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The Chloroform Controversies

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Abstract
It was the introduction of ether by Morton in 1846 that provided the necessary conditions for the development of Modern Surgical practice. Previous to its use Surgery was swift and brutal, its scope confined to the body surface, i.e. the evacuation of pus, amputation of limbs, excision of superficial tumours. It is revealing to examine the operations performed in the Royal Infirmary, Edinburgh, in the years 1831-34, a total of one hundred and forty, an average of thirty-five a year. Hovell remarks, "Although in 1829 the staff of the Royal Infirmary included surgeons of great reputation, very few operations were performed, and the operation theatre served little purpose."

It is hard today to realise the impact of the new discovery on the medical profession, yet in a very short time ether was to be supplanted by chloroform. I have often wondered why this happened. History is rather vague on this point. The major objection appears to have been its unpleasant smell. I suspect there were other reasons. The entrepreneurs of the time, realising the importance of the event, were anxious to participate in it. A frantic search for new drugs began and in November 1847 Simpson of Edinburgh used chloroform, first in obstetrics and then nearly six months later in general surgery.

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THE CHLOROFORM CONTROVERSIES

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In retrospect one feels it was unfortunate that this potent drug was discovered and used so soon after the introduction of ether, as most doctors of the period were ill-equipped to handle it. Almost from the time of its inception, chloroform was beset with controversy, often bitter, frequently uninformed, always unsavoury. Dissension arose as to who deserved the credit for its 'discovery'. It was prepared by Souberain in France and Guthrie in America, used as an anaesthetic by Heyfelder and Flourens but in animals, Jacob Bell and William Lawrence of London had tried it out in a weak mixture with alcohol and abandoned it. Waldie, a Liverpool chemist, had suggested its use to Simpson, who acted on the suggestion. How does one distribute the honours? Simpson had the courage to use it in clinical practice and the energy to publish his results before anyone could beat him to it. On these grounds he deserved the credit. Perhaps he could have been more generous in his acknowledgements, but it was not a generous age.

With the introduction of chloroform, the use of ether rapidly declined, and it is hardly surprising that within two months the first death under chloroform was reported. On January 28th, 1848, Hannah Greene, a fit young woman aged 15, died two minutes after the induction of anaesthesia. Other reports of a similar nature soon followed. The 'unexplained' death of healthy young adults caused considerable anxiety in the profession, particularly in England and America. In Scotland up to this time no death had been reported. Briefly, the following situation developed. The

Medical profession in England and America postulated that chloroform acted primarily on the heart muscle, producing acute Cardiac Syncope. This occurred irrespective of dose and concentration, and the Cardiac Syncope occurred before the cessation of breathing. Simpson and his supporters, later known as the Edinburgh School, claimed they had not experienced a single death from its use. Primary Cardiac Syncope did not occur: death was always secondary to severe respiratory depression, i.e. to overdosage. They taught, "Watch the respiration and the circulation will look after itself." They believed that death was avoidable and unnecessary and said so in no uncertain terms.

By 1858 fifty deaths had been reported in England and America, and there is reason to believe that many more had been concealed. The Edinburgh School claimed no deaths, although there is evidence now available that one patient died in 1853. In this they were supported by John Snow, probably the first professional anaesthetist (an Englishman), who reported a series of four thousand cases without trouble. Snow carried out a series of experiments on dogs, using a measured concentration of less than 4% chloroform diluted in air. He observed that first the respiration was depressed, then abolished. The heart continued to beat forcibly. If the anaesthetic was withdrawn and artifical ventilation was instituted the animals recovered; if not, the heart failed. He concluded that Cardiac Syncope was secondary to respiratory failure. If the dosage and concentration were carefully controlled there was no danger. He developed a dosimetric method for the administration of the drug and his results were unsurpassed. However, in the years following, reports of sudden death under chloroform continued, and by 1864 they numbered 124. The positions of the two sides were deeply entrenched, and the Royal Medical and Chirurgical Society (now the R.S.M.) set up a committee to examine the problem. They concluded that inhalation of a mixture of 2-4% chloroform in air was safe. If these concentrations were exceeded the risk of Cardiac and Respiratory depression increased. In effect the published report of this committee led to the abandonment of chloroform in England. Scotland, however, continued to use it, and it was not surprising when, at the 43rd Annual General Meeting of the British Medical Association in Edinburgh in 1875 the Section of Surgery passed a resolution "that it is desirable a committee be appointed to enquire and report on the use of chloroform." This committee was an extraordinary one. It consisted of fifteen members, many of them distinguished. They hailed from the four corners of the British Isles — Aberdeen, Edinburgh, Dublin, London. It is not surprising that it did not meet till 1877, when Spenser Wells the chairman suggested that the Scientific Grants Committee should engage a competent investigator to do the work. This, however, was refused, and a sub-committee, all of whose members belonged to Glasgow, was appointed. The Glasgow Committee report concluded that chloroform was more dangerous than ether. Their findings delighted the English, incensed Edinburgh and achieved little change. The etherists were happy, the chloroformists unimpressed.

In the years following the Glasgow report, ether was becoming the anaesthetic of choice. Then in 1889 an extraordinary situation arose. Surgeon Major Lawrie, Principal of the Hyderabad Medical School, announced at the annual prizegiving day his experiments with chloroform. He claimed 128 dogs had been given chloroform till they died, and in no case was the heart affected until the respiration had ceased. In the Medical School many thousands of chloroform anaesthetics had been administered without a single death. He added a few appropriate(!) remarks about London and Glasgow and their committees.

