THE FIRST ANESTHESIA DEATH WITH SOME REMARKS SUGGESTED BY IT ON THE FIELDS OF THE LABORATORY AND THE CLINIC IN THE APPRAISAL OF NEW ANESTHETIC AGENTS *

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WITH as much emphasis as there is at present on the accomplishments of the laboratory in the examination of anesthetic agents, it may be healthful to consider the possibilities of the clinic as well, in the evaluation of these substances. It may strike you with some surprise that the self-evident need for cooperation between the clinic and the laboratory in the appraisal of anesthetic agents could ever have been questioned. Actually, for example, until recent times (that is, for sixty years following the first anesthesia death), many able laboratory workers denied, with a certain amount of positiveness, the truth of statements made by good clinicians who investigated the cause of sudden death from chloroform. Unfortunately for the laboratory workers, they were incorrect in their statements as to the chief hazard present. The good clinicians were right from the first death onward. I should like to review briefly for you the first death and the ensuing controversy. From this controversy we can perhaps get a clearer insight into the proper role of the laboratory and of the clinic in the evaluation of new anesthetic agents.

The first death recognized as due to anesthesia occurred on the 28th day of January, 1848, some fifteen months after the general introduction of anesthesia into medicine and two months after Simpson had used chloroform in midwifery. The case is described quite fully in a reporter's notes taken at the inquest (1):

"An inquest was held . . . on view of the body of Hannah Greener, a girl of 15 years of age, who died on Friday the 28th of January [1848] under the influence of chloroform, administered in order to allay sensibility while undergoing a painful surgical operation."

John Rayne, a member of the patient's family stated: "The deceased was an illegitimate child, whose mother died in childbirth. She . . . had been much thrust about. She suffered a great deal in her feet, and about four months ago she became an inmate of the infirmary at Newcastle-upon-Tyne, where she had one of her toe nails taken off [under ether]. After she left the infirmary she returned to her father's but

* From the Anesthesia Service of the Massachusetts General Hospital, Boston, Mass. Read before the meeting of the American Society of Anesthetists, Inc., in New York, Feb. 13, 1941.

her toes still continued bad. Mr. Meggison, surgeon, of Wickham, was called in to attend her, and it was considered advisable to remove the nail from the great toe of her right foot."

Mary Greener, step-mother of the deceased, had the following to say: "Her father . . . said she had better not have the stuff to make her insensible, as she complained of it having caused a heaviness in her head for some days after she had taken it [ether] in the infirmary. She said she would not have her nail taken off without it. We were all agreeable that Mr. Meggison should perform the operation and give her the stuff. She was in good health generally before she went into the infirmary [for the first operation]; she fretted while there. . . . She grew thinner in the infirmary; and she also got thinner after she came out. . . . She complained of pain in the chest. . . . She never did that before she went to the infirmary. She suffered much pain in her toes. . . . I think it was the pain being so great that prevented her thriving."

Mr. Thomas Meggison, surgeon, having been duly cautioned said, "Hannah Greener died under my hands . . . while under the influence of chloroform, which I had given her for the purpose of producing insensibility during the operation of removing one of her toe nails. . . . She never complained of pain in the chest to me. . . . I seated her in a chair, and put about a teaspoonful of chloroform into a tablecloth, and held it to her nose. After she had drawn her breath twice she pulled my hand down. I told her to draw her breath naturally, which she did, and in about half a minute, I observed the muscles of the arm become rigid, and her breathing a little quickened, but not stertorous. I had my hand on her pulse, which was natural, until the muscles became rigid. It then appeared somewhat weaker—not altered in frequency. I then told Mr. Lloyd, my assistant, to begin the operation, which he did, and took the nail off. When the semicircular incision was made she gave a struggle or jerk, which I thought was from the chloroform not having taken sufficient effect. I did not apply any more. Her eyes were closed, and I opened them, and they remained open. Her mouth was open and her lips and face were blanched. When I opened her eyes they were congested. I called for water when I saw her face blanched and I dashed some of it in her face. It had no effect. I then gave her some brandy, a little of which she swallowed with difficulty [and it rattled in her throat, according to Mr. Rayne]. I then laid her down on the floor, and attempted to bleed her in the arm and jugular vein, but only obtained about a spoonful. She was dead, I believe, at the time I attempted to bleed her."

