explanation of the absence of return of the string to the isoelectric position before the occurrence of each new contraction is not apparent.

The effect of small doses of adrenalin upon the heart under the influence of low tensions of chloroform vapour.

In the first instance, it will be convenient to describe the result of injecting adrenalin, when the cat is under the full influence of chloroform; the sequence of events is similar to that described in the following typical experiment. An animal was anæsthetised with chloroform of 2 per cent. strength, which was gradually reduced to 1.5 per cent.. Thirty-one minutes from the commencement of the experiment, the anæsthesia was well established at this percentage; a faint corneal reflex was present, and the heart beat regularly at a rate of 160 per minute; the mean blood pressure was low, namely, 63 mm. Hg.. Under these conditions, 0.065 milligrammes of adrenalin chloride were injected intravenously. Approximately twenty seconds after the injection irregularities commenced to show themselves in the electrocardiogram, the first premature beat being an accompaniment of the rise of blood pressure, which had at this point reached a height of 90 mm.. The premature ventricular contractions became more numerous as the pressure rose to 100 mm. and irregular mechanisms were encountered, which were similar to those previously described as occurring under the influence of light chloroform anæsthesia alone, (cp. Fig. 4, *VI*, and Fig. 5*). The

* The similar mechanisms described by Kahn² were obtained in dogs deeply anæsthetised by a mixture of chloroform and ether. (Communication by letter).

blood pressure having reached a maximum of 120 mm., the heart, 64 seconds from the time of injection, settled down into a regular tachycardia from a single point, probably located in the left or apical portions of the ventricular musculature. One minute later, the blood pressure had fallen to 105 mm., and the heart was beating at a regular rate of 210 per minute, and its mechanism was normal.

When the animal is under low percentages of chloroform vapour, the injection of adrenalin is followed by results which are far more profound than those obtained in animals under the higher percentages. It may be that, when the injection is administered, the heart is presenting the irregularities commonly found under light anæsthesia, or it may be that it is beating regularly; but independently of its initial condition, and provided that the anæsthesia is light, the injection of 0.016 milligrammes or more of adrenalin chloride is followed by the appearance of multiple premature ventricular contractions, and finally the disorder of the mechanism culminates in fibrillation. This sequence of events is exemplified in the following description of the result of a second injection of adrenalin into the same animal, which was the subject of the experiment already recorded.

At the conclusion of the previous observation, the percentage was reduced to 0.5 per cent., and the injection of 0.065 milligrammes of adrenalin chloride was given fourteen minutes later. At the moment of injection the blood pressure was 130 mm. Hg., and the pulse rate 277 per minute, the mechanism of the heart beat being one of alternate beats generated in two separate ventricular foci, and the curves being similar to those shown in Fig. 6. This mechanism continued for seventeen seconds, and at the end of this time, the blood pressure measured 145 mm.. The mechanism of the heart then suddenly changed to one in which beats from a number of foci followed each other at a rate of 230 per minute, and this continued for a period of two seconds, the blood pressure rising abruptly at the same time to 180 mm.. At the conclusion of this period, the ventricles fibrillated.

In another instance in which the same quantity of adrenalin was injected under 0.5 per cent. chloroform, the heart at first beat quite regularly at a rate of 120 per minute, it then passed suddenly into a condition of irregular tachycardia, generated in multiple ventricular foci. This lasted for seventeen seconds and terminated in ventricular fibrillation. The latter part of the tachycardia and its passage into fibrillation is shown in Fig. 7.

As a rule the onset of ventricular fibrillation terminates the experiment, for the ventricles fail to recover from it; but complete recovery from fibrillation lasting three seconds has been seen in one animal. From a number of kymograph tracings in our possession, it is obvious that permanent recovery from well established fibrillation is a rare event in the cat. In the above mentioned instance, a further injection under 0.5 per cent. vapour caused fibrillation, from which there was a temporary recovery, lasting some six seconds, the heart passing again into fibrillation, which, on this occasion, persisted.

When there is recovery from fibrillation, the mechanism at the offset is similar to that seen at the onset; tachycardias of the several forms described are present. The normal sequence is re-established with the administration of higher percentages of chloroform.

Briefly, the irregularities produced by adrenalin in small doses, when the animal is under *high* percentages of chloroform, are of the same nature as the irregularities produced by low percentages of chloroform alone; whilst small doses of adrenalin in the presence of low tensions of chloroform ultimately produce the highest grade of disorder, which is known to effect the ventricle, namely, fibrillation.

The electrocardiographic curve corresponding to ventricular fibrillation has been incidentally referred to by Kahn² and also by Jolly and Ritchie.¹ When the ventricle first passes into so-called fibrillation, its tone is increased, the visible movements are very active, and the oscillations are almost, but not quite, regular at a rate of 400 to 800 per minute. During this stage, a series of conspicuous and slow undulations usually occurs in the record, and this is well seen in Fig. 8. The curve as a whole shows a waxing and waning in the excursion of the oscillations at a rate of about 50-60 cycles per minute. The slow undulations are apparently associated with waves of tone change in the muscle, probably similar to the peristaltic waves spoken of by McWilliam.⁷ This stage of fibrillation, from which recovery is evidently possible in the cat, gradually gives place to a second condition in which the ventricle becomes more distended and in which the slow undulations are absent or inconspicuous, and in which the rapid oscillations occur at a slower rate (300-360 per minute) and in a far more irregular fashion. This mechanism, from which recovery has not been observed, is shown in Fig. 9. Similar appearances were seen by one of us in a series of experiments upon obstruction of the coronary arteries, experiments which frequently terminate in ventricular fibrillation, and similar changes have been noted also where fibrillation has been induced by faradic stimulation. The change from one type of fibrillation curve to the other, therefore, is not confined to experiments under chloroform and adrenalin; further, by whichever of these means fibrillation is induced, it is preceded by tachycardia of ventricular origin.

DISCUSSION.

The hearts of cats, influenced by low tensions of chloroform vapour alone, or by adrenalin in the presence of high percentages of chloroform, exhibit disorders of mechanism of a very definite type. So far as our observations are concerned, the disturbances result purely from the production of new impulses in the ventricles. The nature of these impulses has been fully discussed by one of us in a recent publication,⁶ and the beats have been termed *heterogenetic* on account of the short pauses which precede them and because they do not appear to stand as essential integers in a rhythmic

series of beats. Interpreting the events, in the light of the hypothesis put forward, we may state that the irregularities resulting from chloroform administration, are the outcome of an ever increasing tendency towards the production of heterogenetic beats ; at first isolated and generated from a single foci, these beats subsequently become more numerous, and arise from several foci ; eventually the rhythm of the ventricle is entirely dominated by impulses of this nature, and immediately prior to the onset of the final inco-ordination in the adrenalin experiments, a number of foci are active. Final fibrillation can only be regarded as a further step in the train of events ; it is believed that it results from the activity of a number of new foci of pathological or heterogenetic impulse formation, and that a grade of inco-ordination is produced in the ventricular musculature, such as precludes the output of blood from the organ and brings the circulation to a speedy standstill.

Chloroform in low percentages produces an enhanced irritability of the ventricle, a condition in which there is a widespread discharge of pathological impulses from the musculature, or a condition in which there is a tendency to such discharges. A further interference, such as is brought about by adrenalin injection, is followed by the highest grade of ventricular disorder, *i.e.* fibrillation, and death results. The method in which the adrenalin acts on hearts, whether, for instance, by directly affecting the heart muscle or indirectly through its pressor action, is not a matter which concerns the present investigation, and cannot be discussed here. It is apparent, however, from the foregoing considerations that the heart under low tensions of chloroform vapour may be in a condition which is the immediate antecedent of ventricular fibrillation. This is obviously a matter of important clinical interest in relation to the causation of sudden death under chloroform anæsthesia.

The experiments are also of interest in that they help to elucidate the pathology of ventricular fibrillation. They appear to confirm the supposition that this disorder of the musculature results from the generation of, heterogenetic or pathological impulses from a number of foci in the chamber itself.

The tachycardias observed under low tension chloroform vapour are of importance ; they are of purely ventricular origin, and cannot be ascribed to any central nervous disturbance. They illustrate the value of the electrocardiographic method, for in the absence of records of this nature, the heart mechanism might be and probably has been mistaken for a normal or sequential one ; and the acceleration of heart rate might be readily ascribed to altered innervation. It is necessary to emphasise the danger of serious fallacy when conclusions are drawn from sudden accelerations or retardations of pulse rate as recorded by a mercurial or membrane manometer. Mechanical records of this kind fail to provide the experimenter with an analysis of the heart mechanism and the changes in rate are too often interpreted as the result of central nerve influences.

CONCLUSIONS.

1. Low tensions of chloroform vapour, administered to cats, produce high grades of irregularity of the heart. The irregularities are due to the production of new impulses in the ventricular musculature.

2. Small intravenous injections of adrenalin chloride produce, under high percentages of chloroform vapour, a condition of irritability in the ventricle, which is similar to that observed to result from low percentages of chloroform alone.

3. Low tensions of chloroform administered to cats together with small intravenous injections of adrenalin chloride ultimately produce the highest grade of ventricular disorder, *i.e.*, ventricular fibrillation.

4. Ventricular fibrillation is the result of the origin of impulses at a number of separate foci in the ventricular musculature.

5. The irregular and rapid heart beat referred to in the introduction of this paper as a common accompaniment of the administration of low percentages of chloroform, and as a precursor of isolated instances of death from ventricular fibrillation in cats, is in fact a transitional stage towards ventricular fibrillation.

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THE GRAVE SPINAL CORD PARALYSES CAUSED BY SPINAL ANESTHESIA

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IN 1945 three verified cases of spinal arachnoiditis and paralysis following spinal anesthesia were reported (44) from the Neurological Service of Bellevue Hospital. An attempt was made at that time to bring these and other sequelae to the attention of surgeons and anesthetists. The incidence of these sequelae has not diminished. Unfortunately, it is not generally known, and still less widely accepted, that spinal anesthesia may result in temporary or permanent neurological complications: paralyses or continuing nerve root pain.

Since Pitkin introduced his so called "controllable" spinal anesthesia in 1928, this method of anesthesia has come to be almost a routine procedure for many surgeons and some hospitals, sometimes without adequate consideration of the patient, the character of the surgery, and certainly with little conscious regard for possible complications. In 1933, Foss and Schwalm wrote, "Spinal anesthesia can be used . . . in operations below the diaphragm with far greater safety than most surgeons at present seem to believe." In 1947, Ericsson provided the prevailing opinion: "Spinal anesthesia appears in increasing degree to have few or no contraindications."

The literature contains many contradictory reports concerning the incidence of complica-

tions. Orth (1925), Babcock (1928), Pitkin (1929), Foss and Schwalm (1933), Forgue (1934), Sebrechts (1934), Emmet (1935), and Lundy (1942) deny that spinal anesthesia properly performed could result in any complications.

On the other hand, Urban mentioned complications as early as 1907, and Kaiser reported further after-effects in 1921. Lindemulder (1932) wrote, "It must be recognized that there may be certain definite residuals after spinal anesthesia." Jarmen (1934) gives an incidence of paralysis of 0.01 per cent; Hyslop (1933) reports an incidence of central nervous system sequelae as 0.5 per cent; Nicholson and Eversole (1946) found 0.024 per cent of neurological complications at the Lahey Clinic; and Schildt (1947) reports an incidence of complications as 0.01 per cent. Minnit and Gillies write, "To say that one has not seen these complications is only half an answer, because one has probably not looked for them."

These neurological complications have been discussed in numerous reports in the literature. They may occur immediately in association with the spinal anesthesia or after an interval of time when they are not recognized as being associated with the spinal anesthetic. At the Swedish Central Hospital in Orebro, the complications were considered to be rare until Gunnar Thorsen made his compre-

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hensive study in 1947 and now "this point of view is changed." Thorsen states, "They are not rare and not negligible." Schildt adds, "From the use of any of the present-day spinal anesthetics there may follow serious nervous symptoms which depend upon (probable chemotoxic) injuries of the spinal cord or its membranes." Madan (1944) writes, "There is still a lack of perfect controllability and safety and there is a lack of thorough knowledge."

Spinal anesthesia was first produced in 1885 by Corning in man and dogs. Fourteen years later Bier introduced spinal anesthesia with cocaine for clinical surgery. However, cocaine was too toxic and its use was discontinued. In 1903 Fournier developed stovaine, and in 1904 Einhorn produced novocain. Since then, numerous other derivatives or combinations have been prepared. All are toxic in varying degree.

Animal experiments carried out by Van Lier (1907), Wossidlo (1908), Spielmeyer (1908), Klose and Vogt (1909), Davis, Haven, Given, and Emmet (1931), Lundy, Essex, and Kernohan (1933), and Macdonald and Watkins (1937) resulted in agreement that the etiological toxic agent is the anesthetic substance, though there is disagreement as to the specific mode of action. The injuries are located in the spinal cord most marked near the site of injection; the nerve roots and spinal ganglia are often spared. There are: (1) constant but varying degrees of meningeal reaction with cellular proliferation and infiltration which may progress to cicatrization; (2) changes in the ganglion cells of the gray matter with "swelling, rounding, chromatolysis, achromatosis, and disappearance of cell fibrils"; (3) swelling and fragmentation of the axis cylinders of the nerve roots, especially in the posterior and lateral columns together with degenerative changes in the fiber tracts of the spinal cord, most marked below the lower dorsal segments of the cord; (4) peripheral degeneration of the myelin sheath of the spinal cord. The pathological changes seen in these animal experiments are the same as those seen at operation or post mortem in patients who have had complications after spinal anesthesia.

In 1927, Franke reported a case with marked leg weakness, sensory disturbance, and difficulties with micturition and defecation after

spinal anesthesia with novocain. The patient died of pneumonia on the sixth postoperative day. Postmortem examination revealed swelling of 2 inches of the lumbar region of the cord, with a somewhat softer area above. Hemorrhages were found up to the medulla. Microscopic examination detected hemorrhage and damage of the myelin sheaths. Lindemulder (1932) described inflammatory changes in the leptomeninges and brain substance in 2 patients who died soon after spinal anesthesia. Brock, Bell, and Davison (1936) found in a patient with total flaccid paralysis of both legs produced by spinal anesthesia: "extensive destruction of the myelin sheath, axis cylinders and glia, mostly at the periphery of the cord and at the zones of entrance of the posterior roots. The ganglion cells of the anterior and lateral horns were also slightly involved." Kamman and Baker (1943), with a similar clinical result immediately after spinal anesthesia, found an adhesive leptomeningitis of the middle and lower thoracic segments of the spinal cord. In some areas the pia-arachnoid was hyalinized. In this area of the cord, the posterior columns were replaced by a large area of softening. The remaining white and gray matter was severely damaged. Demyelination was prevalent in the lateral and posterior columns in and below the lower thoracic segments. Ferguson and Watkins (1937), in autopsies on 3 cases of cauda equina syndrome, found on cord sections "some increased hyaline changes in the vessel walls and in addition some marginal pallor of the cord in the sacral region, but no other definite changes. Marchi sections were negative. Sacral nerves showed fine vacuolation and evidence of recent degeneration." Critchley (1937) described a case of spinal cord softening following spinal anesthesia. A week after the administration of 2 cubic centimeters of spinocaine in the third lumbar interspace his patient developed back pain. One month later there occurred motor and sensory paralyses. On pathological examination there was massive softening of the spinal cord, maximal at the level of the upper lumbar enlargement. The veins in the affected areas showed endophlebitis or thrombosis, while arteries showed signs of acute necrosis or "necrotizing arteritis."

