BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 19 1938

ASPECTS OF THE HISTORY OF ANAESTHETICS*

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I feel that since I am neither a medical historian nor an anaesthetist I owe an explanation to this Section for my choice of subject. The history of the discovery of anaesthesia has been worked over with meticulous care, partly because of the dramatic suddenness with which it occurred, and partly because of the unhappy controversies which marred much of the history of this remarkable advance in human knowledge. The subject, therefore, is not merely well-trodden ground, but, as regards the pitfalls and entanglements with which it abounds, is as uninviting as some abandoned battle area. None the less I venture upon this dangerous field because the whole subject has great interest for the pharmacologist.

Pharmacology is one of the youngest of the medical sciences; it is, indeed, a growth chiefly of the twentieth century, and in consequence has very little history. Only three discoveries of major importance to pharmacology were made in the nineteenth century—namely, anaesthetics, antiseptics, and endocrine therapy—and of these only the first is favourable for historical survey.

Endocrine therapy was initiated by the discovery of the action of thyroid, which constituted the beginning of a new branch of science, but this subject is still developing at great speed; it obviously is not yet approaching maturity, and hence is at present unsuited for historical treatment. Antiseptics suddenly assumed a dominant importance in surgery, but the development of aseptic technique caused their importance to decline as rapidly as it had grown and their history is too irregular to be of general interest.

The discovery of anaesthetics is the only pharmacological advance of major importance made in the nineteenth century that has reached mature development and therefore can suitably be treated from the historical aspect.

The importance of this discovery for the history of pharmacology is further increased by the fact that this was the first occasion on which the synthetic products of the organic chemist were used to produce a therapeutic effect of major importance. Since then the use of such compounds has developed steadily, and to-day they form the chief basis of therapeutics. Modern pharmacology may therefore be said to have begun with the introduction of anaesthetics, and indeed the only later events of comparable importance in the history of the science are the introduction of thyroid therapy and the discovery of

salvarsan, which respectively initiated the sciences of endocrinology and of chemotherapy.

These are adequate reasons for a pharmacologist taking a special interest in the history of anaesthesia, and a general survey reveals outstanding facts that are of great importance in relation to the problem of how a profession reacts to the impact of new ideas and a new technique. It is, moreover, of interest to study the course of discovery and to note the points at which progress was rapid and those at which halts occurred, since such a study gives hints regarding the factors which influence the advance of scientific knowledge.

Sudden Discovery of Surgical Anaesthesia

A casual survey of the discovery of anaesthesia suggests that it took place with almost explosive rapidity. In 1844 Wells produced surgical anaesthesia with nitrous oxide, in 1846 Morton did the same with ether, and in 1847 Simpson introduced chloroform. In September, 1846, the possibility of surgical anaesthesia was not generally recognized; by the end of November, 1847, chloroform and ether were in widespread use, and both nitrous oxide and ethyl chloride were known to be possible anaesthetics. In 1846 the only mention of anaesthesia in the *Lancet* was a short note on the new use of ether in the last number, while less than four months later (April 10, 1847) the editor referred to ether as "a remedy which has already produced such an unparalleled influence on the practice of surgery in this country," and mentioned that the number of operations had doubled. Throughout 1847 the *Lancet* maintained a special column describing "operations without pain."

The essentials of modern anaesthetic practice were therefore mastered almost within a year. Many advances have been made since then, but it will be generally agreed that ether, nitrous oxide, and chloroform are together more important than all other known agents. An anaesthetist could manage better if confined to the three agents mentioned than he could if deprived of these three and allowed his choice of all others.

This period of remarkable advance was followed by a long period of quiescence, and it is only during the last fifteen years that a really active search for new agents has begun again.

More detailed examination of the development of knowledge shows that it was not quite so abrupt as suggested above, but none the less the suddenness of the initial advance is the outstanding feature in the history of anaesthesia, and the factors that caused this phenomenon are of obvious interest.

