Harold Griffith Memorial Lecture

The Griffith legacy

Sir Keith Sykes MA MBBChir FRCAnaes HonFFARACS HonFFA(SA)*

1992 was the anniversary of Crawford Long's use of ether in 1842, and Griffith and Johnson's introduction of Intocostrin into anaesthetic practice in 1942. Harold Randall Griffith was born in Montreal in 1894 and died in 1985. He interrupted his medical studies to serve in the first world war and was awarded the Military Medal for gallantry at the battle of Vimy Ridge. Griffith qualified from McGill University in 1922. After spending a year studying homoeopathic medicine, he joined his father's general practice and became the anaesthetist to the Homoeopathic Hospital in Montreal. He succeeded his father as Medical Director of the hospital (now renamed the Queen Elizabeth Hospital) in 1936 and retired in 1966. Griffith was a superb clinical anaesthetist. He was an early advocate of detailed anaesthetic records, and was responsible for the introduction of both ethylene and cyclopropane into Canadian practice, later teaching himself to intubate under these two agents. Griffith was one of the first to be concerned with standards of patient care. He introduced postoperative recovery and intensive care units into Canadian practice and played a major role in postgraduate teaching. He was unstinting in his support of organisations designed to further the progress of anaesthesia and was the first President of the Canadian Anaesthetist's Society. He was one of those responsible for inaugurating the World Federation of Societies of Anaesthesiology and was President of the First World Congress of Anaesthesiology in 1955. It is remarkable that the introduction of curare into anaesthetic practice was delayed until 1942, since curare had been used in anaesthesia some 30 years previously. However, it was probably Griffith's confidence in his own clinical abilities which enabled him to seize the opportunity when it was offered.

En 1992, nous avons célébré l'anniversaire de l'utilisation de l'éther par Crawford Long en 1842, et l'introduction en anesthésie de l'intocostrin par Griffith et Johnson en 1942. Harold Randall Griffith est né à Montréal en 1894 et y est mort en 1985. Ses études furent interrompues par la première guerre mondiale au cours de laquelle il mérita la médaille militaire pour son courage pendant la bataille de Vimy. Griffith finit ses études à l'université McGill en 1922. Après une première année d'étude de la médecine homéopathique, il retrouva son père en pratique générale et devint l'anesthésiste de l'hôpital homéopathique de Montréal. Il succéda à son père comme directeur médical du même hôpital (maintenant l'hôpital Reine Elizabeth) en 1936 et prit sa retraite en 1966. Griffith fut un extraordinaire clinicien. Dès le début, il insista sur la méticulosité des dossiers anesthésiques. Il introduisit l'utilisation en clinique au Canada de l'éthylène et du cyclopropane, sous lesquels il apprit à intuber par lui-même. Il fut un des premiers à s'intéresser à la qualité des soins. Il implanta les salles de réveil et de soins intensifs dans la pratique médicale canadienne et joua un rôle très important dans l'enseignement spécialisé. Son soutien aux organisations dédiées au progrès de l'anesthésie fut toujours inébranlable et il devint le premier président de la Société canadienne des anesthésistes. Avec d'autres, il inaugura la Fédération mondiale des sociétés d'anesthésie et fut président du premier congrès mondial d'anesthésiologie tenu en 1955. Comme le curare avait déjà fait apparition en anesthésie 30 années auparavant, il est à remarquer que son utilisation en anesthésie clinique ne débuta qu'en 1942. C'est probablement grâce à la confiance qu'il avait en sa compétence clinique qu'il put saisir à ce moment l'opportunité qui s'offrait à lui.

The year 1992 is the anniversary of two events which have been of crucial importance to our speciality. The first occurred on March 30th 1842 when Crawford Long, a Physician practising in Jefferson, Georgia, removed a small tumour from a boy named James Venable, whilst the patient was rendered insensible to pain by the inhalation of ether vapour. This was probably the first time that a surgical operation had been performed under anaesthesia. Almost a hundred years later, on the 23rd of January 1942, Harold Griffith administered the muscle relaxant preparation "Intocostrin" to a 20-year-old plumber undergoing appendicectomy under cyclopropane anaesthesia in the Homoeopathic Hospital, Montreal, and so started a new era in anaesthetic practice. It is, perhaps, surprising that curare was not accepted into anaesthetic

*Emeritus Professor, University of Oxford.