Except for Sebrechts, there is general agreement that bilateral headache, localized especially to the forehead and behind the eyes, occurs following both simple lumbar puncture and spinal anesthesia. Some authors claim the incidence is about the same in both, while others believe the incidence is greater after spinal anesthesia. In addition, there is "greater liability to a severe and protracted course (of headache) and to occasional development of complicating features (80) after spinal anesthesia. The frequency of these varies considerably. Koster and Weintraub (1930) report 10 per cent of 6,000 cases. Ashworth (1933) found it in 4.9 per cent of 184 cases. Falk (1931) reported an incidence of 6 per cent. Hingson, Ferguson, and Palmer (1943) reported an incidence of 1 per cent of 5,150 patients. Thorsen (1947) in a compilation of over 50,000 cases cites the frequency as approximately 18 per cent. The etiology must be primarily related to the mechanics of lumbar puncture plus the additional effect of the anesthetic agent. The primary cause in most cases seems to be a leakage of cerebrospinal fluid with possible alteration of the spinal fluid dynamics. Approximately 80 per cent of patients with headache after spinal anesthesia have lowered spinal fluid tension. This is rather more common in women. Also, there is a statistical difference in age groups, headache being more common before the ages of 40 to 50. In approximately 60 per cent of the patients with headache, there is the added complaint of dizziness. In a small number of cases this symptom occurs alone.

Aseptic, purulent, and chronic adhesive meningitis have been reported to occur after spinal anesthesia. Aseptic meningitis is characterized by fever, stiff neck, headache, and the presence of a Kernig sign. Spinal fluid examination shows an increased number of cells, but normal sugar and no organisms. This clinical picture is seen to begin almost immediately or within 60 hours postoperatively. Such meningeal reaction is usually mild and transient, though stupor and delirium may occur. The increased number of cells rapidly returns to normal and the spinal fluid protein also returns to normal if it had been elevated. A total of 49 cases has been reported to date,

and Orkin in a summary of 45,966 cases of spinal anesthesia by 20 authors gives an incidence of 0.26 per cent.

A considerable number of cases of purulent meningitis have been described following spinal anesthesia. It is said to occur in a proportion of approximately 1 case to every 800 spinal anesthetics (71). Meningococci were implicated in 2 cases, pyocyaneus in 4 cases, streptococci in 5 cases, tubercle bacilli in 2 cases, and spore-bearing rods and coli have also been responsible (71). This complication was fatal in each case until the appearance of antibiotic drugs. Though it was not the direct result of the anesthetic agent, it did occur as a complication of the procedure.

However, severe progressive complications are sometimes seen as the result of the already described chronic type of leptomeningitis with formation of adhesions and thick cicatricial bands. The postmortem findings in the case reported by Kamman and Baker have been described. Hammes (1943) reported 2 patients with a syndrome of a slowly ascending myelitis who were found to have a cerebrospinal fluid block. Exploratory laminectomy in 1 of these cases revealed pachymeningitis. Hewer (1933) described a patient, who was found at laminectomy 9 months after administration of 15 cubic centimeters of 1:1500 percaine in the first lumbar interspace, to have a constricting band of adhesive arachnoiditis about the lower part of the cord and upper part of the cauda equina. Haynes and Smith (1942) reported the case of a 24 year old man who developed the clinical signs of cervical cord involvement 4 days after use of a pontocaine glucose solution as a spinal anesthetic. Cervical laminectomy 2 months later revealed a cervical arachnoiditis; some improvement followed lysis of many adhesions. The operative findings in 3 cases were described by one (44) of us in 1945. Thorsen has found 26 other cases in the literature, including Weigeldt's report of a patient who developed flaccid paraplegia 3 months after spinal anesthesia. Pathological examination revealed intense adhesions extending caudally from a point 11 centimeters below the olivary body.

Even cerebral injuries have been reported in association with spinal anesthesia. These cases

have been considered to be nonspecific and not directly related to the anesthetic agent. The vasoconstrictor paralysis which occurs through blocking of the anterior nerve roots produces a sudden fall of blood pressure and diminution of cardiac output. Hingson and associates believe this occurs only when the level of anesthesia extends above the eighth thoracic spinal cord segment. The fall in blood pressure is responsible for a cerebral anoxia. This is sometimes further increased by impaired respiration and may lead to changes in consciousness, personality, hemiplegia, hemiparesis, convulsive disorders, and like conditions.

Several authors have reported convulsive disorders with or without hemiparesis occurring 5 to 15 days after spinal anesthesia. Arnheim and Mage (1931) describe 3 cases of hemiplegia which occurred 1 and 3 days after operation and in which the patient died 3, 7, and 10 days later. Dickson Wright (1933) in a discussion of Ashworth's paper mentioned 2 cases of acute mania after the administration of 8 cubic centimeters of 1:1000 percaine. Critchley (1933) thought cerebral angiospasm or a small thrombosis due partly to an associated vascular disease was responsible for the mental confusion and transient hemiplegia occurring immediately following spinal anesthesia. Behrend and Riggs (1940) reported 21 fatal cases due to cerebral damage. Pathological findings in these cases correspond closely to those found in animal anoxia experiments. Belinkoff (1945) reported 4 cases with coma developing as an acute collapse associated with a sudden fall of blood pressure.

Encephalitis has been described following spinal anesthesia. Maclachlan (1931) described the case of a 38 year old woman who developed an encephalitis on the fourth postoperative day after a hysterectomy for fibroids. Brock, Bell, and Davison (1936) also presented a similar case of encephalitis. In both cases there were permanent residual signs. Donovan, Beretevide, and Rechniewoski (1928) and Hyslop (1933) described cases of meningoencephalitis. Martin (15), in 1937, reported a case of ascending myelitis following spinal anesthesia which eventually progressed to affect the brain.

The cranial nerves, with the exception of the first, ninth, tenth, and eleventh have been reported involved either singly or infrequently in combination following the administration of a spinal anesthesia. Ergova (1939) reported an incidence of 3.2 per cent for cranial nerve involvement in 128 cases. Forgue and Basset (1928) estimated the frequency to be up to 0.5 per cent. Thorsen found an incidence of 173 cases after 68,179 spinal anesthetics or 0.25 per cent from the combined reports of 46 published papers. The frequency in these papers varied up to 5 per cent. The usual trouble is a paresis of the oculomotor nerves, especially the abducens. This sixth nerve is affected in over 90 per cent of all cranial nerve paralyzes following spinal anesthesia. It is unilateral in 75 per cent of the cases, the right nerve being more often involved than the left. The onset of symptoms usually occurs at the end of the first week but varies between the third and twenty-first postoperative days; it may be preceded by headache, nausea, dizziness, stiff neck, photophobia, and finally diplopia. Paralysis of the abducens nerve was first reported by Becker and Landow in 1906. By 1929, Blatt had collected over 100 cases; at the present time, over 500 cases have been reported. One-half of the cases improve within a month and almost every patient recovers spontaneously within a few weeks to a few months.

The anterior and posterior roots, the cord, as well as the peripheral nerves have been reported affected by spinal anesthesia. Clinical manifestations of irritation or impairment of the nervous structures are usually found as soon as anesthesia fades. At times, however, clinical symptoms are not present until days or weeks later. Then there may be motor weakness or paralysis with cord involvement. The paralysis is at first flaccid and later becomes spastic. Involvement of sensory fibers or tracts may be responsible for pain, paresthesia, or a varying degree of loss of sensation. Bladder and bowel dysfunction as well as disturbance of sexual function are not infrequent. Hasler (15) (1937) thought interference with the nervous mechanism of the bladder leading to urinary retention is the most common sequel of spinal anesthesia.

Lindemulder (1932) believed pain in the extremities, especially the legs, due to a radiculitis was a common sequel to spinal anesthesia and described 3 cases in which the pain with muscle tenderness persisted for several months. Brock and associates (1936) reported a syndrome of lumbar radiculitis beginning 3 weeks after operation. Jones (1932) had a case of sciatic pain lasting 6 months. Critchley had a case of a sacral radiculitis occurring 24 days after spinal anesthesia, and 2 cases of radiculomyelitis with evidence of more widespread involvement of the roots and spinal cord. Klein (1924) and Dassen (1931) described cases of myeloradiculitis. Hingson and associates (1943) reported 14 cases of decreased or painfully increased sensation of one or more nerve trunks. In most cases, pain cleared spontaneously but some received therapeutic nerve blocks with repeated novocain injections. Nicholson and Eversole (1946) described 3 cases of peroneal neuropathy. Loeser (1933) reported 5 cases of peripheral neuritis, occurring 1 to 3 weeks after intrathecal use of procaine, characterized by pain and paresis radiating along the course of the nerve and also involving motor fibers. This condition involved the ulnar nerve in 2 cases, radial nerve in 1 case, sciatic nerve in 1 case, and the lateral cutaneous nerves of the thigh in 1 case.

In 1937 Ferguson and Watkins reported 14 cases of cauda equina syndrome which almost immediately followed spinal anesthesia with heavy duracaine. They could find only 16 other similar cases in the literature. Characteristic of this syndrome were: (1) retention of urine occurring within 24 hours, lasting for 1 to 4 weeks and followed by incontinence for several weeks; (2) incontinence of feces with loss of anal sphincter tone (6 cases improved in less than 1 month; 3 cases improved in 3 months); (3) impairment of sensation in the buttocks and occasionally extending down the back of the thigh; (4) impairment of muscle strength in the lower extremities; and (5) alteration of the ankle jerk. Since this evaluation there have been additions. Critchley (1937) reported 8 cases, Yaskin and Alpers (1945) 2 cases, Aikenhead (1945) 3 cases, and there have been individual reports as well. White-Morguecho (1939) reported 19 cases of

slight bladder paresis and of rectal incontinence in a series of over 3,000 cases. Pierson and Tomey (1940) described 1 case of neurogenic dysfunction of the bladder in a 60 year old man in which retention was relieved by presacral nerve resection after 2½ months. In some cases cystometric and cystoscopic studies were carried out after an interval of several months and revealed trabeculated hypertonic bladders with residual urine.

More extensive cord involvement following administration of spinal anesthesia has also been recorded. Devraigne, Suzor, and Laennec (1927) described a transient quadriplegia. Koster and Weintraub (1930), and Brock and associates (1936) mention cases of flaccid paraplegia occurring immediately after spinal anesthesia. Nonne and Denne (1928) reported a case of degenerative myelitis. Yaskin and Alpers (1945) had 1 case of primary lateral sclerosis syndrome with spastic crural paraparesis, and 1 case of incomplete thoracic transverse myelitis. Smith (1933) added a case of complete transverse myelitis occurring at the ninth thoracic segment on the seventeenth postoperative day. Ashworth (1933) mentions the case of a 51 year old man, who had an unsatisfactory spinal anesthetic with spino-caine, and sustained a complete paralysis of the cord below the ninth dorsal segment.

The incidence of death from spinal anesthesia has been variously reported as (a) 5 in 120,000 cases (2), (b) none in 250,895 cases (5), (c) 3 in 4,010 cases (54), (d) 2 in 5,150 (37). Foss and Schwalm (1933) and Lienhoop (1936) believed the mortality rate was no greater for spinal than for ether anesthesia.

CASE 1. D. K., a woman physician aged 29 years, was delivered on May 15, 1947 of a full term child. Because of a recently arrested tubercular infection, the delivery was accomplished by cesarean section under continuous spinal anesthesia. The anesthetic agent was 4½ per cent procaine and ¾ per cent ephedrine; a total of 130 milligrams of procaine was administered in 1½ hours. The anesthetic was introduced through the third lumbar interspace and a level of anesthesia up to the umbilicus was obtained. As the effect of the anesthetic cleared, the patient became aware of a low back pain radiating symmetrically into both sacroiliac regions and down the posterior aspects of the lower extremities to the ankles. The pain gradually eased but did not disappear during the next 5 days, at which time she

tried to stand and felt the same severe radiating pains down both legs. During the next few days the pain somewhat subsided so that on the ninth postoperative day she was able to get out of bed. At that time she further experienced an excruciating throbbing pain in the lower dorsal region which radiated upward into the head. This pain was completely relieved in the recumbent position, but was aggravated by sneezing. Subsequent attempts to reproduce this pain were unsuccessful. Four weeks after the operation, pain was slight and her only restriction on movement was an inability to bend forward.

Six weeks postoperatively she had a sudden exacerbation of pain on trying to rise from bed, and she continued to have excruciating pain during that week. In the seventh week she fell to the right when she tried to pick something from the floor, and was unable to arise except by leaning heavily on her left side. The following day she noted weakness in both lower extremities. During the next 10 days there was a rapid progression of symptoms. She became ataxic and felt "as though she was walking on cushions." She complained of formications of the skin of both legs and thighs. There was a numbness of the lower portion of the body which corresponded to a definite sensory level below the umbilicus for pin prick, temperature, and touch, as tested by the patient herself. Heel-to-knee ataxia was also marked. By the eleventh week there had developed numbness and stiffness in both ankles and feet; she was able then to walk very slowly with the help of a stick. During the fourteenth postoperative week, position and vibratory sense in both lower extremities was found to be absent.

A general physical examination on August 29, 1947 showed no significant abnormalities, except as later reported on the roentgenogram. There was no evidence of any new or active lesion in the lungs. Neurological examination showed a moderate weakness of both lower extremities but no muscle atrophy. There was marked heel-to-knee ataxia. Deep tendon reflexes were active throughout and equal in all extremities. The upper abdominal reflexes were markedly diminished. The lower abdominal reflexes were absent. Bilateral Babinski toe signs were present. The sensory examination showed a sensory defective level at the eleventh dorsal segment, and a zone of hyperesthesia at the first lumbar segment on the right.

Roentgenograms of the chest revealed linear densities in the upper portions of both lungs with some evidence of lateral traction of the mediastinal pleura along the cardiac contour. This was attributed to the old pneumothorax with a re-expansion of the lung. Roentgenograms of the vertebral column had no abnormalities. Lumbar punctures were unsuccessful on 4 separate occasions and a diagnosis of adhesive arachnoiditis secondary to spinal anesthesia was made.