* Presidential address to the Section of Pharmacology, Therapeutics, and Anaesthetics at the Annual Meeting of the British Medical Association, Plymouth, 1938.

Factors Leading to the Discovery

The advance was essentially the mastery of a successful technique. There are two easily recognizable types of advance in knowledge. In one case something new is discovered the existence of which had previously been unsuspected; for example, the discoveries of x rays and of radium. The other case is when the aim is obvious but the means of attainment are lacking, and the advance consists in finding the right technique. The discovery of anaesthesia was of this latter kind, for the alleviation of the pain of operations was an obvious aim indicated by ordinary motives of humanity, and since classical times medicine had been acquainted with the stupefying power of many drugs. Sir J. Y. Simpson (1871) pointed out that there was evidence of the regular use of stupefying agents such as opium and mandragora in both classical and mediaeval surgery. Curiously enough, this knowledge appears to have been lost at about the Renaissance period.

The essential importance of establishing an efficient technique will, I think, explain the history of the oldest of the anaesthetics—namely, nitrous oxide—though at first sight this history is very surprising.

Nitrous Oxide

The discovery of the pharmacological actions of nitrous oxide is of special local interest, since it is closely associated with the West of England. Sir Humphry Davy, who was born and bred near Penzance, began studying for medicine by being apprenticed to a surgeon apothecary in Penzance, but in 1798, when 20 years old, he went to work under Dr. Thomas Beddoes at the Medical Pneumatic Institution in Bristol. After two years of work (1800) he published his *Researches, Chemical and Philosophical, chiefly concerning Nitrous Oxide*. This volume is a model of a pharmacological research complete in all its stages. It starts with a masterly investigation of the chemical properties of nitrous oxide, proceeds through a series of well-planned pharmacological researches upon a wide variety of animals, continues with an investigation into the actions of the gas on man, and concludes with a brilliant deduction regarding its therapeutic value. On the last point Davy's actual words were (p. 556):

"As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place."

The only criticism to be made of these experiments is that Davy took somewhat extreme risks with his own life, since he repeatedly inhaled nitrous oxide to the point of unconsciousness and proved that the gas "could be respired without danger by a human animal for a much longer time than that required for the death of smaller quadrupeds in it." Among his many discoveries was the demonstration that pure nitrous oxide produced death in animals, but that unconsciousness, with subsequent revival, could be produced by nitrous oxide mixed with a little oxygen or ordinary air.

Davy's brilliant researches bore no immediate fruit. Hickman (Wellcome Museum, 1930), a country practitioner in Shropshire, made a series of attempts in 1824 to produce surgical anaesthesia by inhalation of gases. He published a pamphlet showing that dogs could be rendered unconscious with carbon dioxide, could be operated on in this condition, and afterwards recovered. In a memorial to Charles X (1828) he stated that anaesthesia could be produced by certain gases. The memorial was referred to a commission of the Académie Royale de Médecine, but the only member interested was the famous Baron Larrey. Nineteen years later the rapporteur of this commission (Gérardin) stated that nitrous oxide was one of the gases mentioned by Hickman. The latter died in 1829, aged 29, having received no encouragement either in England or in France. He certainly demon-

strated the possibility of producing surgical anaesthesia by the inhalation of carbon dioxide, but the extent to which he investigated nitrous oxide is doubtful.

Neglect of Davy's Work on N₂O

The use made of Davy's brilliant researches does not increase one's respect for human intelligence, since the suggestion about anaesthesia was almost completely ignored for forty years, while the fact that nitrous oxide produced a ludicrous form of intoxication was eagerly seized upon and exploited. Progress, however, occurs through unexpected and unpromising paths, and these silly demonstrations proved of ultimate value. Horace Wells, the surgeon dentist of Hartford, Connecticut, saw one of these displays of laughing-gas, and on December 11, 1844, arranged for the gas to be used upon himself, and achieved the painless extraction of a tooth under anaesthesia. Apparently he had never heard of Davy's suggestion. Wells tried to demonstrate the use of gas at Massachusetts General Hospital, but the demonstration was a failure, and the sensation attending the discovery of ether anaesthesia two years later caused nitrous oxide to be neglected and forgotten. In 1863 Colton in New York popularized the use of pure nitrous oxide in dental operations, and in 1868 Edmund Andrews of Chicago showed the advantages of using nitrous oxide with 10 per cent. of oxygen—a method that Davy had investigated on animals nearly seventy years previously. Nitrous oxide was established in general use in Great Britain about 1870.