The Lancet challenged Lawrie in an Editorial, but he replied "I hold there is no such thing as chloroform syncope". He offered £1000 to the Lancet if they would send a representative to repeat the Hyderabad experiments. The Lancet accepted the offer, and appointed Lauder Brunton, F.R.S., a distinguished pharmacologist, to undertake the investigation. The results reported by Brunton (known as the 2nd Hyderabad Commission) confirmed Lawrie's findings in every respect.

The Lancet, under some pressure from the profession, remained obdurate and took the line that animal experiments were not acceptable. It was unfortunate that Lawrie used unscrupulous methods in an attempt to advance this case for chloroform and eventually the Lancet, the academics and the Medical Profession declined to regard his claims as serious, although the experimental evidence was not challenged.

The controversy went on. At this period many distinguished Physiologists, Gaskell and Shaw, Leonard Hill and McWilliam, Sherrington and Walker became interested in the problem, and although the by-products of their work, cross circulation technique, Wallerian degeneration of nerves, were important, the problem remained confused. Briefly, the work of the physiologists confirmed the belief that chloroform acted on the heart, but only during deep anaesthesia when very high concentrations were used. This was in direct conflict with the clinicians who insisted that death occurred during light anaesthesia (during induction) when the concentration of drug was low. It was not till 1911 that Levy appeared to provide the answer. He administered chloroform to cats receiving an infusion of adrenalin. Many of these animals developed ventricular fibrillation and sudden death. He concluded that chloroform per se did not cause Cardiac Syncope, an exciting cause had to be superadded. He cited as such causes, the release of adrenalin, inhibition or stimulation of the vagus, anoxia and strong sensory stimuli. It should be clearly understood that he *did not* perform experiments to prove this. One is inclined to ask why indigenous adrenalin in the frightened cat was not enough to produce sudden death. However this explanation matched the clinicians' concept of sudden death in light anaesthesia, and the use of chloroform was largely discontinued.

At about this period a second objection to the use of chloroform was raised, i.e. its effect on the liver. Cases of acute hepatic necrosis following its use began to appear in the Journals, and 'Delayed chloroform poisoning' became a clinical entity. It is interesting to speculate why fifty years elapsed before reports of its effect on the liver appeared in the English Journals. One possibility is the rapid advances being made in Surgery. Surgeons were beginning to explore the abdominal cavity: these operations were longer, required muscle relaxation and hence the dose and concentration of chloroform used would be much higher.

A review of the literature from 1900-1925 in an attempt to assess the incidence, and the factors responsible for causing liver damage in man, was unsatisfactory. Many are reports of isolated cases. Even the pathological criteria of acute hepatic necrosis varied, from evidence of 'fatty degeneration' to the classical picture of acute cellular destruction. Data from the pre-operative state of the patient is vague, time of operation, dosage and concentration of drug used were rarely mentioned and the only conclusion possible was that acute hepatic necrosis was a rare complication of patients undergoing Surgery and chloroform anaesthesia. Its incidence seemed to be more frequent in three groups of patients: the very young, the toxic, and women suffering from the toxaemia of pregnancy.

The experimental work in animals was much more conclusive. Stiles showed that under his experimental conditions chloroform could produce acute liver damage. However, it must be stressed that these experiments were designed to destroy the animal. The animals received choloroform day after day for many hours — the dosage, although not recorded, must have been immense — until they died and autopsy revealed acute liver damage. Autopsy also revealed serious bronchopneumonia and severe renal damage. In these experiments chloroform was not used as an anaesthetic agent.

However, the fear of cardiac and hepatic failure banished chloroform from anaesthetic practice, although it must be admitted that a few sturdy chloroformists ignored the evidence, which was contrary to their experience, and continued to use the drug, in some instances surreptitiously.

The introduction of Halothane, an halogenated hydrocarbon with many properties similar to chloroform, in 1956, led us to attempt a reassessment of chloroform. This had been done by Waters in 1951, but it was felt that it should be used in the context of Modern Anaesthesia, i.e. where the anaesthetic agent provides sleep, analgesia and areflexia, but not muscle relaxation.

HEPATOTOXIC EFFECTS

These were studied in thirty-eight patients, half receiving Halothane and half chloroform. The transaminase tests were used to assess acute hepatic damage. These tests were carried out pre-operatively, 24 hours post-operatively, and on the third day after operation. There was no significant difference in the two groups of patients, and there was no evidence that either of these agents produced liver damage. Furthermore, in a ten-year period 1958-68 many thousands of patients

have received chloroform and no clinical evidence of Acute Hepatic Necrosis has ever been recorded.

CARDIOVASCULAR EFFECTS

In analgesic doses, pulse and blood pressure are normal. Contrary to some teaching, arrythmias do not occur. With deeper planes of anaesthesia the pulse slows and the blood pressure gradually declines. With gross overdosage the heart would cease in asystole. Even in deep anaesthesia, provided ventilation is adequate arrythmias are very rare.

CONCLUSION

In the last ten years chloroform has been used extensively to provide sleep, analgesia and areflexia, but not muscle relaxation. In this context no serious cardiovascular or hepatotoxic effects have been noted. It is a potent drug, its effects being similar to that of Halothane, it has the advantage of being very much cheaper. In retrospect the Edinburgh School were right, but the profession as a whole were not ready for its use. The ensuing misuse of chloroform, led to it being abandoned.

ANSWERS TO DIAGNOSTIC PROBLEM

(See page 12)

A. Distended colon.

B. Carcinoma of the hepatic flexure of the colon.