At present this physician has paralysis in both legs. Her only improvement has been a slight return of sensation in patchy areas of both lower extremities.

A course of x-ray therapy was given without benefit. Physiotherapy helped considerably by teaching her how best to use the remaining musculature.

Allergic history: The patient had a typical penicillin allergic reaction prior to her delivery. A rash developed over the area that was painted with merthiolate during her delivery. A skin test, for sensitivity to the anesthetic used, was carried out and was found to be negative.

CASE 2. P. P., a man aged 50 years, was admitted to Bellevue Hospital on May 3, 1949 with the chief complaint of numbness of both feet and nocturia. His past medical history revealed a gunshot wound in 1922. The bullet passed through the right ear and emerged from the left temporomandibular region. There occurred then an infection of the right mastoid bone which required a right mastoidectomy. As a result he has a right peripheral facial paralysis, loss of air conduction in the right ear, a hypesthesia on the right side of the pharynx, right palatal weakness, and a marked paresis of the left upper limb. He had an operation for a gastric ulcer in 1937 and a herniorrhaphy in 1944. Two years later he developed a recurrence of gastrointestinal symptoms and also noticed that he could no longer have erections or ejaculations. On January 9, 1949 he was readmitted to the same hospital for a subtotal gastrectomy. The operation was done under continuous spinal anesthesia with the usual strength of procaine crystals dissolved in cerebrospinal fluid and injected through the interspace between the third and fourth lumbar vertebrae. The patient remained in the hospital for 2 months before his discharge to a convalescent home.

At the time of his discharge he felt his legs were numb, but thought this was due to the long period in bed. He was in the convalescent home for a month and during that time found his legs were getting progressively weaker so that he had to use a cane for support.

General physical examination on admission to Bellevue Hospital was entirely within normal limits. On neurological examination he was found to have a broad based gait and a positive Romberg test. There was much weakness of flexion of both thighs on the abdomen and at the knee joints. Dorsiflexion of the feet was not weak. The deep tendon reflexes were overactive but equal. The plantar responses were flexor. The abdominal reflexes were equal and active. There was a level of reduced perception of pain at the groins; observers reported this level at the umbilicus bilaterally. Position and vibration sense were lost below the iliac crests.

Roentgenograms of the skull and vertebral column were normal. Eight attempts to obtain spinal fluid by lumbar puncture were unsuccessful. An unsuccessful traumatic cisternal puncture produced vomiting and headache. A laminectomy was performed between the twelfth thoracic and third lumbar vertebrae. The meninges and spinal cord were inspected. The pia-arachnoid was thickened, translucent, and firmly adherent to the dura. The spinal roots were

enmeshed in numerous fibrous adhesions. A small amount of fluid escaped at the first incision into the subarachnoid space. A fine rubber catheter could not be passed beyond 3 inches above and 2 inches below the operative area; no additional spinal fluid could be obtained. We believed there was a diffuse arachnoiditis up and down the spinal cord.

After the operation the patient was able to lift his legs off the bed. This was not possible before surgery. During the next few days, however, he had increased difficulty in voiding and this gradually developed into frequency and incontinence of urine. A transurethral prostatectomy was carried out to reduce the residual urine in the bladder. A repeat neurological examination a month later confirmed all the previous findings.

Allergic history: No history of allergy was obtained. Skin test for the anesthetic used was negative.

CASE 3. R. R., a woman aged 23 years, was admitted to Bellevue Hospital in March 1948 for rehabilitation. This patient had been in good health before December 1946 when she had a cesarean section under continuous spinal anesthesia with procaine by the usual method of administration. In April, 1947 she noticed a numbness over her abdomen at the level of the umbilicus, and the onset of weakness in her right lower limb. During the next 2 months this weakness progressed and she became aware of additional weakness in the left lower limb. At the same time she noted a urinary disturbance which consisted first of urgency, and later incontinence of urine.

She was admitted to hospital for investigation of these complaints. A neurological examination then revealed her as having a waddling gait with bilateral foot drop, more marked on the right. There was marked weakness of both lower limbs, the right being more affected than the left. The deep tendon reflexes of the lower extremities were overactive and bilateral Babinski toe signs were present. A sensory reduction level was found below the tenth dorsal segment and overperception of pain between the seventh and tenth thoracic vertebrae. Position and vibration sense were not perceived below this level. Roentgenograms of the vertebral column were normal. A lumbar puncture was attempted but no spinal fluid could be withdrawn. Pantopaque was inserted into the cisterna magna and both roentgenograms and fluoroscopy showed a complete subarachnoid block at the level of the seventh thoracic vertebra. A laminectomy of the fifth, sixth, and seventh thoracic vertebrae revealed a markedly swollen and congested cord with an overlying adherent arachnoiditis. After the operation the patient developed a complete paraplegia with bladder and bowel incontinence.

Neurological examination on admission to Bellevue on March 23, 1948 verified the above neurological status. There was no thinning of the muscles of the lower limbs. The strength of the abdominal muscles was markedly decreased. There was anes-

thesia below the level of the seventh thoracic vertebra. The patient was given physiotherapy and rehabilitation exercises.

CASE 4. E. R., a man aged 63 years, was admitted to Bellevue Hospital on February 17, 1949 for rehabilitation. For the previous 8 years he was known to have a blood pressure of 180/100. For a period of 2 years he was slightly unsteady in his gait but had no impairment of sensation in the lower extremities. The Romberg test was negative. On January 15, 1948 a right hernioplasty for an incarcerated right hernia was done under spinal anesthesia. The anesthetic agent was 12 cubic centimeters of 1 in 1,500 nupercaine which was introduced in the interspace between the first and second lumbar vertebrae. Shortly after the spinal anesthetic was injected the patient became cyanotic and apneic for 1 to 2 minutes. The next day he had a left hemiplegia, weakness of the right lower extremity, incontinence of feces, and retention of urine. On the third day after the operation he was found to have a flaccid paresis of both lower extremities. Six weeks later, a suprapubic cystotomy was done because of repeated urinary infections.

General physical examination showed no abnormalities other than a blood pressure of 200/120. The vessels of the fundi showed moderate arteriosclerotic changes. The pupils were slightly irregular but reacted briskly to light and accommodation. There was slight increase in tone on passive movements of the left upper limb. There was moderate wasting and weakness of all muscle groups in the lower extremities, the left extremity being more affected than the right. Both limbs were spastic and were maintained in a position of mild flexion. The deep tendon reflexes were overactive in the upper limbs, the left side more than the right. The knee jerks were barely elicited; the ankle jerks were absent. Bilateral Babinski toe signs were present. Sensation was intact except for the absence of bladder and bowel sensation. A lumbar puncture revealed clear fluid under normal pressure. Manometrics indicated no block and spinal fluid chemistries were normal. A diagnosis of a cerebrovascular accident and spinal cord pathology secondary to spinal anesthesia was made. The patient was given physiotherapy and rehabilitation exercises.

CASE 5. J. S., a woman aged 26 years, was admitted to Bellevue Hospital on January 17, 1949 for rehabilitation. She was well until December 4, 1947 when she had had a cesarean operation under continuous spinal anesthesia. The spinal anesthetic used was 65 milligrams of procaine. It was introduced through "the third lumbar intervertebral space" and a level of anesthesia was obtained up to the umbilicus.

On the fourth or fifth postoperative day she complained of pain in the low back region at night and a feeling "like the banging of a hammer" over this area. Six weeks postoperatively she still complained of backache and also of numbness in both feet. Two weeks later, she walked "like drunk" and tripped

over her feet. Ten weeks after operation, there developed weakness at both knees and she fell when she tried to walk. She noticed the absence of painful sensation and position sense in her feet, and found she had bowel and bladder incontinence.

A laminectomy was performed on April 23, 1948 between the fifth and eighth thoracic vertebrae inclusive. The extradural fat and the dura were normal. The arachnoid was thickened and adherent to the cord producing a pocket of clear fluid at the site of the operation. The cord was thinned to about half its usual diameter and was displaced to the left.

A neurological examination on admission to Bellevue Hospital revealed slight wasting of both calf muscles. There was moderate weakness of both the extensors and flexors, the former being more affected, the muscles on the right more than those on the left. There was moderate weakness of dorsiflexion of both feet but the right side was definitely the weaker. The flexor muscles of both feet had good power. The knee jerks and ankle jerks were overactive, the right being more active than the left. On plantar stimulation there was an extensor response on the left but an equivocal response on the right. The superficial abdominal reflexes were present in the upper quadrants only. Position and vibratory senses were absent below the costal margin. Pain, touch, and temperature senses were impaired below the level of the tenth thoracic vertebra bilaterally with greater impairment for pain between the tenth thoracic and first lumbar segments on the right. A diagnosis of adhesive arachnoiditis secondary to spinal anesthesia was made. The patient was taught ambulation and elevation activities necessary for the maintenance of daily function.

CASE 6. R. G., a man aged 49 years, was admitted to Hospital on May 11, 1949 with umbilical pain. A diagnosis of incarcerated umbilical hernia was made and an emergency operation performed under spinal anesthesia. The anesthetic agent used was 120 milligrams of metycaine in a 10 per cent solution. It was diluted in 2 to 4 cubic centimeters of spinal fluid, and introduced between the third and fourth lumbar interspace. Anesthesia was obtained approximately to the level of the umbilicus. The only immediate postoperative complication was urinary retention, and the patient continued to have a residual urine until he was discharged from the hospital on May 17, 1949. Nine days later he returned to the same hospital because of increasing difficulty with micturition. Neurological examination on the following day showed normal deep tendon reflexes and a questionable sensory diminution over the first left sacral segment. A diagnosis of benign hypertrophy of the prostate and postspinal anesthetic atonia of the bladder was made. A transurethral resection was done on June 9, 1949.

A neurological examination 3 weeks after his readmission showed barely perceptible reflexes in the lower limbs with occasional fasciculations but no muscle wasting, and a suggestive level of diminished sensation at the eighth dorsal segment on the right.

This sensory change was most marked over the first and second lumbar segments and over the pubic area. On lumbar puncture the spinal fluid was clear but contained 5 white cells per cubic millimeter. The initial pressure was 230 millimeters of water. The spinal fluid protein was 37 milligrams per cent. The Wassermann test was negative. The patient was discharged on July 6, 1949.

Shortly thereafter he was admitted to Bellevue Hospital with the chief complaints of inability to void, numbness in the perianal region, increasing constipation, and decrease in spontaneous erections. The urological service made the diagnosis of a neurogenic bladder with an enlarged median bar of the prostate, and a second transurethral resection was performed. Following this operation he was able to empty his bladder by the Credé method. He was then transferred to the neurological service for further evaluation of the neurological condition. On general physical examination there were no significant abnormalities. The blood pressure was 134/72. The rectal sphincter was normal. The prostate was not enlarged and no nodules were felt. On neurological examination, the positive signs were found confined to the lower trunk and extremities. The lower extremities were symmetrical with no evidence of muscular wasting or fasciculations. There was weakness of flexion of the left thigh on the abdomen and weakness of extension of the left leg on the thigh. No other muscle weakness was found. The heel-to-knee test was well done. The knee jerks were diminished bilaterally. The ankle jerks were absent. On plantar stimulation the response was flexor. There was diminished sensation to pin prick and light touch in the perianal region, and in an area extending forward over the perineum and genitalia. The same sensory diminution was found over the posteromedial aspects of both thighs to about 8 centimeters above the knees, and over the posterolateral aspects of both thighs and legs extending to the dorsum of the feet. This was more marked on the right side. Vibratory sense was decreased below the knees. Position sense was intact. Deep pain was felt.

The hematocrit and urinalysis were normal. The acid phosphatase was never above 1.7, the alkaline phosphatase 4.5. On lumbar puncture the spinal fluid was clear and colorless. It did not have cells and the pressure was 156 millimeters of water. The Wassermann test was negative. The colloidal gold was negative. The protein was within normal limits. A diagnosis of cauda equina syndrome secondary to spinal anesthesia was made. The patient was discharged to be followed in the clinic.

Allergic history: No allergic history was obtained. A skin sensitivity test for the anesthetic used was negative.

CASE 7. S. K., a woman aged 45 years, was admitted to Bellevue Hospital on May 4, 1948 with the chief complaint of inability to walk. Three weeks earlier on April 16 she had had a laparotomy under spinal anesthesia because of severe intermittent

lower abdominal pains with increasing abdominal distention. The anesthetic agent was 13.5 cubic centimeters of 1:1,500 nupercaine, and 1.5 cubic centimeters of 50 per cent solution of glucose. The postoperative diagnosis was a fibrous band constricting the proximal loop of ileum. Immediately following the operation she was found to have a flaccid paralysis with a total loss of sensation below the umbilicus.

On admission to Bellevue Hospital the general physical examination revealed no other abnormality than a prolapsed rectum. Neurological examination showed a congenital convergent strabismus. There was no cranial nerve involvement. The upper limbs were normal. There was a flaccid paralysis with urinary incontinence and constipation. The sensory examination showed a sensory defective level on the right side at the second lumbar vertebra with anesthesia below this segment. On the left side there was an area of diminished sensation from the tenth thoracic to the first lumbar vertebra with anesthesia below the first lumbar segment. On lumbar puncture the spinal fluid was clear with a pressure of 120 millimeters of water. There were no cells. The spinal fluid protein was 36 milligrams per cent and the Wassermann test was negative. Roentgenograms of the skull and vertebral column were normal. Re-examination 10 months later showed no significant change other than generalized wasting of the lower limb musculature, left greater than right, and severe shooting pains along the anterior and posterior aspects of the thighs. These pains had supervened some months earlier and were only partly relieved by a bilateral spinal chordotomy.

Allergic history: no allergic history was obtained. A skin sensitivity test for the anesthetic used was negative.

CASE 8. J. P., a pastor aged 51 years, was in good health until March 10, 1945 when he was operated upon for the removal of the gall bladder under spinal anesthesia. The anesthetic agent used was 18 milligrams of pontocaine with dextrose. It was introduced "into the third lumbar intervertebral space." A general anesthetic was later administered.

Immediately after the operation he was aware of numbness below the umbilicus and inability to move his lower limbs. Bladder and bowel control were lost; the patient became impotent and still is so. He was confined to bed for 5 months. In September 1945 he was permitted out of bed but required two crutches to get about. In February 1946, he had to undergo another operation for removal of stones from his bladder. On this occasion a general anesthetic was used with no additional postoperative sequelae.

The patient was re-examined on April 28, 1949. At this time he was able to walk, with help, for a short distance but with much difficulty. There were no abnormalities above the costal margin. The muscles of the left thigh were somewhat atrophic and there was marked weakness in flexing the left thigh on the abdomen. The left knee jerk was absent and the right knee jerk diminished. Both ankle jerks were

equal and active. The plantar responses were both abnormal. The abdominal reflexes were absent. There was some diminution of sensation over the third left lumbar segment and over the skin area supplied by second sacral nerves; and a total loss of sensation over the third, fourth, and fifth sacral segments. Vibratory sense was lost below the iliac crests. There was bladder incontinence and constipation. The bulbocavernosus reflex was absent. A diagnosis of cauda equina or conus lesion, secondary to spinal anesthesia was made. The patient has been helped by rehabilitation but his neurological picture has remained essentially the same.