Harold Randall Griffith Lecture delivered at the 10th World Congress of Anaesthesiologists, The Hague, Netherlands, June 17th 1992.

Accepted for publication 22nd December, 1992.

practice at an earlier date, for there had been many other attempts to use curare for the treatment of convulsive or spastic conditions and it had been used in anaesthesia some thirty years previously. However, it will become apparent that it was Griffith's character and clinical acumen which finally secured its place in clinical anaesthetic practice. The widespread recognition of Griffith's role in the introduction of muscle relaxants has tended to overshadow his immense contributions in other fields. For this reason I have chosen a title which stresses the totality of his contributions to anaesthesia.

The anniversary of the introduction of curare was commemorated by the Canadian Post Office which issued a Griffith stamp as part of a medical issue which included such other distinguished names as Frederick Banting, the co-discoverer of insulin; the physician Jennie Trout; and the neurosurgeon Wilder Penfield. The anniversary was also celebrated at the 4th International Neuromuscular Meeting in Montreal in May 1992, whilst the Canadian Journal of Anaesthesia published a special supplement to celebrate the occasion[1] and Richard Bodman and Deirdre Gillies published a biography of Griffith in the "Canadian Medical Lives" series.[2] I should like to acknowledge my debt to both these sources.

Harold Randall Griffith was born in Montreal in 1894 and died in 1985. His father, Dr. A.R. Griffith, was a physician who had also trained in Homoeopathic Medicine, and ran a large general practice in Montreal. He was one of the founders of the Homoeopathic Hospital, which opened its doors in 1894, and subsequently he became its Medical Director. Harold was the second of four sons, and another son, James, subsequently became a surgeon. Harold went to school in Montreal and, in 1910, won a scholarship to McGill University. He embarked on a combined Arts and Science course and had completed the B.A. and commenced his first year of medical studies when the First World War broke out. Like many of his generation, he believed that the war would only last a few months and on October 14th 1914 he volunteered for service in the army. For the first three years of the war he served in the 6th Field Ambulance of the Canadian Expeditionary Force and, in 1917, won the Military Medal for gallantry at the battle of Vimy Ridge. He then discovered that the British Navy was using medical students as doctors on board the smaller ships and transferred to the British Navy to serve as a Probationary Surgeon Sub-Lieutenant on HMS Lapwing until the end of the war. During the Second World War he served as a Wing Commander in the Royal Canadian Air Force; he thus had the rare distinction of having served in all three services.

When Griffith returned to Montreal in 1918 to continue his medical studies he lived in the Homoeopathic Hospital, where his father was the Medical Superintendent, and here he gained a great deal of practical experience in tasks which ranged from the scrubbing of floors to the administration of anaesthetics. He must have displayed some skill as an anaesthetist even at that early age for in 1922, whilst still a medical student, Griffith wrote his first paper describing his experience in the administration of some 400 anaesthetics.[3] He qualified from McGill University in 1922, and after a further year's study of homoeopathic medicine at the Hahnemann Medical College in Philadelphia, he returned to Montreal where he joined his father's large general practice and also took over responsibility for the anaesthesia at the Homoeopathic Hospital. He succeeded his father as Medical Director of the Homoeopathic Hospital (now renamed the Queen Elizabeth Hospital) in 1936, and held the position of Medical Director until 1965 and Chief of Anaesthesia until 1966.

I remember visiting him at this hospital in 1955. He was a quietly spoken, modest and very friendly person, who was obviously greatly respected, not only by his residents, but also by the surgeons and theatre staff. Although my memory of that day is now somewhat hazy, I do remember that he spent a great deal of time showing me round the operating rooms and other facilities, even though I was a very junior trainee and had arrived at the hospital without any advance warning.

What, then, was it that made this very unassuming man such an important force in anaesthesia during his lifetime? First and foremost, he was a very experienced and highly skilled clinical anaesthetist. In his first paper, which won the Second prize in the McGill Medical Society Senior Prize Competition in 1922, he describes the problems of anaesthetizing patients with the techniques then in common use – namely ether, chloroform and nitrous oxide-oxygen.[3] It is obvious from the detailed description of the techniques he used that he was a very perceptive observer who was deeply concerned about safety, postoperative complications, patient comfort and his own relationship with the surgeon. His careful approach to anaesthesia is illustrated by the immaculate anaesthetic records included in his paper. Although Harvey Cushing had advocated the recording of blood pressure during operation some 25 years previously, this was still not a common practice and so Griffith felt it necessary to spell out four good reasons for so doing:

1 It gives the anaesthetist a satisfactory knowledge of the condition of the patient – especially valuable when shock is feared.
2 It shows the surgeon at a glance the actual condition without having to depend on the judgement of an anaesthetist who may be a stranger.
3 It provides a permanent scientific record for statistical

purposes, and for consultation if the patient comes up for another operation.