In view of the present importance of nitrous oxide this history is very extraordinary. It would appear that Davy established the possibility of anaesthesia with gas and oxygen, that this invaluable discovery was completely neglected for forty years and its true value not established for seventy years, while in the intervening period the gas maintained a steady popularity in virtue of its power to produce a ridiculous intoxication.

Before judging such apparent stupidity too harshly it is well, however, to consider the probable limitations imposed by imperfections of technique. The genius of Davy was unique, and although he could produce nitrous oxide pure enough to permit him to inhale it repeatedly to the verge of unconsciousness, yet it is probable that few others had a similar skill. For example, in 1847 Orfila gave the following account of his experiments with nitrous oxide (Hickman, 1930):

"J'ai répété leurs [Davy *et al.*] expériences, et j'en ai éprouvé de si vive douleur dans la poitrine et une telle suffocation, que je suis resté convaincu que si j'eusse continué l'expérience, je n'en serais pas revenu."

Nunneley in 1849 came to a similar negative conclusion, for he experimented on some 300 cats with a wide range of possible anaesthetics, and concluded that his experiments were "quite sufficient to show that nitrous oxide never could be employed as an anaesthetic and that the inhalation of it is not altogether so harmless as is generally stated."

It must have been very difficult indeed to produce a satisfactory nitrous oxide anaesthesia when the gas available was of doubtful purity and the most portable form of container was a balloon. There are therefore circumstances palliating the failure of the medical profession to utilize the gift which Davy offered them, but, even so, one cannot claim that the history of nitrous oxide redounds to the credit of anyone except Davy and Wells. Indeed, an enemy of our profession might claim that it showed extreme slowness and conservatism in accepting the gift offered by science.

Ether Anaesthesia

The history of ether contrasts sharply with that of nitrous oxide. Ether was one of the earliest known of the synthetic organic drugs, and its synthesis was

described by Valerius Cordus in 1546. In 1794 Dr. R. Pearson used it in the treatment of phthisis (Gardner, 1847) and suggested its investigation to Beddoes. After a few trials at the Pneumatic Institute it was found to be serviceable as an anodyne. Apparently its intoxicating powers soon became fairly common knowledge. Dr. Graham, of "celestial bed" fame, was accustomed about 1802 to inhale ether several times a day (Lee, 1847). In 1818 a note believed to have been written by Michael Faraday was published which pointed out that ether had intoxicant effects similar to those of nitrous oxide.

The medical profession was therefore fairly well acquainted with the intoxicant action of ether, and many persons probably knew that excess of ether might lead to unconsciousness. In 1844 Jackson and Morton witnessed Wells's abortive demonstration with nitrous oxide, and in 1846 Morton used ether for the painless extraction of teeth. On October 16 he administered ether for a surgical operation in Massachusetts General Hospital. Morton was more fortunate than Wells; his public demonstration was a complete success, and the speed with which its fame spread round the world is truly remarkable.

On December 19, 1846, a tooth was extracted under ether in London, and two days later the drug was used for two operations performed by Liston at University College Hospital; within a few days the fame of ether had spread to Edinburgh and to Paris. Sir J. Y. Simpson (1847a) immediately (January 19, 1847) used ether to relieve the pain of childbirth, and within three months it had revolutionized surgical practice in Great Britain.