CASE 9. J. E., a man aged 25 years, was admitted to Bellevue Hospital on March 31, 1947 with the complaints of weakness and numbness of the right lower limb, incontinence, impotence, and a trophic ulcer on the sole of the right foot. This patient was in good health until June 1942 when he was admitted to an Army hospital for a left hernia and hydrocele operation. He received a spinal anesthetic.

Three days after the operation he noted frequency of urination and constipation. When he was allowed out of bed 18 days later, he noticed a right-sided limp. During the following weeks he was aware of weakness in the right lower limb and tingling sensations along the posterior aspect of this limb. He had an ache in the lower lumbar region which was aggravated by coughing and sneezing. He found that he was impotent. In November 1942, he was readmitted for evaluation to an Army hospital for 3 months, but discharged with little change in symptoms.

Until July 1943 he performed limited duties as an administrative clerk, but was readmitted to hospital because of marked tingling and progressive weakness in the right lower limb, and the appearance of a prominent mass on the right buttock. He was discharged after 3 weeks of bed rest. In September 1943, he began to notice that he was wetting his bed at night. In December of that year he was again admitted to an Army hospital for a myelogram and an operation on the mass in his buttock. The latter was not removed but was diagnosed by biopsy as consisting of muscle, fat, fibrous tissue and dilated veins. The pantopaque myelogram showed a spotty distribution of the opaque substance in lumbosacral area. He was discharged to a Veteran's hospital with a 100 per cent disability pension in March 1944.

At the time of admission to Bellevue Hospital 3 years later, a general physical examination revealed a scar in the left inguinal region; a chronic ulcer at the outer aspect of the sole of the right foot; and, a soft flabby mass on the right buttock. Neurological examination was normal above the costal margin. He had slight muscle wasting in the right leg but could carry out a full range of motion with both lower limbs. There was, however, a weakness of the dorsiflexor and plantar flexor muscle groups on the right. Both knee jerks were sluggish. The left ankle jerk was also sluggish and the right ankle jerk was absent. The plantar responses were flexor. The

abdominal reflexes were present but diminished. Co-ordination was intact. There was an impairment to all forms of sensation below the eleventh dorsal segment on the right and the first lumbar segment on the left. A diagnosis of a lesion of the cauda equina and conus secondary to the spinal anesthesia was made. The mass in the right buttock was clearly telangiectatic, and caused a preoperative diagnosis of a pre-existing vascular anomaly of the lower spinal cord.

The patient had a laminectomy from the eleventh thoracic to the second lumbar vertebra under ether anesthesia on April 9, 1947. The dura was opened for its entire exposed length. Through the arachnoid a mass of varicose veins was seen. The arachnoid was then incised and a dense mass of varicose veins was seen at the upper end of the exposed cord. Further investigation revealed a large mass of blood vessels on the right side under overhanging edges of the lateral portion on the right lamina of the first lumbar vertebra. A small green mass was observed on the right side anteriorly. A small piece of this was removed by careful dissection. On microscopic examination it was found to consist of fibrous tissue in which were embedded large clumps of yellowish-brown pigment. This gave the positive Prussian blue reaction for hemosiderosis. Vessels were dissected free from the roots and were coagulated with a mild current. During the dissection two of the vessels ruptured, but the bleeding was controlled. Coagulation of some of the vessels decreased their bulk considerably. The wound was then closed.

Convalescence was prolonged and complicated by repeated urinary tract infections. At the time of discharge from hospital in August 1947, there had been no improvement in muscle strength. There was a slight reduction of the sensory impairment in the left lower limb. Bladder control was unchanged. Bowel sensation was lost and large protruding internal hemorrhoids formed. He continues to be impotent. The ulcer on the foot persists.

CASE 10. A. M., a man aged 61 years, had an abdominal-perineal resection and a coccygectomy for adenocarcinoma of the rectum; 760 milligrams of 3.3 per cent novocain was administered as a continuous spinal anesthesia. He remained in the hospital for 2 months following this operation.

At the time of discharge he was able to walk but with much difficulty because of pain and paresthesia in both lower extremities. He had reported numbness and tingling in both legs below the knees, especially on the right, since recovery from the anesthesia. Ten weeks after operation, he noted a progressive weakness of his lower limbs and involuntary flexor spasms of the right hip and knee joints. The lower extremities were cold, stiff, and sore. On neurological examination then there was atrophy of symmetrical muscle groups in the lower limbs and a diminution of muscle strength with poor co-ordination. He had a spastic "scissors gait." The deep tendon reflexes of the lower extremities were overactive but equal. There was a left Babinski

toe sign. The superficial abdominal and cremasteric reflexes were absent. There was decreased perception of pain below the sixth dorsal segment bilaterally. Vibration and position sense were impaired in both lower limbs. Light touch sense was intact. Lumbar puncture revealed clear, colorless fluid under initial pressure of 50 millimeters of water, but with a definite manometric block. A second lumbar puncture later failed to obtain any fluid. Arthritic changes were seen on the roentgenograms of the dorsal spine. There was no evidence of any metastatic lesion. Other laboratory data were within normal limits. The sedimentation rate was not elevated. The patient was discharged from the hospital without any improvement 5 months after the operation.

CASE 11. M. P., a woman aged 39 years, was admitted to Bellevue Hospital on September 12, 1949, with a 5 week history of pain which radiated down the posterior aspect of the right lower limb to the ankle, and was increased by coughing and sneezing or other straining. In addition, there was a more recent feeling of numbness in the toes of this foot. She had a history of a similar pain in the left lower limb in 1937. It disappeared after 6 weeks of rest in bed except for a feeling of stiffness and aching in the lower back when she bent down or moved heavy objects. In 1947 she first noted the pain in the right lower limb but it improved after a period of 2 weeks' rest in bed, leaving a residual aching in the low back area.

The general physical examination did not reveal any abnormality. The anal sphincter tone was good. Blood pressure 152/90. The neurological examination was normal above the costal margin with overactive reflexes in the upper limbs. The patient was in pain with every movement of her body, particularly those involving her back and lower limbs. There was a marked list to the left with the pelvis tilted higher on the right side. Walking was slow and difficult due to pain. There was a marked spasm of the paravertebral muscles of the low back, especially on the right side with a loss of the normal lumbar lordosis. A right lumbar scoliosis was present. There was no wasting of any muscle groups but a definite weakness of dorsiflexion of the left foot was noted. The power of the other muscles was difficult to evaluate because of the pain on movement. There was a bilateral Lasègue sign. The knee jerks were overactive but equal. The ankle jerks were absent. The plantar responses were flexor bilaterally. Sensation was intact except for a possibly diminished touch sensation on the dorsolateral side of the right foot.

Complete blood count and hemogram were normal. A lumbar puncture revealed clear spinal fluid under normal pressure. It contained 1 lymphocyte. The spinal fluid protein was 72 milligrams per cent. The Wassermann and colloidal gold curve were normal. A pantopaque myelogram demonstrated an almost complete subarachnoid block at the fourth lumbar interspace.

On September 27 an interlaminar exploration was done at this level. At the request of the anesthetist consent was given for spinal anesthesia for this operation. The anesthetic agent was a mixture of about 5 per cent pontocaine, glucose, and neosynephrine. The period of anesthesia lasted 1 hour and 55 minutes. The blood pressure fell immediately to a low level but responded to ephedrine. Later it became low again and 1 milligram of neosynephrine was given intravenously to return the blood pressure to a normal level.

On exposure, a large protruding nucleus pulposus was found at the fourth lumbar interspace and was seen to be exerting pressure on the roots bilaterally, but more on the right side. This herniated disc was removed extradurally and the wound closed. There were no known complications till the third postoperative day when she complained of difficulty in voiding and was found to have a patchy sensory loss in the lower limbs. On the fourth day, both gluteal muscles were found to be weak. The anal sphincter tone was markedly reduced. There was impaired sensation about the anus and diminished sensory perception on the lateral aspects of the sole of the right foot. On the thirteenth postoperative day she was still unable to void spontaneously and had an increasing weakness of the right lower limb with resultant difficulty in walking. The sensory changes persisted. On the nineteenth postoperative day, there was marked weakness of the left lower limb particularly of dorsiflexion of the left foot. There was definite diminution of sensation over the right sacral segments and a small patch of impaired pain sensation in the perianal region of the left buttock. There was also a sensory diminution to pain and touch over the dorsolateral surfaces and soles of both feet. The patient was constipated and had no rectal sensation. She was discharged unimproved.

CASE 12. Personal communication by courtesy of Doctor Frederick A. Fender, San Francisco: "A partial gastrectomy (under spinal anesthesia) was carried out on a 50 year old otherwise healthy man, for the treatment of ulcer, in April of 1949. Ten weeks after his operation there was a 10 day episode of pain in the midline back with coughing and sneezing. A few days after this pain disappeared, the patient noticed difficulty in walking and balancing. To make a long story short, the condition progressed to paraplegia. The striking thing about this case is that the appearance of the cord, at laminectomy, was exactly like the cord you have described: strangulating arachnoiditis."

COMMENT

The neurological complications of spinal anesthesia occur in those regions of the central nervous system or its membranes most closely situated to the site of injection of the anesthetic compound. This is attested by the reported cases, together with operative and post-

operative observation. These sequelae are rarely due to direct injury since such accidents are not found after lumbar puncture. In rare cases, marked symptoms occur in patients who complain of severe pain during the injection of the anesthetic; intramedullary hemorrhage has been reported (32, 71) in a fatal case of spinal anesthesia. On introduction of the effective agent into the subarachnoid space dilution and diffusion occur, but not before considerable absorption and fixation have taken place near the site of injection where the membrane and nerves are in contact with the full concentration of the anesthetic drug. This is important when correlated with the experimental work of Lundy, Essex, and Kernohan who reported, "the concentration of the drug is as important as the total dose so far as permanent effects are concerned."

Macdonald and Watkins have shown the concentration of the necessary anesthetic chemical substances in the anesthetic solution other than the anesthetic drug cannot produce paralysis. Moreover, experimental evidence has demonstrated that the anesthetic substance *does* have a myelolytic effect on the cord, most marked caudally and that "the posterior aspect and the periphery of the cord seem to be principally involved" (33).

In a large proportion of cases in the literature the site of injection has been at the level of the conus medullaris or even the lumbar enlargement of the spinal cord. Arnheim and Mage, in a study of 68 cases, found that in 27 cases injection was above and in 41 cases below the second lumbar vertebra. Newell states, "Spinal puncture can be made for the purpose of introducing an anesthetic agent anywhere from the fourth lumbar interspace up into the thoracic region!" His sole objection to administration at the higher levels is the increased possibility of "respiratory or circulatory collapse." Therefore, he recommends that the injection be made at the first lumbar interspace for upper abdominal operations, second lumbar interspace for lower abdominal operations, and third lumbar interspace for surgery of the perineum or extremities.

The contraindication to the use of spinal anesthesia in pre-existing disease of the central nervous system has already been dis-

cussed. Lundy and associates (53), however, go most absurdly and fallaciously far, writing, "Judging from our experiments, it seems probable that when paralysis follows the use of ordinary doses of spinal anesthetic agent, the spinal cord was previously diseased." Critchley reported 1 case of multiple sclerosis, 1 of progressive muscular atrophy, and another of neurosyphilis with the suggestion that spinal anesthesia may have been the precipitating agent of these diseases. Additional literature is available in which there has been reported an acute onset or exacerbation of central nervous system syphilis after spinal anesthesia (25, 69). Ericsson reported a case of paraplegia occurring immediately after spinal anesthesia for abdominal surgery in a 68 year old man who had a history of temporary paraplegia at the age of 20. The postmortem diagnosis 1 month later was "hemorrhage into the spinal cord."

Wyburn-Mason found that venous angiomatosis of the cord occur in 3 to 4 per cent of cases of laminectomy. Kaydi (1889) made a detailed study of the veins of the spinal cord and found that dilatations and tortuosities of these vessels were not uncommon, particularly on the posterior aspect of the cord. Case 9 of our series was seen to have marked varicosities of the spinal cord at the time of laminectomy. We do not doubt that these had been present before the administration of the anesthetic. However, this patient had had no complaints and had been on full active duty in the Army of the United States until the time of his herniorrhaphy. The paralysis, sensory loss, bladder and bowel incontinence, and impotence were caused by giving a spinal anesthetic. These palsies could not have been brought on by the use of any other form of anesthesia.

Federighi has commented on the increased sensitivity to spinal anesthesia in pregnancy, and notes that several deaths have been recorded after intrathecal injection of small doses of anesthetic preparations. Two cases of death within 45 seconds, after intrathecal injections of 2 cubic centimeters of amylocaine are reported by Walker and Matthews. After death of the mothers, successful cesarean sections were carried out. Bourne and Williams in

1948 record their opinion based on their experience in Queen Charlotte's Lying-in-Hospital and St. Mary's, London: "There is, we fear in this country a considerable number of young healthy pregnant women who stand condemned to death by spinal anaesthesia for Caesarean Section." Three of our patients sustained their symptoms as the result of spinal anesthesia for a cesarean operation.

A cautious approach has also been advised in elderly hypertensive patients with arteriosclerotic vessels, because of the possibility of the rapid and marked lowering of blood pressure in spinal anesthesia.

We do not question the advantages of the excellent and admirable relaxation of the abdominal musculature produced by spinal anesthesia. On the other hand, one cannot underestimate the gravity of the many possible complications nor the probability of their permanence; nor can we overlook the fact that often spinal anesthesia has to be supplemented by general anesthesia.

Spinal anesthesia has many dangers, far too little appreciated by surgeons and anesthetists.

SUMMARY

In summary, we have attempted to review the literature of this subject. We have reported 12 cases of grave paralyzes following the use of spinal anesthesia; these in addition to 3 other cases published by one of us in 1945 (44). It is to be noticed that throughout the literature there is a huge variation in the figures given of complicating nervous system symptoms. An explanation for such lack of uniformity in figures may very well be found in the fact that often and in the majority of our cases spinal cord symptoms appeared some considerable time after the patient had been discharged from surgical care, so that the surgeon and anesthetist and, indeed, occasionally the patient were unaware of the relationship of the progressive paralysis of the legs to the previous spinal anesthetic.

So, spinal anesthesia is accompanied by many definite and terrible dangers which are far too little appreciated by surgeons and anesthetists.

From a neurological point of view, we give the opinion that spinal anesthesia should be

rigidly reserved for those patients unable to accept a local or general anesthetic.