4 It gives the anaesthetist something to do which will keep his mind on the patient during a tedious operation.

These four statements are very revealing for they show that he was a very conscientious anaesthetist, that he was concerned about his relationship with the surgeon, that he had an analytical mind and was continually striving to improve his standard of practice and, above all, that he had a sense of humour!

In 1923, the year Griffith became the anaesthetist to the Homoeopathic Hospital, ethylene was introduced into anaesthetic practice and Griffith immediately started to use it in Montreal. Two years later he had an unfortunate experience with a laryngeal spasm during ether anaesthesia in a 180 kg man, which resulted in the death of the patient, and he resolved that he would teach himself to intubate the trachea. He first learnt how to visualise the vocal cords under deep ether anaesthesia but then taught himself to perform the much more difficult task of endotracheal intubation under the very light levels of anaesthesia provided by nitrous oxide or by ethylene. He was the only anaesthetist in Montreal to use ethylene and he described the technique of intubating under this agent at a meeting in Boston in 1928, and in papers published in 1929 and 1932.[4-6] He later commented that the audience at the Boston meeting had listened politely but had not asked many questions since "at least 75% of the so-called anesthesiologists in that audience had never passed an endotracheal tube."

However, Ralph Waters of Madison, Wisconsin, was in the audience and was very impressed by the paper. He introduced himself to Griffith and the two became firm friends. It was Waters who invited Griffith to join the Anaesthetists Travelling Club, a small group composed mainly of distinguished American anaesthetists. Frank McMechan, who founded the International Anesthesia Research Society, and Wesley Bourne, later to become the first Professor at McGill University, were also members of this club, which aimed to reduce the isolation felt by these relatively few early pioneers of specialist anaesthesia. In 1933 Griffith visited Waters in Madison, Wisconsin, and was impressed by the new agent cyclopropane. The pharmacology of this agent had been studied in animals by Lucas and Henderson in Toronto in 1929,[7] and the drug had later been given to local volunteers, amongst whom were Henderson, Lucas and Sir Frederick Banting, one of the co-discoverers of insulin, who had been awarded a Nobel Prize for his work in 1923. Griffith used the agent for the first time in Canada on the 30th October 1933[8] and continued to advocate its use until he ceased to give anaesthetics in 1966. Cyclopropane became a popular anaesthetic in many centres and was commonly used for the relatively small number of thoracic operations that were performed at that time. The need for a completely closed circuit and for manual assistance to ventilation caused Griffith to become an early advocate of the cuffed endotracheal tube, and he frequently criticised those who never used endotracheal intubation. He also introduced the concept of the bronchial blocker to Canadian thoracic surgical practice.

Griffith's second major contribution to anaesthesia was his concern with standards of anaesthetic care. He was well aware of the mercenary practices of many of his contemporaries and was openly critical of the employment of nurse anaesthetists for economic reasons. He was an intensely honest man who continually sought to determine the cause of any anaesthetic complication and he, and his good friend Robert Macintosh at Oxford, both campaigned for honest reporting of anaesthetic complications and deaths so that anaesthetists might learn from the mistakes of others. It is difficult for us nowadays to realise how competitive anaesthetic practice was in the thirties and forties. There were few anaesthetic specialists and most anaesthetics were given by the patient's general practitioner, a nurse, a medical student or even a theatre porter. The anaesthetist rarely billed the patient directly and was often dependent on the surgeon for his livelihood, so it is not surprising that complications were hushed up and deaths often blamed on the mythical entity "status lymphaticus." In England Macintosh's calls for a study of anaesthetic deaths were repeatedly turned down by the authorities and it was not until 1949 that the Association of Anaesthetists of Great Britain and Ireland set up a committee to investigate deaths under anaesthesia, the report finally being published in the Journal "Anaesthesia" in 1956.[9] It is unfortunate that, even today, there are still some anaesthetists who refuse to cooperate with national or local enquiries into morbidity and mortality associated with anaesthesia and so hinder the attainment of greater safety for the patient.