Sir John Fife, surgeon (pathologist): "I made a *postmortem* examination of the body of Hannah Greener . . . [it was] that of a well-grown girl. . . . The external appearance of both lungs, over the whole surface, but especially in the inferior portions, was that of organs in a very high state of congestion. They were mottled with patches of a deep purple, bluish or scarlet hue. They were everywhere crepitant—

the pulmonary tissue was filled with bloody froth. . . . The heart contained dark fluid blood in both its cavities; very little in the left.

"In my opinion the cause of death was congestion of the lungs, and that congestion I ascribe to the inhalation of chloroform. Of the power of chloroform to occasion such congestion no doubt can be entertained after the experiments of Dr. Wakely and Dr. Glover on animals."

Robert Glover, surgeon: "I have heard the evidence and fully agree with it. . . . I consider chloroform more dangerous than ether; and that has been my opinion from the first. The effect of chloroform will depend much on the constitution."

"The jury then retired, and, after a few minutes' absence, returned with the verdict [that] 'the deceased, Hannah Greener, died from congestion of the lungs, from the effect of chloroform, and that no blame can be attached to Mr. Meggison, surgeon, or to his assistant, Mr. Lloyd'—the jury was dismissed." But the trial in the medical journals had only begun.

"We were soon awakened from our dreams of the delightful influence of the new agent [chloroform], by the occurrence of unfortunate and painful consequences, which had not followed in this country on the practice of etherization," wrote John Collins Warren (2). As Clark (3) put it, "chloroform made such an easy success that at first it seemed that there would be no scope for Simpson's zest and talent for controversy." His talent for controversy got a considerable stimulus by this first death. He had an article (4) on the subject in print fifteen days after the patient's death. He said, "The unfortunate patient certainly died when under the influence of chloroform, not, however, as I believe, from *its* effects, but from the effects of the means used to revive her. . . . With the best of motives water and brandy were poured into the girl's mouth and allowed to rest in and fill up the pharynx of the patient. . . . It was impossible for the patient, in her weak and torpid state, to inspire through a medium of water and brandy, any more than it would have been possible to inspire if the whole head and face had been inevitably submersed in the same fluid. [Sir James's vivid picture is hardly supported by the inquest report.] The girl died, then, as I conceive, . . . choked or asphyxiated by the very means intended to give her life."

Great, not to say acrimonious, discussion over the first death was still in progress when a second death (5) occurred, under like circumstances, this time in America. This must have chilled Simpson's enthusiasm for the controversy, coming as it did, less than a month after the first death.

Other deaths followed. The first 4 were analyzed by Francis Sibson (6) who said, "We are obliged, then, from the experience of these cases, to conclude, that in man the death (from chloroform) is usually instantaneous, and due . . . to paralysis of the heart." The clarity of Dr. Sibson's insight was not limited to this statement. Dr. Snow (7) says

Sibson suggested that the blood passing from the lungs to the heart, and through the coronary arteries, is more highly charged with the vapor than that in any other part of the body, and may cause paralysis of the heart, even before general sensibility is induced.

"The impression (8) created by [the two first] deaths from chloroform was so great, that when a third occurred in Boulogne, the Minister of Public Instruction invited the French Academy of Medicine to investigate the subject. A report presented by Malgaigne, the President, entirely absolved chloroform from any responsibility for the fatal accident on the grounds that the small amount of chloroform taken (5 grams!) and the extreme rapidity of death could not implicate chloroform, which could [according to him] endanger life by asphyxia alone."