Reception of the Discovery

The manner of the reception of the news of the discovery of anaesthesia in Great Britain is thus described by a contemporary (Miller, 1848):

"It fell on no dull or idle ears. It was taken up, tried, and speedily re-echoed; and in a few days it filled the island. The profession were surprised, excited, charmed in the mass; and more especially those on the sunny side of the grand climacteric. The elderly gentlemen had their preconceived and heretofore settled notions sadly jostled and disturbed; not a few grew irritable, and resented the interference, but the thing was too fast, the first impulse too strong, and the promoters too numerous and nimble to be so obstructed."

In the case of nitrous oxide it was necessary to explain and palliate the inertia of our profession, but the history of the reception of the discovery of ether is wholly creditable, for its use appears to have sped round the world as fast as the posts could carry the news.

The contrast between the fate of the two drugs suggests a kind of all-or-none effect where a discovery depends on the attainment of an adequate technique. In such a case if the results are immediately convincing and obvious, and the introduction is attended with reasonable good fortune, the discovery attains a momentum that sweeps away opposition. If, on the other hand, there are hitches owing to imperfect technique or mere bad luck, then a discovery of comparable importance may peter out and be forgotten for a generation.

The introduction of ether as an anaesthetic was attended by many unfortunate circumstances on which it is unnecessary to dwell. There was a quarrel between Jackson and Morton, an attempt at secrecy and a patent. All who are condemned to survey modern medical literature will sympathize with the bad luck of Crawford W. Long, a rural practitioner in Georgia who in 1842 used ether to produce anaesthesia in several operations. He had been so impressed by the injunctions of his professors not to swell medical literature by premature publication of incompletely verified work that he did not publish his results until 1853. Hence the most laudable of motives caused him to miss much well-deserved fame.

Incidentally the attempt to take out a patent was eagerly seized upon as a pretext for opposition to a new idea. The following was the reaction of the *Philadelphia Medical Examiner* to anaesthesia in December, 1846 (Hoff, 1937): "We are persuaded that the surgeons of Philadelphia will not be seduced from the high professional path of duty into the quagmire of quackery by this will-o'-the-wisp." After a passing reference to the ethics of using a patent medicine and a lament for the decadence of Boston, the editor concluded that "physicians and quacks will soon form one fraternity."

The credit for the discovery of ether was a subject of prolonged inquiry and controversy, but the matter was well summed up by Jacob Bigelow in 1870 in a letter to Simpson (1871): "As far as we know, he [Morton] is the only man, without whom anaesthetic inhalation might have remained unknown to the present day." I feel that this is the final criterion in apportioning credit for an advance. Discoveries are scarcely ever the sole work of one person. All research workers stand on the shoulders of their predecessors, and if current knowledge is adequate to suggest a possible advance to one person, it is nearly certain that the same idea will have occurred to many others. There is, however, a world of difference between a bright idea and a successful achievement, and the main credit must always go to the man who possessed the energy and determination and skill to demonstrate the possibility of progress along some new path.

Chloroform

The discovery of chloroform was the third outstanding event in the discovery of anaesthesia. The trial of chloroform by J. Y. Simpson and his friends, and its successful use as an anaesthetic for major operations at the Royal Infirmary of Edinburgh on November 15, 1847, are celebrated historical events. The first operation was performed by Professor Miller, and was witnessed by Dumas the chemist and by Christison. There has been debate on the extent to which Simpson was helped or even anticipated by others, and since this is a matter of special interest to Edinburgh, I feel justified in digressing briefly to discuss this point.

Christison (1886) in 1868 wrote the following account of his colleague's achievement:

"In 1832 Soubeiran in Paris and Liebig in Germany simultaneously discovered chloroform. In 1835 Dumas ascertained its leading physical and chemical properties and its correct elementary constitution. In 1838 Dr. Formby of Liverpool first used it as a medicine inwardly as a soothing antispasmodic. In 1842 Dr. Mortimer Glover, a young Edinburgh graduate, discovered by experiment that it is a powerful narcotic poison, and that one of its effects as such is to produce insensibility."