Griffith was also concerned for the patient at a much more personal level. He was one of the first to advocate appropriate premedication and an intravenous induction and, in a paper published in 1937 entitled "Anaesthesia from the patient's point of view," he strongly supported the need for a preoperative visit, for discussion of the choice of anaesthetic with the patient, and for silence in the induction room.[10] He also wrote:

> "that if it helped patient's morale they should be allowed to keep false teeth, blackened eyelashes or a toupee until after induction of anaesthesia"!

In 1943 Griffith learnt of John Lundy's post-anaesthetic recovery room at the Mayo Clinic, and within a short time he had organised a similar unit in his own

hospital in Montreal, combining it with the blood transfusion department. He was also one of the first in Canada to develop an Intensive Care unit and acute coronary care unit. During the Second World War he ran intensive courses for the training of anaesthetists for the armed forces and, with this experience, was later to play a major role in the development of the excellent postgraduate anaesthetic teaching programme in Montreal.

Griffith's third major contribution, which stemmed directly from his concern with standards of care, was his unstinting support of organisations designed to further the progress of anaesthesia. He was the first President of the Canadian Anaesthetists' Society, the President of the International Anesthesia Research Society, Vice-President of the American Society of Anesthesiologists and was one of those responsible for establishing the World Federation of Societies of Anaesthesiology and running the First World Congress in 1955.

How, then, did he come to make his other major contribution, the introduction of curare into anaesthetic practice, some 400 years after Europeans first learned of the properties of the arrow poison?

The first known account of the use of poisoned arrows by the South American Indians was in Pieter Martyr d'Anghera's "De Orbe Novo" published in 1516. Pieter Martyr was an Italian who rose to a high position in the church and was then attached to the Court of Isabella of Spain. There he met and entertained travellers who had returned from the New World, subsequently incorporating their tales in a series of letters to his friend Cardinal Ascorio Sforza in Rome. In one of his letters he described how some of the Spaniards had been attacked by the natives with poisoned arrows and then continued with a description of the preparation of the arrow poison.[11] He wrote:

> "The arrows are dipped in juice obtained from certain trees. There are old women skilled in its preparation who, furnished with the necessary materials, are shut in for two days to distil the ointment. When the house is opened, if the women are well and not found lying on the ground, half dead from the fumes of the poison, they are severely punished and the ointment is thrown away as valueless."

It was obviously not advisable to be an old woman in South America at that time!

Although there were a number of further reports of the use of poisoned arrows over the next two hundred years, South America was virtually closed to foreign exploration by other than military forces. In 1735 Charles Marie de la Condamine, a Member of the French Academy of Sciences, was chosen to lead an expedition to make a series of measurements designed to settle the controversy as to whether the earth was flattened round the equator or at the poles, and was given permission to use Quito, the capital of Equador, as the centre for his operations. During his 10 years in South America he explored some of the inland areas and, finally, made an amazing journey down the whole length of the Amazon. He was the first person to describe the use of a blow pipe to propel the poisoned arrows and the first to report that death occurred within one minute after inoculation of the poison into a hen.[12] He was also the first person to bring some of the poison back to Europe and to demonstrate its properties in the University of Leiden. Brocklesby[13] and Herissant[14] later used these samples in further experiments with the poison. Herissant, after narrowly escaping death from the poison on two occasions, proceeded to undertake a particularly macabre series of experiments on dogs, rabbits, cats, horses, moles, pigs, rats, mice, young wolves and even a bear and an eagle! In 1769 Edwin Bancroft, a physician, naturalist and explorer, who had spent five years in South America, listed the ingredients used to make the poison but concluded that the proportions of each ingredient varied from tribe to tribe.[15] He described how the bark from the roots of the various plants was heated in water and how the Indians then extracted the poison by squeezing the bark with their bare hands, noting that they took good care not to have any broken skin when they did so!