Paralysis below the waist is too large a price for a patient to pay in order that the surgeon should have a fine relaxed field of operation.

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Cooperative Study

Summary of the National Halothane Study

Possible Association Between Halothane Anesthesia and Postoperative Hepatic Necrosis

*Subcommittee on the National Halothane Study of the
Committee on Anesthesia, National Academy of Sciences-National Research Council*

Following extensive laboratory investigation, halothane (Fluothane), 1,1,1-trifluoro-2,2-bromochloroethane, was introduced to clinical anesthesia in England in 1956 and in the United States in 1958, and in its early years of use appeared to have an impressive record of safety. Careful consideration had been given to the possibility that halothane, in common with many other halogenated compounds, might damage the liver. Studies of hepatic function in the experimental animal and in man gave no indication of halothane-induced hepatic damage, but isolated reports of massive hepatic necrosis following halothane anesthesia soon appeared¹⁻³ and suggested the need for further investigation. In December 1961, the Committee on Anesthesia of the National Academy of Sciences-National Research Council (NAS-NRC) designated a study group to report periodically on all clinical aspects of halothane anesthesia and to give special attention to any evidence of association with fatal postoperative hepatic necrosis. In October 1962, a subcommittee of three was appointed to make recommendations on the need for and the feasibility of a clinical study of the relationship of halothane anesthesia to hepatic necrosis.

The subcommittee found the evidence insufficient to establish or refute a causal relationship between halothane and postoperative hepatic damage. Postoperative mortality from all causes was estimated at approximately 2%, but the number of deaths attributable to massive hepatic necrosis was thought to be very small, perhaps one death in 10,000 operations. No data were available on the incidence of hepatic necrosis in patients receiving other anesthetics or on the role of preexisting hepatic disease, viral hepatitis, or prolonged operative shock as etiological factors in postoperative hepatic failure. For these reasons, preliminary plans were drawn up for a randomized clinical trial, and a pilot study was begun in one medical center.

In May 1963, a drug warning was issued by the manufacturer on the basis of 12 new cases of fatal hepatic necrosis that followed surgical procedures in which halothane was used; several of the deaths followed cholecystectomy. The warning stated that "the administration of halothane to patients with known liver or biliary tract disease is not recommended." In the same month the NAS-NRC Subcommittee on the National Halothane Study was appointed, its members representing anesthesiology, statistics, internal medicine, pathology, and surgery. The National Halothane Study was initiated in June with funds provided by the National Institute of General Medical Sciences. It was recognized at the outset that the study would be large and difficult, but it was agreed that halothane was a drug of such potential value as to justify the most careful examination of the imputed risk as well as overall safety.

For editorial comment see page 811.

Before the subcommittee completed its plans for a cooperative study several additional cases of hepatic necrosis were reported. Some institutions had come to the point of sharply restricting the use of halothane to a few specific indications, but most potential collaborators probably would have cooperated in a randomized trial, and they did continue to use halothane during the course of the National Halothane Study. Thus, the ethical issue might not have been an overriding factor if the clinical trial had seemed the only way of obtaining data on which to base an inference. Considerations of feasibility and effort, however, strongly favored the retrospective survey as a first step and one that could possibly make a large clinical trial unnecessary. The plans for a clinical trial were discontinued in favor of a survey of experience in the years before the issue of hepatotoxicity had been seriously raised.

Fifty-four medical centers volunteered to participate in the collaborative retrospective study. When provided the exacting requirements of the proposed

For complete list of participants, see page 788.
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protocol, 16 of them, in view of limitations of personnel and problems in record retrieval, decided against participation. The protocol was tested and refined in a pilot study of the December 1962 records of the remaining 38 institutions. Three withdrew, and 35 contributed data on the four-year period from 1959 through 1962; 34 met the requirements of the protocol, and their data constitute the basis of the subcommittee's report.

The following is a summary of the major findings. A complete report will be published by the NAS-NRC.

Objectives

The primary objective of the study was to compare halothane with other general anesthetics as to incidence of fatal massive hepatic necrosis within six weeks of anesthesia. An equally important objective was to compare halothane with other general anesthetics as to total hospital mortality within six weeks of anesthesia, because it was recognized that, even if halothane were responsible for death from hepatic necrosis more often than were other anesthetics, the incidence would probably be small compared to an estimated overall operative mortality of approximately 2%. Indeed, a slight superiority in overall mortality for halothane could well outweigh any excess of deaths resulting from massive hepatic necrosis.

Design of the Study

It was anticipated that the incidence of fatal massive hepatic necrosis could be very small and that differences in the effects of anesthetics on total mortality might also be small. If the death rate is about 2% and it is desired to detect differences measured in tenths of 1%, then it is necessary to take a sample large enough to include many thousands of deaths. The experience of 1 million operations appeared to constitute a study of appropriate size. To bring so large a body of experience under scrutiny, it was necessary to obtain data from a large number of hospitals for a period of several years. A four-year period was chosen, and the participation of many hospitals served to broaden the medical experience upon which any conclusions ultimately would be based. Since it was in 1963 that several new reports of massive hepatic necrosis following halothane anesthesia precipitated widespread concern, and since this concern may well have subsequently influenced the selection of anesthetics, the survey was limited to the four-year period 1959 through 1962.

Deaths.—To determine the number of deaths, the protocol required each hospital to report postoperative deaths that occurred in the hospital within six weeks of general anesthesia and to abstract the case records, categorizing them by the type of anesthetic used at the patient's last operation.

Population Sample.—To provide information on the population of patients from which the deaths were gathered, each hospital was required to re-

port the number of administrations of general anesthetics in the survey period, categorized by anesthetic agents, and to abstract the records for a randomly selected sample of these cases.

Death Rates.—The information from deaths and population sample was used to calculate crude rates and to adjust these crude death rates within each anesthetic practice for differences in type of operation and such variables as age, sex, and physical status. For technical reasons, death rates are defined as deaths over deaths plus estimated administrations. This differs slightly from the usual method of calculating death rates but does not interfere with comparisons and interpretations.

Massive Hepatic Necrosis.—All deaths which were thought to represent massive hepatic necrosis were reported, and a photocopy of the chart as well as sections of hepatic tissue were submitted for review by an invited panel of six pathologists with a special interest in hepatic disorders. The protocol provided that members of the panel of pathologists should independently (1) describe the morphologic features in each tissue submitted and estimate the degree of necrosis without knowledge of the anesthetic or the clinical history; and (2) review, following step (1), an abstract of the clinical history, again with the anesthetic unknown, and express an opinion as to possible etiologic factors which might have caused the microscopic lesion.

Monthly Reports.—The protocol required that the participating institutions provide for each month: (1) a count of the total number of cases in which general anesthesia of all types was used; (2) for the random sample of general anesthetics, a list of individual cases along with chart number and date of operation; (3) a list of all hospital deaths occurring within six weeks of the administration of a general anesthetic, along with the patient's chart number and date of death; (4) coded abstracts of the clinical records of all patients who died within six weeks of general anesthesia and of those identified in the random sample, containing chart number, age, sex, date of discharge or death, whether necropsy was performed, whether massive hepatic necrosis was described at necropsy or given as a clinical diagnosis, cause of death, other clinical diagnoses, anesthetics used, physical status (evaluated preoperatively), duration of anesthesia, operations in the previous four years, and previous exposure to halothane; 100 two-digit operation codes were provided for coding operative procedures; (5) a list of final diagnoses for each abstracted case in which necropsy was performed; (6) photostatic copies of the relevant portions of the clinical record and blocks or slides of hepatic tissue from all cases with indications of massive hepatic necrosis, possible massive hepatic necrosis, or hepatitis.

Institutions were identified only by code numbers. After tabulation and coding, when the data were transferred from punch cards to computer

tapes, institutional code numbers were changed to afford maximum anonymity.

Results

During the four-year period of study, general anesthetics were administered approximately 856,500 times in the 34 hospitals providing data for this report. There were 16,840 deaths, and in 11,289 of these necropsy was performed; 10,171 of the necropsies included examination of the abdomen. Thus, complete necropsies were done in 60.4% of the cases.

Variations in Anesthetic Practice.—For comparisons anesthetic agents were separated into the following anesthetic practices: (1) halothane, (2) nitrous oxide-barbiturate, (3) cyclopropane, (4) ether, and (5) "other." When combinations of halothane, cyclopropane, and ether were used, they were placed in the fifth category, called "other." General anesthetics not included in the first four classes were also classified as "other."

The use of halothane increased from 11% in 1959 to 48.5% in 1962 (Table 1); simultaneously the use of nitrous oxide-barbiturate, cyclopropane, and ether fell proportionately. There were marked differences in anesthetic practice from one institution to another; these are shown in Table 2. Thus the use of ether varied from none to 38.5%, cyclopropane from 0.2% to 48%, and nitrous oxide-barbiturate from 1.9% to 73.3%. The use of halothane varied from a low of 6.2% to a high of 62.7%.

The choice of anesthetic used for several repre-

Table 1.—Percentage Distribution of Anesthetic Practice, by Year*

Year	Halothane	N-B†	Cyclopropane	Ether	Other	Estimated No. of Administrations
1959	11.0	35.5	20.5	17.3	15.7	207,261
1960	22.7	28.4	18.8	14.3	15.8	211,421
1961	35.1	23.4	16.4	9.6	15.5	210,728
1962	48.5	15.5	13.4	6.9	15.7	227,105
Total %	29.8	25.5	17.2	11.9	15.6	
Number	254,896	218,221	147,358	102,014	134,026	856,515

*Numbers vary slightly or may not add to the exact total due to rounding.

†N-B=nitrous oxide-barbiturate.

sentative operative procedures is listed in Table 3. Certain anesthetics used frequently for one operation were used rarely for another. For example, cyclopropane was used commonly for hysterectomy but almost never for craniotomy. There was also considerable variation in the choice of anesthetic for patients of differing physical status. A striking example of this, as will be seen later, was the increased use of cyclopropane in patients of poor physical status and in patients undergoing emergency surgery, while ether was rarely used under these circumstances.

The physical status of patients was recorded preoperatively in accordance with the classification of the American Society of Anesthesiologists as follows: (1) no complicating systemic disturbance, (2) moderate complicating systemic disturbance, (3) severe complicating systemic disturbance, (4)

Table 2.—Percentage Distribution of Anesthetic Practice, by Institution

Institution	Halothane	N-B	Cyclopropane	Ether	Other	Estimated No. of Administrations
1	41.7	38.6	0.2	14.4	5.1	39,891
2	43.9	19.3	19.7	6.0	11.1	9,537
3	10.6	57.0	11.1	2.0	19.2	24,828
4	38.9	26.9	12.1	9.2	12.8	29,232
5	22.8	16.2	48.0	2.7	10.2	32,887
6	27.9	39.4	3.0	6.0	23.8	30,261
7	23.6	12.4	37.6	6.2	20.2	11,419
8	39.8	17.6	1.6	28.0	13.1	91,225
9	13.1	35.0	6.0	38.5	7.3	55,455
10	46.3	19.5	17.8	10.8	5.7	29,230
11	35.4	16.4	10.3	22.6	15.4	26,255
12	32.6	12.0	47.3	0.9	7.2	25,137
13	32.3	8.5	23.0	2.6	33.7	6,893
14	19.2	23.8	26.4	0.5	30.1	27,086
15	13.2	27.8	31.6	10.8	16.6	30,272
16	11.3	51.1	8.7	1.4	27.5	16,076
17	17.4	12.9	3.6	38.3	27.7	19,760
18	24.0	23.0	26.9	18.9	7.2	8,900
19	39.1	34.8	15.5	2.8	7.9	18,329
20	6.2	10.7	45.8	14.7	22.5	47,509
21	34.4	23.1	19.5	2.5	20.5	65,154
22	45.4	12.1	25.1	4.2	13.2	31,162
23	21.7	38.4	34.8	0	5.1	9,776
24	16.2	73.3	5.6	1.2	3.7	15,291
25	37.5	8.4	25.7	3.6	24.8	8,447
26	46.2	34.4	5.0	4.9	9.5	37,661
27	33.2	16.1	17.3	6.3	27.1	27,259
28	43.1	41.8	0.7	12.4	2.1	7,062
29	62.7	5.7	11.1	1.2	19.3	3,917
30	52.3	22.7	7.6	0	17.4	4,407
31	32.8	26.5	19.0	10.8	10.8	12,490
32	53.3	11.8	13.9	1.1	19.9	15,532
33	21.2	39.9	9.0	9.7	20.2	26,826
34	11.3	1.9	42.7	2.8	41.4	11,354
Total	29.8	25.5	17.2	11.9	15.6	

Table 3.—Percentage Distribution of Anesthetic Practice, by Selected Operations

Operation	Halothane	N-B*	Cyclopropane	Ether	Other	Estimated No. of Administrations
Hysterectomy	20.0	16.1	31.6	15.6	16.7	41,018
Cholecystectomy	28.9	17.3	30.8	12.3	10.7	13,783
Cholecystectomy and/or common-duct exploration	32.0	20.6	23.9	10.6	12.9	6,263
Cholecystectomy and other procedures	23.4	17.3	27.9	16.4	15.0	7,631
Gastrectomy	19.1	11.7	30.0	22.3	16.9	16,065
Craniotomy	56.3	22.3	1.0	11.9	8.5	16,773

*N-B = nitrous oxide-barbiturate.

extreme complicating systemic disturbance, (5) emergency classes 1 and 2, (6) emergency classes 3 and 4, and (7) moribund.

Hepatic Necrosis.—The panel on pathology examined sections of the liver microscopically in 946 cases in which massive hepatic necrosis was suspected. In 222 cases, the panel confirmed the presence of hepatic necrosis not obscured by autolysis and not explainable by tumor, infarct, or abscess. Eighty-two of the 222 were scored as massive necrosis, 115 were intermediate, and 25 minimal.

The extent of necrosis was rated by each pathologist independently on a scale from zero (none) to 4+ (total parenchymal destruction). These ratings were averaged and the cases were separated into three categories: massive, average score 2.6+ or above; intermediate, 1.6+ to 2.5+; and minimal necrosis, 1.5+ or below. Minimal necrosis was considered to be a commonplace and negligible occurrence in any necropsy population and these cases were thereafter disregarded.

The 82 cases of massive hepatic necrosis were collected from the 10,171 necropsies, or approximately one in 125 necropsies, and approximately one in 10,000 administrations of general anesthe-

sia. Careful checking and rechecking of data-collection procedures ensured that practically all instances of massive hepatic necrosis among the necropsied cases were detected. There was no reliable way, however, of estimating the incidence of hepatic necrosis in the 5,551 cases in which necropsy was not performed or in the 1,118 in which partial necropsy, which did not include abdominal examination, was performed.