Gilmour (1908) states that Dr. Black of Bolton used chloroform as a medicine in 1833. It is said that Glover tried chloroform on human subjects (Davidson, 1908). Furnell, working under John Bell and Co., London, is said to have experimented on himself in the summer of 1847. Christison states that in March, 1847, the French physiologist Flourens proved that the inhalation of chloroform causes in animals precisely the temporary anaesthesia caused by the inhalation of ether.

Events Leading to its Use

Christison also made the following statement in 1870:

"On asking Dr. Matthews Duncan to repeat a remarkable statement he made to me a few months ago, relative to his concern with the discovery of the anaesthetic virtues of chloroform, he gave it to me thus. One day when Sir James Simpson and he were in Dr. Gregory's laboratory at the College, he (Dr. Duncan) got possession of every liquid in the laboratory which he imagined 'would breathe.' Four or five bottles were thus carried off, and chloroform was one. At this time the correspondence with Mr. Waldie about anaesthesia and the suggestion by that gentleman to try chloroform had not been heard of by Dr. Duncan. One forenoon Dr. Duncan made trial of the chloroform. He had previously

experimented on himself with various substances, but found none suitable. On trying chloroform, he was convinced that the article sought for was found. The same or next evening the trial was repeated by Dr. Keith, Sir James, and himself. This was the trial which is now a matter of history; but the previous trial has never been noticed."

Dr. Duncan was at that time assistant to Sir James Simpson in his scientific work, and undertook this special inquiry under his general guidance. With regard to the earlier trials noted above, it may be mentioned that the only commercial form in which chloroform was available was a weak alcoholic solution termed "chloric ether," and this was used in most cases.

The David Waldie mentioned above, who was chemist to the Apothecaries' Company in Liverpool, devised a method of separating pure chloroform from chloric ether. On November 29, 1847, he gave the following account at Liverpool of the manner in which he suggested the use of chloroform to Simpson:

"The vapour of the so-called chloric ether seems to have been tried as a substitute for sulphuric ether in February or March last,* but without very satisfactory results, which indeed could scarcely be expected, unless the vapour of alcohol possessed the same properties, it being composed principally of alcohol. When in Scotland, in October last, Dr. Simpson introduced the subject to me, inquiring if I knew of anything likely to answer. Chloric ether was mentioned during the conversation, and being well acquainted with its composition and with the volatility, agreeable flavour, and medicinal properties of chloroform, I recommended him to try it, promising to prepare some after my return to Liverpool, and send it to him. Other engagements and various impediments† prevented me from doing this so soon as I should have wished, and in the meantime Dr. Simpson, having procured some in Edinburgh, obtained the results which he communicated to the Medico-Chirurgical Society of Edinburgh on the 10th of November, and which he published in a pamphlet entitled: 'Notice of a New Anaesthetic Agent as a Substitute for Sulphuric Ether in Surgery and Midwifery.'"

Simpson wrote in a footnote to the pamphlet mentioned that Mr. Waldie had named chloroform to him as worthy among others of a trial. Waldie emphasized the fact that he had played only a small part in the discovery of the anaesthetic properties of chloroform, but thought that Simpson might have been more generous in his recognition of this help, since he had recommended the trial of pure chloroform, which at that date was not known as a commercial article.

These accounts suggest that Simpson was, as Waldie complained, somewhat economical in his recognition of the help he received both from Waldie and from Matthews Duncan. Nevertheless the popular tradition that associates Simpson's name alone with the introduction of chloroform would appear to be substantially correct. The discovery of surgical anaesthesia was not a revolution in ideas, but the attainment of a goal which others had striven for without success. After the establishment of ether many persons up and down the country were trying out all likely volatile fluids. The essential advance was not the idea of trying chloroform but the provision of proof that not only did it produce anaesthesia but that in some respects it appeared to be superior to ether.