The first truly scientific experiments with the poison were performed in 1780 by the Abbé Felix Fontana in Florence. He showed that curare fumes were not poisonous and that direct application of the poison to a nerve had no effect.[16] Thirty years later Benjamin Brodie began to experiment with some of the samples of poison which had been brought back to England by Edwin Bancroft. Brodie made the very important observation that when he gave the poison to animals the heart continued to beat after the respiration had ceased.[17] He also showed that he could keep the animal alive by forcing air into the lungs with a bellows.[18]

The next major author in the history of curare is Charles Waterton, who, in 1804, moved to British Guiana to manage his family's plantation. Between 1812 and 1824 he undertook a series of expeditions to the interior which resulted in his classic book "Wanderings in South America," first published in 1825.[19] He gave detailed descriptions of how the natives used poisoned darts fired from a long blow-pipe, poisoned arrows or poisoned spears to catch their prey, and noted that they could kill an animal at a range of 100 metres. Waterton tested the poison on dogs, an ox, and a sloth in South America, and was present when Brodie and a veterinary surgeon named Sewell repeated the artificial ventilation experiment on a donkey at the Veterinary College in

London in 1814. His description of the experiment is a classic:

> "A she-ass received the wourali poison in the shoulder, and died apparently in 10 minutes. An incision was made in its windpipe, and through it the lungs were regularly inflated for two hours with a pair of bellows. Suspended animation returned. The ass held up her head and looked around; but the inflating being discontinued, she sunk once more in apparent death. The artificial breathing was immediately recommenced, and continued without intermission for two hours more. This saved the ass from final dissolution; she rose up, and walked about; she seemed neither in agitation nor in pain. The wound, through which the poison entered, was healed without difficulty. Her constitution, however, was so severely affected, that it was long a doubt if ever she would be well again. She looked lean and sickly for above a year, but began to mend the spring after; and by Midsummer became fat and frisky." He added "The kind hearted reader will rejoice on learning that Earl Percy, pitying her misfortunes, sent her down from London to Walton Hall, near Wakefield. There she goes by the name Wouralia. Wouralia shall be sheltered from the wintry storm; and when the summer comes she shall feed in the finest pasture. No burden shall be placed on her and she shall end her days in peace." In later editions he added as a footnote to the original description: "Poor Wouralia breathed her last on the 15th of February 1839, having survived the operation nearly five and twenty years." She also received an obituary in the local newspaper!

By the mid-nineteenth century physiology was getting into its stride and from 1850–62 the French physiologist, Claude Bernard, conducted a series of experiments on the mode of action of the poison.[20] These showed that there was no failure of conduction along the nerve and that the muscle would still respond to direct electrical stimulation, thus leading to the conclusion that the drug must block conduction from the nerve to the muscle fibres. However, we had to wait for the studies of Henry Dale and William Feldberg in the 1930's, and Eleanor Zaimis and William Paton in the 1950's, to clarify the differing actions of the depolarising and non-depolarising blockers at the muscle end-plate.

Although little was known about the chemistry and pharmacology of the poison, this did not deter clinicians from attempting to use the crude preparation. Mr. Sewell, a veterinary surgeon, treated a horse suffering from tetanus with curare and artificial ventilation. It survived for 24 hours but died the next day from abdominal distension.[21] Francis Sibson, the Resident Apothecary and Surgeon at Nottingham General Infirmary, wrote to Waterton in 1838 suggesting that curare might be used in patients with rabies. However, Waterton would only agree to provide curare if he was present at the administration. Shortly afterwards Police Inspector Phelps was bitten on the nose by a rabid dog; unfortunately, he expired before Waterton could reach Nottingham. Sayre and Burrall[22] in the USA and Spencer Wells[23] in England were the first to report the use of curare in the treatment of patients with tetanus, but although there were further isolated attempts to use curare in other spasmodic conditions such as strychnine poisoning, rabies, and epilepsy most of these failed, firstly, because there was an enormous variation in the potency of the different preparations and, secondly, because a dose which produced an adequate therapeutic effect also paralysed the muscles of respiration, and methods of maintaining artificial ventilation for long periods had not yet been developed. Curare was even tried in anaesthesia; in 1912 Läwen, a Leipzig surgeon, described its use to relax the muscles during closure of the abdomen,[24] whilst De Caux, an enigmatic English anaesthetist, used it several times in 1926 but never published his findings.[25]

Interest in the therapeutic use of curare was revived by Ranyard West, an English physician, who reported the successful reduction of neurological spasticity with curare in 1932.[26] In 1934 Leslie Cole, a physician working at Addenbrooke's Hospital in Cambridge, described the use of subcutaneous curare in the treatment of two patients with tetanus, one of whom survived.[27] Shortly afterwards West described the treatment of ten cases of tetanus with an intravenous infusion of curare with one survival.[28,29] West was using a crude preparation of curare and later warned of the danger of acute bronchospasm.[30] However, it was West who encouraged Harold King to attempt the isolation of d-tubocurarine from a specimen of crude curare and this was successfully accomplished by 1935.[31] Although tubocurarine was commercially available from 1936,[32] it does not appear to have entered clinical use until Gray and Halton commenced their studies in Liverpool in 1944.[33]