If the 115 cases of intermediate hepatic necrosis are added to the 82 with massive destruction, the combined incidence is 1 in 4,400 (or 2.3 in 10,000) administrations of general anesthesia. On the other hand, any inferences drawn from the data on intermediate necrosis should be weighed with caution. The study was designed to detect massive hepatic necrosis, and cases with less than massive necrosis were culled only to avoid missing an occasional instance of the more extensive lesion. Accordingly, principal attention was directed, as planned, to the group with massive hepatic necrosis.

Operations were grouped for purposes of analysis on the basis of low, middle, and high death rate. The low-death-rate category consisted of operations on the mouth and eye, herniorrhaphy, dilatation and curettage, hysterectomy, cystoscopy,

Table 4.—Observed and Expected* No. of Cases of Massive Hepatic Necrosis Following High-, Middle-, and Low-Death-Rate Operations

Operation Group and Status†	Halothane	N-B‡	Cyclopropane	Ether	Other	Total
Low death rate						
Necrosis observed	2	0	1	0	0	3
Necrosis expected	0.7	0.9	0.6	0.4	0.5	3
EA	86.7	105.3	67.5	50.1	57.4	367.0
Rate, per 10,000 EA	0.23	0	0.15	0	0	0.08
Middle death rate						
Necrosis observed	13	6	17	4	7	47
Necrosis expected	16.1	11.1	7.5	4.9	7.9	47
EA	146.2	101.3	68.1	44.3	67.5	427.4
Rate, per 10,000 EA	0.89	0.59	2.50	0.90	1.04	1.10
High death rate						
Necrosis observed	11	9	7	1	4	32
Necrosis expected	11.3	6.0	6.1	3.9	4.7	32
EA	21.8	11.6	11.7	7.6	9.1	61.7
Rate, per 10,000 EA	5.05	7.78	5.99	1.31	4.40	5.18
Operation unknown						
EA	0.2	0.1	0	0	0.1	0.4
Total						
Necrosis observed	26	15	25	5	11	82
Necrosis expected	24.4	20.9	14.1	9.8	12.8	82
EA	254.9	218.2	147.4	102.0	134.0	856.5
Rate, per 10,000 EA	1.02	0.69	1.70	0.49	0.82	0.96

*The rates of necrosis expected were computed by distributing the observed necrosis cases proportional to the number of estimated administrations. For example,

$$\text{Necrosis expected (halothane)} = \frac{\text{Total EA} \times \text{EA (halothane)}}{\text{Total EA}} = \frac{3 \times 86.7}{367} = 0.7.$$

†EA = estimated administrations. Figures for EA are in thousands.

‡N-B = nitrous oxide-barbiturate.

Table 5.—Distribution of Massive Hepatic Necrosis, by Operation and Anesthetic Practice

Operation	Halothane	N-B*	Cyclopropane	Ether	Other	Total	Estimated No. of Administrations
Oral	1	1	80,218
Craniotomy	3	3	16,773
Endoscopy	1	1	15,696
Lung	1	2	1	4	10,023
Heart with pump	6	9	1	1	2	19	8,683
Heart without pump	1	1	7,948
Mediastinum	1	...	1	2	4,195
Cholecystectomy only	1	...	1	2	13,783
and/or common-duct exploration	2	2	6,263
with other major surgery	...	2	2	7,631
Subphrenic abscess	1	1	197
Exploratory laparotomy†	2	...	5	...	2	9	18,370
Gastrectomy	2	...	3	1	2	8	16,065
Small bowel	2	1	1	4	5,394
Large bowel	1	1	17,893
Closure evisceration	1	1	1,239
Large vessel	...	2	4	...	3	9	7,212
Sympathectomy, adrenal	1	1	3,156
Spleen, liver	2	...	1	1	...	4	3,112
Caesarean section	1	1	2,476
Hydrocele	1	1	11,648
Fracture, closed	1	1	9,535
Muscle	1	1	16,884
Fracture, open	1	...	1	10,371
Plastic	2	2	40,389
All others	521,361
Total	26	15	25	5	11	82	
No. of estimated administrations	254,898	218,223	147,356	102,015	134,023		856,515

* N-B = nitrous oxide-barbiturate.

† Exploratory laparotomy included inoperable cancer (2), lysis of adhesions (3), and evacuation of hematoma and control of hemorrhage (4).

and plastic procedures. The high-death-rate group included craniotomy, open-heart operations, exploratory laparotomy, and large-bowel procedures. All other operations were arbitrarily categorized as middle death rate. (Mammoplasty, in which no deaths occurred, was omitted from the above classification. Consequently, the total estimated administrations are 528 cases short of the total for the study.)

Hepatic necrosis occurred more frequently after operations associated with high death rates (Table 4). Thus, there were three cases of massive necrosis following 366,992 low-death-rate operations (or approximately 0.1 per 10,000), 47 following 427,355 middle-death-rate operations (1.1 per 10,000), and 32 following 61,719 high-death-rate operations (5 per 10,000). The distribution of massive hepatic necrosis by operation and anesthetic practice is presented in Table 5. Nineteen, or nearly one fourth, of the cases followed open-heart operation with cardiopulmonary bypass, although these procedures accounted for only 1% of all operations in the study. Operations on the large blood vessels (primarily the aorta), gastrectomy, and exploratory laparotomy (such as lysis of adhesions for relief of intestinal obstruction, confirmation of

inoperable neoplasm, control of hemorrhage, and drainage of abscess) were also associated with a relatively high incidence of massive hepatic necrosis.

Contrary to expectations, an increased incidence of massive hepatic necrosis following biliary tract operations did not occur. An estimated 27,677 patients underwent cholecystectomy and/or common-duct exploration or with other major surgery, and massive hepatic necrosis occurred in only six of these, a rate somewhat less than for most other abdominal operations. One of the six patients had received halothane, whereas halothane was administered for approximately 30% of the cholecystectomies and/or common-duct exploration (Table 3). Massive hepatic necrosis occurred in an additional three patients who had undergone a biliary tract procedure at a previous operation within six weeks of death, and one of these had received halothane.

The highest rate of massive hepatic necrosis followed administration of cyclopropane, particularly in the middle-death-rate group, as shown in Table 4. Cyclopropane was also the anesthetic with the second highest rate of hepatic necrosis in the high-death-rate group, despite the fact that it was used in only 10% of open-heart operations. The

Table 6.—Observed and Expected No. of Cases of Massive Necrosis Following Multiple Operations,* by Halothane Administration

Massive Hepatic Necrosis	Halothane Administration				Total
	Last & Previous Operations	Previous Operation Only	Last Operation Only	None	
Observed	10	0	0.3	11	24
Expected	4.2	2.7	3.6	13.5	24
Estimated administrations	14,100	9,000	12,000	45,500	80,600

* "Multiple operations" is defined as two or more operations under general anesthesia in the same or successive months.

Table 7.—“Unexplained” Cases of Massive Hepatic Necrosis*

Case No.	Age, yr	Sex	Anesthetic Used	Operative Procedure	No. of Operations Within 6 wk	Day of Post-operative Jaundice†	Day of Death Following Operation†	No. of Previous Exposures to Halothane
55	72	M	Other‡	Cholecystectomy; control postoperative hemorrhage	2	No jaundice	2-2	None
64 ^o	70	F	Halothane	Cholecystectomy and biopsy, liver (normal)	1	14	20	None
91	66	F	Halothane	Excision skin cancer, popliteal area; debridement and graft	2	26-3	31-8	1
97 ^a	67	M	Halothane§	Closure, perforated ulcer; subtotal gastrectomy	2	19-9	19-9	1
98 ^a	16	F	Halothane	Repair lacerated tendons of wrist	1	No jaundice	14	None
99	21	M	Halothane	Craniotomy with biopsy; ventriculogular shunt	2	No jaundice	14-5	1
122 ⁷	58	F	Halothane	Endoscopy; cholecystectomy and repair of hiatus hernia; debride and pack of wound; resuture wound dehiscence	4	30-24-5-1	34-28-9-5	3
255	45	F	Halothane	Laparotomy and biopsy	1	28	35	None
352	75	M	Cyclopropane	Laparotomy and release of adhesions	1	1	1	None

* A case was unexplained if three or more (of four) examiners were unable to explain the extent of hepatic necrosis on the basis of patient's underlying disease, surgical procedure, or recognizable postoperative complication. Evaluation was carried out without explicit knowledge of anesthetic agents used, although four cases had been publicized in the literature.

† Day is given as time following each operation listed.

‡ Nitrous oxide-ether was used for cholecystectomy, ethylene for control postoperative hemorrhage.

§ Alcoholism was a contributing factor.

incidence of massive hepatic necrosis following administration of halothane was virtually the same as that following administration of nitrous oxide-barbiturate or “other” anesthetics, slightly more than with ether, and considerably less than with cyclopropane.

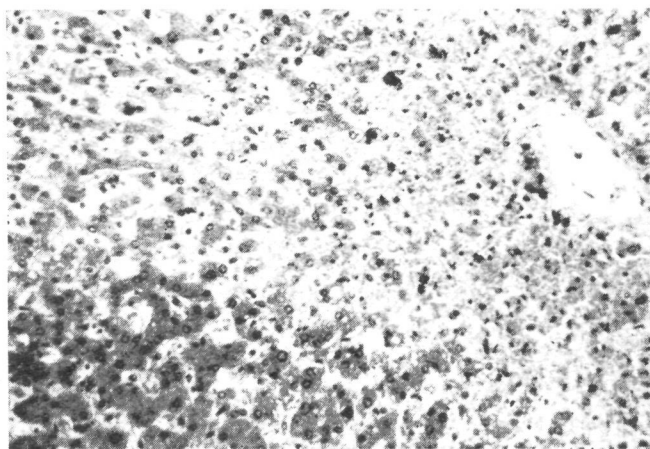
There were 80,600 patients who had two or more operations while under general anesthesia in the same or in successive months. In Table 6 it is seen that the incidence of massive hepatic necrosis was considerably higher (24 per 80,600, or 3 per 10,000) in patients who had undergone multiple procedures than in patients who had not (58 per 775,900 or 0.7 per 10,000), and this seemed particularly true of halothane (10 per 14,100 or 7.1 per 10,000).

Usually there appeared to be an adequate clinical explanation for the massive hepatic necrosis observed at necropsy: shock, especially with prolonged use of vasopressors; overwhelming infection; severe and prolonged congestive heart failure; and preexisting liver disease. In a few cases, however, the underlying reason for hepatic necrosis was not easily established; accordingly, four members of

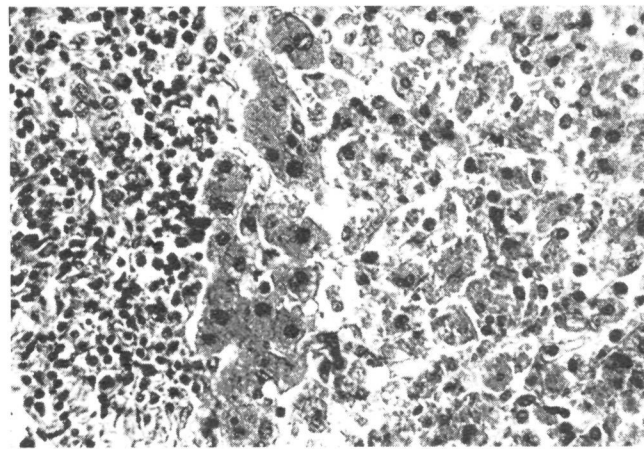
the subcommittee independently reviewed the 82 cases of confirmed massive hepatic necrosis. They classified each case of necrosis as “explained” or “unexplained” on the basis of whether or not the necrosis could be assigned to a recognizable clinical factor. These ratings were made from a summary of the clinical record in which the identity of the anesthetic agents had been deliberately omitted.

Among the 82 cases of confirmed massive hepatic necrosis nine were considered to be unexplained by at least three of the four members of the subcommittee (Table 7); seven patients had received halothane for the final operation, one had received cyclopropane, and one had received “other” (ethylene). Of the nine patients, five had undergone one or more previous operations within six weeks of the final procedure. Of the five, four had received halothane on at least two occasions and the fifth had received ethylene for the final operation, ether for the previous one.

Unexplained liver failure was usually characterized by fever within two or three days after operation, soon followed by jaundice, which deepened progressively, and a tender, palpable liver. Con-



1. “Shock lesion.” Central congestion affects approximately three fourths of hepatic lobule. Liver cells have disintegrated although scattered pyknotic, nuclear fragments are apparent. Kupffer cells contain abundant hemosiderin. There is only negligible inflammatory reaction ($\times 150$).



2. Massive hepatic necrosis with thin, irregular rim of disturbed parenchymal cells in periportal region. Rest has undergone necrosis and consists of coagulated, eosinophilic masses of cytoplasm with and without pyknotic, nuclear remnants. Intermingling of histiocytes and neutrophils is modest ($\times 200$).

Table 8.—Crude Death Rate, by Institution and Anesthetic Practice, Percentage Dying Within Six Weeks

Institution	Halothane	N-B*	Cyclopropane	Ether	Other	Total
1	1.12	0.36	6.73	0.09	1.85	0.73
2	5.13	4.85	8.62	3.72	8.22	6.05
3	0.94	0.74	0.72	0.21	1.02	0.80
4	0.91	1.23	5.91	3.37	5.00	2.39
5	4.24	4.78	2.14	5.78	5.53	3.51
6	1.06	0.86	2.51	3.00	0.83	1.09
7	5.33	3.09	2.23	7.54	7.58	4.53
8	1.81	0.71	3.47	1.16	1.75	1.46
9	3.47	1.30	3.50	1.09	2.47	1.73
10	1.66	2.60	5.36	1.32	4.72	2.66
11	1.36	1.63	3.00	2.02	3.59	2.07
12	2.13	0.99	1.43	2.95	5.92	1.97
13	3.10	2.02	5.83	1.11	2.64	3.45
14	0.54	0.17	0.78	4.00	0.49	0.52
15	1.58	1.51	1.95	1.83	2.74	1.90
16	3.56	2.99	5.47	1.30	2.54	3.13
17	1.49	0.31	2.62	0.24	1.60	0.93
18	3.30	3.53	4.93	0.59	6.57	3.54
19	3.09	1.24	3.31	0.39	5.20	2.58
20	1.44	0.80	1.11	1.84	2.43	1.51
21	1.10	1.21	1.44	1.19	1.31	1.24
22	1.69	2.38	1.73	0.61	3.14	1.93
23	0.84	1.06	0.56	0/0	1.19	0.84
24	5.59	4.39	21.01	13.04	17.28	6.34
25	3.83	6.55	7.11	7.03	9.23	6.41
26	0.71	1.00	4.01	0.54	1.33	1.03
27	1.07	0.68	2.34	0.35	0.66	1.07
28	0.33	0.17	0.00	0.23	1.34	0.27
29	3.50	6.25	7.46	4.00	3.82	4.18
30	5.34	4.50	7.18	0/0	2.54	4.82
31	1.42	0.69	3.22	0.07	1.31	1.42
32	1.63	0.76	3.05	0.00	1.81	1.75
33	3.57	1.29	4.21	2.36	2.90	2.48
34	0.85	2.28	1.53	1.56	1.76	1.56
Total	1.87	1.49	2.54	1.35	2.51	1.93

*N-B = nitrous oxide-barbiturate.

fusion, somnolence, and a flapping tremor developed within a week after the onset of fever. The confusion usually progressed rapidly to coma and death. Hypotension was a late manifestation, usually appearing only on the day of death. The total duration of the illness was brief, the longest interval between the onset of symptoms of liver failure and death being nine days. The course was similar to that associated with fulminant viral hepatitis⁴ and to that associated with delayed chloroform poisoning. In contrast, the patients in whom necrosis was considered explained were seriously ill, usually with shock for many hours or days or, less frequently, with severe congestive heart failure. Half the patients with hypotension became anuric. Jaundice was a less frequent manifestation, usually only terminally. In most cases, hepatic injury was not suspected during life.