It is not my purpose to present a historical review.* I wish simply to call these facts to your attention to illustrate the point mentioned at the outset; accordingly I shall mention only a few of the high lights of the ensuing controversy which pitted good clinicians against able laboratory workers, for in this controversy we can see a clear illustration of the possibilities and limitations of the two fields.

The experimental work of the period had amply shown that gradual overdosage with chloroform leads to a profound depression of the respiration with, first respiratory failure, and then heart failure. The point which was persistently overlooked chiefly by the laboratory workers was that chloroform could also strike at the heart, paralyzing its action even before general anesthesia had been fully established. Curiously enough, only a few recognized this, among whom were the clinicians, Sibson and Snow. They perceived this dual action from the first.

In 1858 Snow (9) analyzed 50 cases of death from chloroform and showed that in 40 of these cases death appeared to arise entirely from heart failure and was not complicated by overaction of the agent on the brain. In only 4 cases did the breathing appear to be embarrassed by the effect of chloroform on the brain at the time the heart failed. "Deaths under chloroform attracted so much attention that committee after committee was appointed to investigate their cause, but the reports chiefly serve to provide a striking proof of the fact that committees are not an effective mechanism for the solution of scientific problems." Clark (loc. cit.) who made the preceding statement has summarized the results of several of these false-finding committees. "A commission which reported to the Society of Emulation of Paris in 1855 concluded that in all instances in which animals were killed by chloroform the action of the heart survived the respiration (Snow, 1858). The Hyderabad Commissions (1888, 1889) concluded that there was no such thing as chloroform syncope and that the heart was the last organ to give in under the action of chloroform (Lawrie, 1891). The *Lancet* (1889) pointed out, however, that this conclusion was opposed to those arrived at by the previous commission appointed by the Royal

* Two exceptionally interesting reviews are those of Hoff (8) and Clark (3).

Medical and Chirurgical Society and by the British Medical Association. A later commission set by the B. M. A. (1903) nevertheless directed all its attention to the question of overdosage of chloroform.

"In 1908 the Commission on Anaesthesia of the American Medical Association concluded that 'all of the accidents of chloroform are due to overdosage' (Haggard, 1908). These commissions included many distinguished physiologists. Their conclusions were perfectly correct as regards the subject they studied—namely, the effect of gross overdosage of chloroform . . . but unfortunately this has no relation to death in the early stages of chloroform anesthesia."

Sibson, Snow and other clinicians knew where the acute danger from chloroform was to be encountered. More than sixty years passed before they were vindicated by Levy in the laboratory. As Clark has pointed out, this far from creditable bit of history suggests clearly the limitation of laboratory methods: "like most methods of exact analysis they yield peculiarly ridiculous results unless they are directed to the correct object."

In evaluating the anesthetic agents we may well ask, what then, are the proper fields of study for the clinic and for the laboratory?

When we speak of a general anesthetic agent in the practical sense we refer to a substance which by an influence upon the central nervous system of a man or an animal temporarily causes a loss of consciousness, reduces sensitivity to painful stimuli, and interrupts reflexes. Many substances are available which influence the central nervous system in this way; but only a few of these substances are useful for general anesthesia, namely, those which abolish pain and relax muscles, for example, but do not seriously interfere with the essential life processes: the respiration, the function of the heart, circulation of the blood, and so on. This leaves us with only about a half-dozen inhalation agents which are satisfactory for clinical anesthesia out of the hundreds of possibilities.

In dealing with the general anesthetic agent we can speak of the reversible depression of the central nervous system as the *primary anesthetic effect.* In such an arbitrary definition as this all other effects of anesthetic agents become secondary, typified by more or less toxic organic actions. As far as the primary effects of anesthetic agents go, they exert their only physiological action on the central nervous system. Incidentally, the central nervous system constitutes only 5 per cent of the adult body weight; 95 per cent of the body weight (where these agents are without their primary anesthetic effect) may dominate the rate at which an anesthetic concentration can be built up, and is in large part responsible for the total quantity of agent which must be employed to produce a given effect. Most of the secondary reactions are effected in this 95 per cent of the body.