Simpson also seems to have the honour of being the first to use anaesthesia in labour, but this advance was almost inevitable after the discovery of anaesthesia, and the question who was first is not important. It is indeed probable that the witch-cult were the real pioneers in the production of "painless labour." They appear to have retained the knowledge of the use of narcotics to produce coma which was common in mediaeval times and lost at a later date. The descriptions of the composition and the use of their "flying ointment" establish this point fairly clearly. They appear also to have used such drugs to relieve the pains of childbirth. Unfortunately the accounts of the witch trials are such a medley of

fact and fiction that one cannot draw from them any certain conclusions. For example, Agnes Sampson of North Berwick was accused of having taken away the "natural and kindly pains of labour" from Euphemia MacCalyan of Edinburgh, and this suggests the use of narcotics; but the account proceeds to state that the pains were cast upon "the wanton cat of the house," which vanished. At the time of the trial the evidence was deemed completely convincing, and both women were burnt alive in 1591, but to-day it is obviously difficult to decide how much, if any, of the tale was true.

Chloroform attained immediate popularity, but it is of interest to note that it narrowly escaped an initial disaster, which might have prevented its employment for decades.

Immediate Success of Chloroform

Chloroform was first used for an operation at the Royal Infirmary, Edinburgh, on November 15, 1847. A test had been arranged two days previously, but Simpson could not attend, and therefore chloroform was not given on this occasion. The operation was for hernia, and the patient died when the first incision was made through the skin (Simpson, 1852). It is very probable that the same tragedy would have occurred if chloroform had been used, when it would certainly have borne the whole blame, and the incident shows how much the initiation of a new therapeutic measure may depend upon good fortune.

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. This, however, was provided for him by the action of certain ministers and medical men who claimed that relief of the pains of childbirth was contrary to the Scriptures. Possibly these ministers hoped to revive some of their old triumphs of the seventeenth century, when the number of midwives they caused to be burnt as witches must have formed a considerable proportion of those practising this profession. Times had changed, however, and it is only fair to the churches in Scotland to record that Dr. Chalmers gave the opinion that if some "small theologians" really took such an improper view they were too foolish to merit serious attention. Simpson, however, plunged with delight into the controversy; he fought his opponents on their own ground—namely, the interpretation of the biblical texts—and scored a fairly easy triumph.

Far longer and more serious was the controversy between Boston and Great Britain over the relative merits of ether and chloroform. This controversy practically ended in 1871, when the *British Medical Journal* threw its great influence on the side of ether.

Investigations of Deaths from Chloroform

Deaths from chloroform soon occurred, and the first case (January 28, 1847) happened to be typical. A girl of 15 had had one great toe successfully removed under ether, and two months later chloroform was given for the removal of the other one. The patient died suddenly within two minutes of the beginning of anaesthesia. The occasional occurrence of sudden and wholly unexpected deaths of this type under chloroform naturally attracted much attention. The history of the investigations made upon this subject in the ensuing sixty years provides chastening reading for laboratory workers, because the early clinical observers at once divined the nature of the phenomenon, while the laboratory workers in later years were persistently at fault.

In 1848 Sibson analysed the first four deaths from chloroform, and concluded: "In all the four cases it is manifest that the immediate cause of the instantaneous death lay in the heart." In February, 1849, it was noted in a case of chloroform death that the blood ceased to flow before the respiration stopped (Nunneley, 1849). Snow (1858) made a masterly analysis of fifty cases of death from chloroform, and showed that in at least forty of these cases death was due to cardiac syncope and not to overaction of chloroform on the brain or medulla.

* Presumably the experiments referred to by Christison.

† His laboratories were burnt down.

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.

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 commissions appointed by the Royal Medical and Chirurgical Society and by the British Medical Association. A later commission set up 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 anaesthesia. It is difficult to believe that any of these commissions could have studied Snow's excellent treatise. In this he describes fully the manner in which overdosage of chloroform kills an animal, and then remarks:

"In examining the recorded cases of fatal inhalation of chloroform, we shall find, however, that they have none of them taken place in this gradual manner; but that in all cases the fatal symptoms, if not the actual death, have come on very suddenly."