The appearance of the liver on histologic examination in the explained cases of massive hepatic necrosis was, in most instances, consistent with

that observed in shock or hypoxia, reflecting the severe circulatory disorders which occurred in almost all of these patients prior to death. These sections were characterized by centrilobular congestion and, ultimately, pooling of sinusoidal blood. Paralleling this was attenuation and disappearance of parenchymal cells with relatively little inflammatory reaction. Fatty vacuolization was mild and limited to the cells bordering upon the necrotic zone (Fig 1).

The appearance on histologic examination of specimens from the nine unexplained cases of massive hepatic necrosis varied considerably. Of the seven unexplained cases that followed halothane administration, six presented a lesion which was thought by the majority of the members of the panel on pathology to simulate the lesions of viral or of certain drug-induced forms of hepatitis. In these lesions the hepatic cellular necrosis was coagulative in character and sinusoidal congestion was a minor feature. Intralobular inflammation

Table 9.—Crude Death Rate for Selected Operations, by Anesthetic Practice, Percentage Dying Within Six Weeks

Operation	Halothane	N-B*	Cyclopropane	Ether	Other	Total
Hysterectomy	0.17	0.23	0.26	0.33	0.41	0.27
Cholecystectomy	0.72	0.88	1.21	1.11	2.63	1.16
Cholecystectomy and/or common-duct exploration	2.29	3.16	4.60	3.63	4.16	3.41
Cholecystectomy and other procedures	4.03	3.30	5.05	3.62	5.14	4.29
Gastrectomy	4.19	5.59	6.25	2.67	5.29	4.84
Craniotomy	9.17	9.74	12.37	6.54	18.46	9.91

*N-B = nitrous oxide-barbiturate.

Table 10.—Postoperative Mortality, by Mortality Level of Surgical Procedure and Anesthetic Practice

Mortality Level of Surgical Procedure	Halothane	N-B*	Cyclopropane	Ether	Other	Total	Percent
			Estimated Administrations, Thousands				
Low	86.7	105.3	67.5	50.1	57.4	367.0	42.8
Middle	146.2	101.3	68.1	44.3	67.5	427.4	49.9
High	21.8	11.6	11.7	7.6	9.1	61.7	7.2
Operation unknown	0.2	0.1	0.0	0.0	0.1	0.4	0
Total	254.9	218.2	147.4	102.0	134.1	856.5	100
			Number of Deaths				
Low	234	209	175	63	163	844	5.0
Middle	2,562	1,757	2,397	837	2,073	9,626	57.1
High	2,066	1,323	1,270	492	1,205	6,356	37.7
Operation unknown	1	3	3	4	3	14	0.1
Total	4,863	3,292	3,845	1,396	3,444	16,840	100
			Death Rate, %				
Low	0.27	0.20	0.26	0.13	0.28	0.23	
Middle	1.72	1.71	3.40	1.86	2.98	2.20	
High	9.48	11.43	10.86	6.47	13.27	10.30	
Total	1.87	1.49	2.54	1.35	2.51	1.93	

* N-B = nitrous oxide-barbiturate.

was variable and usually appeared as an intermixture of histiocytes and neutrophils among the necrotic epithelial cells. The portal areas frequently exhibited a lymphocytic exudate. Fatty degeneration was variable but usually negligible (Fig 2). On occasion, the lymphocytic exudate in the portal area, moderate in the specimen shown in Fig 2, was quite pronounced.

In one of the six unexplained cases following halothane administration in which there was a lesion simulating hepatitis, there were also histological features suggesting superimposed shock. The lesions in the remaining three unexplained cases were consistent with shock; one followed administration of halothane; one, cyclopropane; and one, ethylene ("other").

Death Rates.—The overall crude death rate following general anesthesia and operations was 1.93% (Table 8) with considerable variation among the five anesthetic practices. The lowest overall rate, 1.35%, followed ether administration, and the highest, 2.54%, followed cyclopropane administration. Table 8 also shows that there were large variations in overall death rate among the 34 institutions. The lowest institutional death rate was 0.27%, and the highest was 6.41%, a considerable variation. Some, but not all, of the differences among anesthetic agents and among institutions could be ac-

counted for by differences in operation, age, and physical status. However, the differences among institutions, even after adjustments for such "interfering variables" remain very much larger than the differences among anesthetics.

The mortality for several representative procedures and for the five anesthetic groups is presented in Table 9. In Table 10 is presented the distribution of cases for the five anesthetic practices, divided for analysis into low-, middle-, and high-death-rate operation categories. A large share of the procedures, 43%, and a very small share of the deaths, 5%, were associated with the seven low-death-rate operations. Half the procedures and 57% of the deaths occurred in the middle-death-rate group. The overall death rate in the middle-death-rate operations is about ten times as great as that in the low-death-rate category. The high-death-rate group involves about 7% of the procedures and includes 38% of the deaths; the overall death rate is 45 times as great in the high- as in the low-death-rate group.

Mortality varied considerably among the five anesthetic practices. Mortality following operations with the patient under halothane anesthesia, both overall (Table 8) and following specific procedures (Table 9), was lower than average. Cyclopropane and "other" were generally associated with the highest death rates. The anesthetics compared

Table 11.—Rate of Death (%) Within Six Weeks for Middle-Death-Rate Operations, by Anesthetic Practice and Physical Status of Patient

Physical Status*	Halothane	N-B†	Cyclopropane	Ether	Other	Total
Unknown	1.77	1.52	2.93	1.89	2.31	1.99
1	0.19	0.17	0.33	0.26	0.35	0.24
2	1.52	1.60	2.56	1.49	2.12	1.78
3	6.92	6.92	10.56	5.52	6.89	7.24
4	15.53	15.40	18.64	22.43	18.45	17.27
5	1.12	1.23	1.36	2.08	2.33	1.44
6	10.89	12.19	12.49	14.40	14.41	12.53
7	25.19	23.72	33.75	28.51	38.60	31.48
Total	1.72	1.71	3.40	1.86	2.98	2.20
Standardized death rate	1.94	1.94	2.85	2.12	2.52	2.20
Standard ratio‡	0.88	0.88	1.29	0.96	1.15	

* Physical-status classification is explained in the text.

† N-B = nitrous oxide-barbiturate.

‡ Standard ratio is obtained by dividing the standardized rate by figure 2.21, which is the standardized rate calculated by applying average death rates within anesthetic risk categories to the overall population. This ratio shows whether an agent has a higher or lower death rate than "average," ratios larger than 1 being higher, and less than 1 being lower than average.

Table 12.—Percentage Distribution of Patients With Middle-Death-Rate Operations, by Physical Status and Anesthetic Practice

Physical Status*	Halothane	N-B†	Cyclopropane	Ether	Other	Total
Unknown‡	16.2	16.2	14.9	16.3	17.8	16.2
1	45.1	46.3	40.3	45.8	38.0	43.5
2	25.2	24.6	20.7	24.4	25.9	24.4
3	6.1	6.7	5.6	8.2	9.1	6.9
4	0.8	0.6	1.0	0.5	1.2	0.8
5	4.5	3.3	10.9	2.9	4.4	5.1
6	1.8	1.9	5.6	1.6	3.0	2.6
7	0.3	0.3	1.1	0.4	0.6	0.5
Total estimated administrations, thousands	146.2	101.3	68.1	44.3	67.5	427.4

*Physical status classification is explained in text.

†N-B = nitrous oxide-barbiturate.

‡The numbers in "Unknown" row are large because some hospitals do not use the index for classification.

somewhat differently with one another on death rates in the three groups of operations. As examples: ether appears to be best in the high- and low-death-rate groups, but not in the middle group; "other" appears to be worst in both the high and low groups, but not in the middle group. But before attaching any weight to these comparisons of anesthetics, it is important to recognize that the anesthetic populations need to be balanced or adjusted for such features as the age and sex of the patient, his physical condition, and the particular operation performed.

To illustrate an adjustment for one important variable, Table 11 displays the death rates for each of the anesthetic practices for the middle-death-rate operations, categorized by preoperative physical status. The right-hand column shows that the death rate depended strongly on this variable, ranging from about 0.25% to more than 30%; and Table 12 shows that cyclopropane had a disproportionately large share of patients in physical-status classes 5 (emergency), 6 (emergency), and 7 (moribund), which are the high-death-rate categories. The overall death rate for cyclopropane can thus be expected to be higher simply because of its being administered more frequently to patients in these high-risk groups. Standardizing the death rate for physical status is one way of adjusting for this kind of imbalance; it is calculated for cyclopropane, for example, by taking the cyclopropane death rates for each physical-status category and calculating what the overall death rate for cyclopropane would have been had these rates been applied to the population of the study as a whole. Standardization reduces the death rate for cyclopropane from 3.4% to 2.85% (Table 11). Although an adjustment of 0.5% may seem small, when applied to the 68,109 middle-death-rate cyclopropane operations, the difference comes to about 368 deaths, or 286 more than the total number of massive hepatic necroses

for the entire study. The standardized rates for the other agents are similarly computed. The standardization for physical status has made halothane, nitrous oxide-barbiturate, and ether look somewhat less favorable than they did before, and both cyclopropane and "other" somewhat less unfavorable. Much of the variation in the crude death rates, that is, merely reflects differences in the selection of patients, classified as to physical status.

The death rates can be standardized for each of the interfering variables one at a time, and in the complete report this has been done. But it is obviously desirable to take account of joint effects by adjusting simultaneously for such variables as age, physical status, and operation before comparing death rates for the various anesthetic practices. Methods for making such simultaneous adjustments in a body of data this large and complex are somewhat experimental in character, and one of the important outcomes of this study has been to strengthen and deepen the statistical methodology for such problems. A variety of approaches has been employed and is presented in detail in the complete report; they all lead to very similar interpretations of the data. Table 13 presents a summary of the data based on one of these approaches, called the "smoothed contingency table analysis." This analysis "smooths" the data of a multidimensional contingency table by replacing the original counts by fitted counts based on the one-, two-, and sometimes three-dimensional margins of the original table.

Table 13 gives the main summary statistics for the entire death-rate study insofar as they are discussed in this summary report. This table shows that, for the low-death-rate operations, "other" had much the highest smoothed death rate, although it is only about one third of 1%, and that nitrous oxide-barbiturate and ether had the lowest. For the middle-death-rate operations, the death rates

Table 13.—Death Rates Standardized for Physical Status, Age, and Sex, Percentage Dying Within Six Weeks

Mortality Level of Surgical Procedure	Halothane	N-B*	Cyclopropane	Ether	Other	Total
Low	0.23	0.16	0.26	0.18	0.34	0.22
Middle	1.92	1.97	2.77	1.85	2.58	2.21
High	8.54	9.23	12.58	8.30	10.84	9.33

*N-B=nitrous oxide-barbiturate.

Table 14.—Smoothed Death Rates for Cholecystectomies in Patients of Physical Status 1, 2, and 5,* Percentage Dying Within Six Weeks

Sex	Age, Yr	Halothane	N-B†	Cyclopropane	Ether	Other
Cholecystectomy Alone						
F	0-49	0.05	0.07	0.04	0.04	0.18
M	0-49	0.10	0.14	0.07	0.10	0.43
F	50-69	0.28	0.34	0.35	0.40	0.80
M	50-69	0.54	0.67	0.71	1.12	1.96
Cholecystectomy and/or Common-Duct Procedures						
F	0-49	0.21	0.31	0.18	0.14	0.34
M	0-49	0.41	0.61	0.36	0.39	0.85
F	50-69	1.01	1.39	1.59	1.42	1.44
M	50-69	1.93	2.67	3.17	3.84	3.50

*Physical-status classification is explained in the text.

†N-B = nitrous oxide-barbiturate.

were generally about ten times higher, and ether, halothane, and nitrous oxide-barbiturate definitely had the lowest rates in this category, with "other" and cyclopropane greater by a large margin. The high-death-rate operations exhibited exactly the same pattern as the middle-death-rate operations, except that cyclopropane stood out even more clearly as having the highest death rate among the five.

In this study, the reliability of death rates for ether is much poorer than for the remaining commonly used anesthetics. Not only is ether used less often than the other agents but also it is used much less widely. Half of the institutions used ether in fewer than 5% of surgical operations, and about one half of all the exposures occurred in a particular two of the institutions. These limitations in the basic data require great diffidence in interpreting the death rates for ether.

Cholecystectomies.—The complete report includes death rates associated with specific operations, among which cholecystectomies are of special interest. Table 14 shows smoothed death rates associated with cholecystectomy alone and for cholecystectomy with common-duct exploration, for both sexes, two age groups, and the better physical status groups (1, 2, 5). For these selected groups (chosen because they had cases enough to make them worth presenting), the anesthetics had similar death rates, and halothane had as low a rate as any.

Table 15 shows standardized death rates for cholecystectomies in patients of physical-status classes 1-6; halothane had the lowest rate by 0.4%; nitrous oxide-barbiturate, cyclopropane, and ether had nearly identical rates; and "other" had the highest rate. Standardization was based on operation code, sex, age, and physical status. To check whether halothane's good overall record came primarily from its better performance with patients

in good preoperative physical condition, death rates were also computed for patients in poorer physical-status classes (3, 4, 6) for cholecystectomy and for cholecystectomy and/or common-duct exploration (physical status 7 omitted because of too few cases). For these patients, halothane had lowest or second lowest death rates.

Craniotomy.—The use of halothane for craniotomy was also singled out for careful examination, since the drug warning of May 1963 had also cautioned that halothane may increase intracranial pressure and, by implication, that it might be unsafe for craniotomy. Halothane and nitrous oxide-barbiturate were the most frequently used anesthetics for craniotomy (Table 3), with halothane used 2½ times as often as nitrous oxide-barbiturate and cyclopropane used rarely. Among patients under age 50, halothane had a lower death rate than nitrous oxide-barbiturate; among patients age 50 and over, nitrous oxide-barbiturate had the lower death rate. Ether was used only half as often as nitrous oxide-barbiturate, and ether's death rate was the lowest.