The division of the effects into primary and secondary also marks out for us rather clearly the domain of the laboratory and of the clinic in

the appraisal of new agents. The laboratory worker is concerned with discovering new agents for trial, with determining their physical constants, with examining their primary effects, their speed of action and the factors involved in it; potency, partial pressure necessary in the case of the inhalation agents, and solubility coefficients; their *probable* potentialities and *probable* limitations for clinical use. Agents may, of course, vary widely in their primary effects. Loss of consciousness may be produced, but only poor muscular relaxation may be obtained, and so on. The laboratory worker may detect this and call attention to it, just as he usually detects the common, more obvious toxic effects.

It remains for the clinician to discover the limits of clinical usefulness—the proper fields of usefulness—of such agents in the clinic, not only because an animal is usually the subject in the laboratory and man the subject in the clinic, but also because the various conditions encountered in the clinic are not easily obtainable, if at all, in the laboratory. It is chiefly because of its secondary effects—its toxic organic effects—that an agent which produces a satisfactory reversible depression of the central nervous system may be found unsatisfactory in the clinic, or may be satisfactory for one patient but not for another. In any case, the subtle, the latent toxic effects and uncommon hazards must usually be detected by the clinician in the clinic.

It also falls to the clinician to determine death rate, which, under critical conditions, is one of the most objective criteria we have for estimating the worth of one agent as opposed to another, although I believe everyone would agree that the choice of anesthetic agent in a given case must include many other factors as well as this one.

Judging from the many papers written on the subject of clinical statistics by anesthetists it would seem that such compilation is one of their major occupations. I have said before, and I repeat, one's faith in the value of such studies will be considerably weakened by finding that what purport to be statistical analyses have in all but a few cases failed to take into account the most rudimentary requirements of statistical analysis. The casualness with which statistical analysis is so often undertaken does not alter the fact that it is involved, time-consuming and without value unless the fundamental laws of statistics are vigorously observed. As I have commented before, it is unhappily true that statisticians and their statistics are looked upon with suspicion by the rest of the world. Statistical methods are no substitute for common sense; on the other hand, some use of such methods is necessary if common sense is to be preserved in the handling of quantities of data. If the death rate from an anesthetic agent is 1:1000, we need 10,000 cases, with 10 deaths to find it out. Likewise, if the rate is 1:10,000, we need, again, 10 deaths, or 100,000 cases to establish the death rate.

While some activities belong chiefly in the laboratory and others are possible only in the clinic, it seems clear that the evaluation of anesthetic agents must be inseparably bound up with both. The death rate

from good anesthesia ought to be at least as low as 1:5000 cases. Actually, the death rates from some agents in common use are from two to five times this high. An understanding of the causes of disaster will inevitably lead to the development of methods for laboratory elimination of dangerous agents before patients are subjected to costly trial and error methods. It should be possible to mark out the probable safe limits of usefulness of new anesthetic agents before they reach the clinic in a much more precise way than is now possible. For too long we have had to depend upon the pharmacological methods of the 1850's. An application of physiological technics already well established will, I am convinced, lead to much more precision in the preliminary, in the laboratory estimation of new agents; but in the end, only the clinician can make the final evaluation.

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The Committee on Research of the American Society of Anesthetists, Inc., has received information from the United States Department of Commerce, (Jesse H. Jones, Secretary) National Bureau of Standards, (Lyman J. Briggs, Director) that a pamphlet on Color Marking for Anesthetic Gas Cylinders is being sent to all acceptors of the record, and is available to any interested person. It may be obtained by sending five cents (5¢) for each copy desired to the United States Government Printing Office, Superintendent of Documents, Washington, D. C. Postage stamps will not be accepted in payment. The pamphlet is further designated as "Simplified Practice Recommendation R176–41."