This history illustrates clearly an essential limitation of laboratory methods; like most methods of exact analysis, they yield peculiarly ridiculous results unless they are directed to the correct object. The prolonged failure recorded above has since been redeemed, and to-day it is possible to produce cardiac syncope with chloroform as a laboratory demonstration.

Other Anaesthetic Agents

The discovery of ether and chloroform stimulated intensive research into the properties of other gases and volatile liquids. As already mentioned, Flourens in 1847 described the anaesthetic action of ethyl chloride as well as chloroform. In 1848 Nunneley investigated on cats the anaesthetic action of numerous substances, and incidentally described the effects produced by a mixture of ether and an alcoholic solution of chloroform (A.C.E. mixture). Workers such as Nunneley, Snow, and Richardson examined the anaesthetic properties of a wide variety of gases and volatile liquids. Some of these, such as ethylene, afterwards became established. The general rule that "the good is the enemy of the best" came, however, into operation: nothing was found which showed a clear superiority over chloroform or ether, and in consequence research died down. The generation that had witnessed the revolutionary advance continued to work in the hope of discovering something new and better, but when these died out the younger generations who had been trained with chloroform and ether accepted these and their imperfections as established institutions and scarcely thought of the possibility of major advances.

Continual minor improvements in technique were made, but there was extraordinarily little change until about 1923. Since that date new volatile anaesthetics such as ethylene and cyclopropane have been introduced, intravenous anaesthesia with sodium evipan has achieved great popularity, and a wide variety of methods of basal narcosis has been investigated.

With regard to methods of basal narcosis, it is interesting to note that the use of such substances as urethane and paraldehyde for this purpose was established as a routine method in physiological laboratories by the end of the nineteenth century. The long delay in applying these routine laboratory methods to anaesthetic practice is remarkable.

Points on the Progress of Therapeutic Knowledge

This brief summary of the history of anaesthesia reveals some interesting points concerning the progress of therapeutic knowledge. The problem of anaesthesia is the discovery of the optimum technique for producing a certain well-defined effect. This effect is not an end in itself, but is for the purpose of facilitating surgical procedures. The history of the introduction of anaesthetics shows that that advance tended to be an all-or-none process and that the result was largely dependent on good luck. The whole history of anaesthesia might have been different if Wells had chanced upon a good subject and Morton upon a refractory patient for their first demonstrations of nitrous oxide and ether respectively, while in the case of chloroform it is highly probable that its career would have been arrested by a dramatic tragedy if Simpson had not fortunately been forced to postpone his first public trial of the drug.

The speed with which ether and chloroform were adopted is highly creditable to the medical profession. The process was probably assisted by the fact that at that period medical ideas were in a state of flux. The lethal traditions of the "heroic" era were rapidly being discarded; patients with pneumonia were no longer being bled to death, and quinine was replacing calomel in the treatment of malaria.

The history of anaesthesia after 1847 shows clearly one of the major difficulties attending therapeutic advance. The outstanding fact is that thorough familiarity with a technique is equivalent at least to a 30 per cent. difference in efficiency. If a person has mastered a technique it is not worth his while changing to a new and unfamiliar one unless the change promises some big advantage.

It is obvious that after a technique has become fairly effective the likelihood of any major advance is lessened. The history of engineering shows, however, that continuous small advances can add up to constitute a large effect, and there seems no reason why this should not be true in pharmacology.

Need for Further Technical Advance

I think it will be generally agreed that further progress in the technique of anaesthesia is very desirable. The fact that deaths under anaesthesia are increasing rather than decreasing indicates that we are far from having attained perfection. There is a tendency to assume that because the pioneer advances were due to uncoordinated individual enterprise, therefore this remains the best method. I would suggest, however, that although organization is of little service in promoting original thought, yet there comes a stage of development when further progress can only be made by co-ordinated work. This stage has probably been reached in the development of anaesthesia. To decide whether a new anaesthetic constitutes a significant advance is a difficult task, for not only must its usual action be determined, but it is also necessary to know what chance there is of its producing some rare but unpleasant side-action. These facts can only be ascertained by carefully organized large-scale trials of new agents.