Comment

Hepatic Necrosis.—Massive hepatic necrosis occurred infrequently following general anesthesia and operation in the experience of the 34 hospitals during the years 1959-1962. When necrosis did occur, it could usually be attributed to shock, overwhelming infection, or preexisting liver disease. Nevertheless, there were nine cases among the 82 cases of massive hepatic necrosis for which no clear explanation could be found; in these cases it is reasonable to consider the possibility that hepatic necrosis could have been caused by the anesthetic.

Seven of the nine patients with unexplained massive hepatic necrosis had received halothane during the final operative procedure. Five of the seven died following clinically evident liver failure; this was in contrast to the patients whose massive necrosis was considered explained by prolonged shock or overwhelming sepsis, and in most of whom liver failure was not suspected clinically. The pattern of hepatic injury displayed upon microscopical examination in six of the seven unexplained cases which followed halothane administration resembled that observed in viral or in certain drug-induced forms of hepatitis, again in contrast to the pattern

Table 15.—Percentage Distribution of Death Rates Standardized for All Cholecystectomies in Physical Status 1-6*

	Halothane	N-B†	Cyclopropane	Ether	Other	Total
All Patients	2.05	2.57	2.53	2.44	3.18	2.47
Estimated administrations, thousands	7.8	5.0	7.8	3.6	3.4	27.6

*Physical-status classification is explained in the text. Patients from physical status 7 were omitted because there were too few cases.

†N-B = nitrous oxide-barbiturate.

of the explained group, which was in almost every case consistent with the effects of shock.

It is not possible to say whether these very few cases of unexplained hepatic necrosis, or the apparent small excess of cases of liver necrosis following two or more exposures to halothane, were caused by halothane or whether they occurred by coincidence; for example, they might have been the result of preexisting or unrecognized viral hepatitis, which they resembled both clinically and pathologically. The principal considerations which bring us to question the validity of a cause and effect relationship in these cases are as follows.

There was no certain way to determine whether a patient who died with clinical evidence of liver failure might have been more likely to undergo necropsy if halothane had been administered. A small number of such cases could result in the apparent excess of unexplained massive hepatic necrosis among patients who received halothane, and yet not have a detectable effect on overall necropsy rates, which were almost identical for the five groups. The period of study, 1959-1962, was explicitly chosen to antedate the widespread concern that began early in 1963 and to minimize the likelihood of necropsy bias. Massive hepatic necrosis following halothane administration had been reported as early as 1958,^{1,2} however, and some suspicion must have been entertained during the period of the study.

The possibility of necropsy bias is of even greater concern in view of the approximately 40% of deaths without necropsy (or with partial necropsy in which the abdomen was not examined). This 40% "nonresponse" in necropsy represents such a large rate of nonresponse that confidence limits on rates computed from the completed necropsies would be either so broad as to be useless or based on strong assumptions that we are in no position to verify.

Reports of four of the seven cases of unexplained massive hepatic necrosis following halothane administration had been published,⁵⁻⁷ and an additional two were known to the participating institutions before the study began. The five institutions from which these six known cases came were invited or volunteered to join the study at least in part because of these cases. Thus, the inclusion of these cases in any comparison of hepatic necrosis rates for different anesthetics could lead to a "volunteer" bias in the overall estimate of massive hepatic necrosis following halothane administration. To illustrate the possible effect: if an event has a low rate of occurrence, perhaps 0.2 per institution per observation period, and we were to pick only institutions in which at least one event had occurred, then the method of selection would yield an average of about 1.2, or an upward bias of 1. The effect in the present study is smaller than that in the example because only a few institutions were subject to the effect, but qualitatively it is the same and quantitatively more than enough to

explain the apparent small excess of halothane cases.

Whatever the role of such a "volunteer" bias may have been, one might reasonably ask why care was not taken to ensure a selection of institutions which could have prevented such a possibility. The answer is that the National Halothane Study was designed to detect differences of a very different order of magnitude. It was originally feared that for every reported case of hepatic necrosis following halothane administration there were many unreported and that large differences among various anesthetics might be found. A most important observation of this study is that the many cases of massive hepatic necrosis which were expected to follow general anesthesia and operation did *not* materialize. We must conclude, therefore, that if there is a halothane-related hepatic necrosis, it occurs rarely.

Although the study failed to establish a causal relationship between halothane and hepatic necrosis, no study of this type could completely exclude the possibility of rare causation. Accordingly, until the matter is finally settled, unexplained fever and jaundice in a specific patient following halothane administration might reasonably be considered a contraindication to its subsequent use in that patient. The grounds for this position are to be found, not in this study, but in the usual medical doctrine that any treatment followed by ill effects should ordinarily not be repeated.

Although attention has been directed to patients who received halothane, the possible effect of other anesthetics should not be overlooked. Cyclopropane was followed by a greater incidence of massive hepatic necrosis than any of the other anesthetics. Since all but one of the 25 cases that followed cyclopropane administration were classified as explained, there is reason to believe that the disproportionately large total number might well have been related to the selective use of this agent for patients in shock. The possibility that cyclopropane damages the liver cannot be excluded, however. For example, it is possible that the splanchnic vasoconstriction which occurs as a result of cyclopropane and which is in part responsible for the support of blood pressure may, by decreasing hepatic blood flow, increase the likelihood of hepatic damage in shock.

Finally, it should be noted that since the initiation of the National Halothane Study there have been nine reports published of retrospective surveys of massive hepatic necrosis associated with anesthesia and operation.⁸⁻¹⁶ The total number of anesthetic administrations represented by these reports is 370,000 or more than a third as many as in the present study. The overall incidence of massive hepatic necrosis in these nine institutions was essentially the same as that of the present study, and the incidence of necrosis was almost the same for patients who received halothane as

for those who did not (0.88 and 0.73 per 10,000, respectively). These published reports lend further strength to our conclusion that the harmful effect, if any, of halothane on the liver is very small.

Death Rates.—The death rates reported in Tables 10 through 15 must be interpreted with caution. They can be trusted merely as a summary of experience involving some 856,500 surgical procedures with the contrasts among anesthetic agents largely disentangled from certain other variables which tend to affect surgical death rate: age, physical status, operation, and sex. It cannot be assumed, however, that the differences among death rates are definitely “caused” by the anesthetics. The reason is that we may not have adjusted for the effects of other variables, perhaps very important ones, which also affect the death rate and which may be related, for example, to how the anesthetic agent was chosen. To make the point clear, suppose that in some operations experienced surgeons worked with anesthetists who prefer one of the anesthetics and less-experienced surgeons worked with anesthetists who prefer others. Since these data take no cognizance of the experience of surgeons or of anesthetists, we cannot disentangle the effects of the variable “experience” from the apparent effect of the anesthetic. Bias due to such conceivable interfering variables can be prevented (even if their existence is not recognized) by the use of a randomized clinical trial. Inasmuch as we did not do such a randomized study, we cannot claim the strength of inference that can be obtained only by the use of that methodology. One of our concluding recommendations is that such a study be considered. However, the observed differences in death rate corresponding to the anesthetic make it clear that the overall death rate problem is of an order of magnitude larger in its implications for patient care than that of massive hepatic necrosis.

Toxicology of Dichlorohexafluorobutene.—A possible explanation for hepatic necrosis following anesthesia with halothane was suggested early in the course of this study by the demonstration of a toxic impurity in stock preparations of halothane. It was shown in 1963 that trace concentrations of dichlorohexafluorobutene (DCHF_B) were present in halothane as a result of the manufacturing process.¹⁷ It was later established that, while the average concentration of DCHF_B in stock halothane was 0.018%, the concentration could increase to 0.03% during administration and storage in anesthetic vaporizers. A large number of animal experiments (mouse, rat, rabbit, dog, and monkey) established the extreme toxicity of this material upon inhalation.¹⁸ Considerable species variation was found in the organ systems affected and in the concentration lethal to 50% of the animals. The latter varied over a tenfold range, but in the more sensitive species was uncomfortably close (a factor of five to ten) to the concentrations administered to patients. The lungs and kidneys

were the organs primarily affected and hepatic lesions were demonstrated only in the rat and monkey; in the monkey it was shown that DCHF_B was both concentrated in and metabolized by the liver.

On the basis of the animal findings it was recommended that this contaminant be removed from halothane. This suggestion was adopted by the manufacturer (John B. Jewell, MD, Ayerst Laboratories, written communication, Nov 23, 1965), and the halothane now used in the United States is essentially free of DCHF_B. Thus, although it was not possible to establish a causal relationship between DCHF_B and hepatic necrosis, neither can we completely rule out this possibility. From a practical point of view, the hazard no longer exists.

Summary and Conclusions

A retrospective survey of the incidence of fatal massive hepatic necrosis and overall death rate following general anesthesia in 34 hospitals for the four-year period from 1959 through 1962 was undertaken. Special attention was paid to a comparison of halothane and other commonly used anesthetics with respect to hepatic necrosis and postoperative death generally. The main conclusions are:

1. Fatal postoperative massive hepatic necrosis was a rare occurrence. It could usually be explained on the basis of circulatory shock, sepsis, or previous hepatic disease. The possible rare occurrence of halothane-induced hepatic necrosis following single or multiple administrations could not be ruled out.

2. Halothane, rather than being a dangerous anesthetic, had a record of safety as reflected in an overall mortality of 1.87%, compared to an average for all anesthetic practices of 1.93%. This overall parity of halothane holds up when imbalances in patient populations are taken into account by detailed statistical adjustments. No evidence was found to support the imputed risk of halothane in operations performed on the gallbladder or bile ducts, or in craniotomies.

3. In the middle-death-rate operations cyclopropane and “other” were associated with reliably higher mortality than were halothane and nitrous oxide-barbiturate; in terms of crude death rates there was a nearly twofold contrast. After statistical adjustment to compensate for differences in the populations exposed to the various agents, cyclopropane and “other” had death rates 2.5% or more, compared to approximately 2% for halothane and nitrous oxide-barbiturate, roughly 25% greater.

4. Ether deserves more systematic study; although the death rate following ether administration was lowest of all, the result is unreliable because so few hospitals in the study used it extensively, and so no further conclusions can now be drawn.

5. Of special interest and concern were the large differences in postoperative mortality occurring among the participating institutions. These differ-

ences could not be accounted for by the variations among hospital populations by any of the criteria measured in this study. This matter is discussed further in the full report.

Recommendations of the Committee on Anesthesia and the Subcommittee on the National Halothane Study, National Research Council

1. *We recommend that consideration be given to the initiation of limited randomized studies of death rates associated with anesthetic agents.*

The present study provides baseline data on death rates, frequency of various procedures, and similar data which should be particularly valuable in planning such studies. This study has left unexplained the relatively high death rate of cyclopropane and the observed but possibly misleading low death rate of ether. Although we can trust the indications that ether, nitrous oxide-barbiturate, and halothane had lower death rates, we are not able to say whether they *lead* to lower death rates, rather than merely being in association with them, possibly through bias due to selection. Such trials should not be undertaken unless, when compared to other uses of medical resources, it is thought worthwhile and feasible to realize a reduction in mortality of the order of one in 200 or unless firm baselines for death rates are in themselves regarded as highly valuable. If such objectives are to be sought, it would be advisable to choose operations for the study which have the following characteristics: (1) two or more anesthetics are regarded as equally suitable for the operation; (2) the death rate for the operation is appreciable, say at least 2%; (3) the operation is one which is frequently performed; and (4) necropsy rates can be anticipated to be sufficiently high if necropsies are needed to assure success of the study.

2. *We recommend the establishment of a cooperating group of institutions to serve as a panel-laboratory for the acquisition of trustworthy information on new drugs (not merely anesthetics) as they come into use.*

In the history of medicine, it is doubtful whether any drug was ever more extensively studied both before and after its introduction than halothane. Yet after halothane had been given to patients perhaps 10 million times it was impossible to give firm, reliable answers to many basic questions about its effects. Two such questions were: How does the death rate following operations performed with the patient under halothane anesthesia compare with death rates when other anesthetics are used? Does halothane induce significantly more hepatic dysfunction than other widely used anesthetics? The National Halothane Study attempted to answer these questions by using existing records. Although 856,500 operations were brought under scrutiny, the answers given are predictably and regrettably short of those desired. For example, the important question of nonfatal liver injury was not taken up by the study. The limita-

tions of knowledge on halothane are certainly not peculiar to it. Limitations at least equally compelling apply to nearly any drug introduced in the past. Had a few scores of thousands of administrations of halothane been given in the context of an experimental information-gathering system, similar in kind to a cooperative randomized clinical trial, reliable information might have been acquired for overall death rates, and possibly for nonfatal liver injury as well.

3. *We recommend consideration of the establishment of a registry for the collection of clinical, laboratory, and pathological findings in cases of hepatic necrosis.*

Massive hepatic necrosis is a rare, but usually fatal disease. In some patients it follows what appears to be typical viral hepatitis. Massive hepatic necrosis may also follow certain major surgical procedures, shock, congestive heart failure, and the use of large amounts of pressor drugs. But in some patients the cause of hepatic necrosis is not so apparent. A number of the recently introduced drugs, such as iproniazid phosphate and zoxazolamine, are thought perhaps to be occasionally responsible; similar suspicions concerning halothane formed the basis for the present study.

The National Halothane Study has not entirely ruled out a rare relationship between halothane and massive hepatic necrosis. It will be important to know, as further data accumulate, whether this association will continue, increase, or disappear. New, possibly hepatotoxic, drugs will continue to be introduced and, because of its infrequency, any associated massive necrosis may go unnoticed unless looked for with care. The proposed registry would provide the mechanism for collecting such information.

In designing such a registry, it must be recognized that for many, if not most, purposes effective interpretation of the data requires knowledge of the size and composition of the population from which the registered cases arise. Some registries have no provision for obtaining such "denominator" data and are hampered in carrying out their mission. Possibly such a registry should be developed in relation to a panel such as that mentioned in the second recommendation above, so that the needed background information would be readily available, or in association with an existing registry that has access to information about its population.

In establishing this registry the most careful consideration must be given to the many inherent limitations and pitfalls. These include (1) the historical, nonexperimental nature of the study; (2) the very low incidence of the variable of interest; (3) the loss of data by nonresponse, such as missing laboratory data and failure to obtain necropsy. In addition, there will doubtless be other, possibly serious, difficulties which will become apparent only as experience with such registries develops. It is apparent that, unless the greatest efforts are

made to identify and overcome these problems, neither this nor any other registry can achieve its goal. To the contrary, it will likely generate misleading or erroneous information.

Finally, a decision to establish a project of the magnitude of such a registry should be made in the light of the total needs of the public health and the availability of medical resources.

Generic and Trade Names of Drug

Halothane—*Fluothane*.

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