The history of anaesthesia, like the history of many other therapeutic problems, shows that this country shines much more in pioneer investigation than in the development of techniques that have already been established. The United States and Great Britain together initiated anaesthesia; I do not propose to attempt to estimate the relative importance of the contributions of

the two countries, but they were of comparable importance, and no other country can claim any substantial share in the credit. The recent advances in anaesthesia are, however, divided between Canada, the United States, and Germany. The change in our country's position is regrettable. I would suggest that what is needed is an organization of the methods of study of anaesthetics that will permit the accurate estimation of the value of new methods, which, even if they do not provide any sensational advance, yet may be a significant improvement on established methods.

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H. C. Ling, L. Greene, and S. E. Pai (*Chin. med. J.*, 1938, **54**, 177) record two fatal cases of diphtheria gravis bacteraemia. The first, which is only the second example of the condition to be reported in China, occurred in a boy aged 12 who had a severe attack of faucial and nasal diphtheria and died after about ten days' illness. The gravis type of diphtheria bacillus was isolated from the blood. The second case was that of a girl with grave faucial, laryngeal, and bronchial diphtheria, who died after four days' illness. The gravis type of diphtheria bacillus, together with a non-haemolytic streptococcus, was cultivated from the heart blood seven hours after death.

RADIOTHERAPY IN NON-MALIGNANT UTERINE HAEMORRHAGE*

BY

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Diagnosis

The first point to be considered in cases of abnormal uterine haemorrhage is the question of diagnosis. Only too frequently do we see patients who have complained of irregular or excessive bleeding at or about the menopause for which no attempt has been made to discover the cause. Many patients believe that such irregular bleeding is a normal phenomenon and do not seek medical advice; but in some cases they do so, only to be reassured, and to be told to wait for a month or two, when the bleeding will stop, no vaginal examination or other investigation being made. It is from cases such as these that a large proportion of patients with advanced carcinoma of the cervix eventually come for treatment, after a delay of months and when the prospect of cure is very considerably reduced or it is impossible. It cannot be emphasized too strongly that when such symptoms appear the patient must be examined immediately and thoroughly for the possibility that the symptoms may have causes other than menopausal dysfunction of the ovaries, and especially must a thorough pelvic examination be made, to exclude malignant disease.

Apart from this all-important question of diagnosis I do not propose to deal with the vast subject of malignant disease of the uterus, but to consider those types of non-malignant uterine haemorrhage in which radiotherapy is employed. These cases fall into three categories: (1) bleeding at or near the menopause; (2) bleeding associated with fibroids; (3) bleeding in young subjects.

How Radiotherapy Acts

The manner in which radiotherapy acts in the treatment of these cases has been the subject of considerable discussion. It is generally agreed that when external irradiation by x rays is the method employed the production of amenorrhoea is due to the destructive effect on the more mature follicles of the ovary. Much experimental research has been carried out on this subject, and Regaud and Lacassagne (1927), describing the effects of radiation on normal tissue, give a clear and concise account of the changes that occur. All ovarian follicles can be destroyed if the dose of radiation is large enough; but there is a very great difference in their radiosensitivity, depending on the stage of maturity. Immature ovarian follicles have little radiosensitivity, and escape apparently unscathed even after heavy irradiation. As they develop, their degree of radiosensitivity increases, until finally the mature follicle is very radiosensitive and is destroyed by only a small amount of radiation. In the ovary of a woman at the end of her reproductive life and approaching the menopause the follicles which remain are either mature or approaching maturity, and therefore are highly radiosensitive. In such cases permanent sterilization can be brought about by moderate doses of radiation. With the young subject, however, this is not the case: some follicles are approaching maturity and are therefore radiosensitive; but the majority have not begun to develop, and need much greater doses for their destruction. A frequent

* Read in opening a discussion in the Section of Radiology at the Annual Meeting of the British Medical Association, Plymouth, 1938.