The story then moves to Richard C. Gill in the United States. He was an extrovert character who had worked as a school teacher, a ranger in Yellowstone National Park, and a deckhand on a whaling ship. He obtained a job as a salesman for a rubber company in South America in 1928 but left when trade was hit by the 1929 depression. He and his wife Ruth returned to Equador and, after eight months of exploration, purchased 750 acres of land at an altitude of about 5000 feet on the eastern slopes of the Andes. Here they built what was probably the first dude ranch in South America.[34] For the next

two years they farmed and led an idyllic life on the edge of the jungle. Gill made a number of expeditions to the interior and established excellent relationships with a number of the Indian tribes. He became very interested in a number of their herbal preparations, persuaded the witch doctors to allow him to witness the making of the arrow poison and was even granted the status of witch doctor by the Indians themselves. Just before returning to the USA for a holiday in 1932 he fell from his horse and developed neurological symptoms. These became progressively worse and were eventually diagnosed as being due to multiple sclerosis. However, in 1934, when he was severely affected by a spastic paralysis, his neurologist, Walter Freeman, mentioned the idea of using curare to ameliorate the spasms. This re-awakened Gill's interest in curare and made him determined to return to the jungle. He devised his own highly intensive course of physiotherapy, was able to drive a car by 1936 and by 1938 was able to walk with a stick. Meanwhile he was teaching himself botany, and making detailed plans for an expedition to collect more crude curare. Luckily, he met a wealthy business man, Sayre Merrill, who agreed to finance the expedition.[35] In May 1938 he set out from Guayaquil with an expedition which eventually consisted of four Equadorian assistants, 75 Indian porters and four sub-chiefs, 36 mules and six riding animals, 12 canoes and their crews, and two tons of equipment. The journey to the jungle camp site selected by Gill took three weeks and involved perilous descents through rapids, ravines and thick jungle. They spent five months in the jungle and brought back about 75 plant specimens and some 12 kilograms of crude curare. When he returned to New York he found that the drug firm Merck, who had been supplying a crude preparation to Burman for trial in spastic and dystonic states,[36,37] had lost interest in curare and that their scientists were now studying erythroidine, another alkaloid with curare-like properties.[38] This was, indeed, a bitter blow.

A.E. Bennett, a psychiatrist from Nebraska, was also upset by this decision for he had read Burman's papers and wished to test the effectiveness of curare in the prevention of traumatic complications after convulsive shock therapy. Fortunately, Bennett met Walter Freeman, Gill's neurologist, and learnt that Gill had returned with further supplies. Gill met Bennett in May 1939 and agreed to supply him with the crude drug. Bennett then brought in his pharmacological colleague A.R. McIntyre, to standardise the drug, and Bennett used this preparation in his early trials.[39] In August 1939 E.R. Squibb and Son agreed to buy Gill's supply of the poison and, later that year, one of their chemists, Horace Holaday (whose son Duncan subsequently became a distinguished anaesthetist at the Columbia-Presbyterian Hospital, New York), devised the rabbit head-drop test for measuring the strength of the preparation. No one knew at that time what the active ingredient was and Holaday named the preparation "Intocostrin."

At the time when Bennett introduced curare into psychiatric practice the therapeutic convulsions were produced by the injection of the drug metrazol and were associated with a 20% incidence of dislocations and a 40–50% incidence of compressive spinal fractures.[40] Even the psychiatrists were getting worried! Although many psychiatrists initially refused to use Intocostrin (and, indeed, some continued to oppose its use because they believed that it was the convulsion itself which effected the cure and not the concommittant electrical activity in the brain), the use of Intocostrin spread rapidly. Within a year or two it was used in electroconvulsive therapy when this superseded metrazol as a method of treatment.

Bennett has claimed that the idea of using Intocostrin in anaesthesia resulted from an observation that a pelvic examination could be performed very easily in a patient who had received it for convulsive therapy.[41] Whether this is true or not there seems to be little doubt that a lot of the credit for its introduction should go to Dr. Lewis Wright, a physician who had completed his anaesthesia residency under Rovenstine in New York City, and who was then working for E.R. Squibb. It was he who believed that curare had a potential use in anaesthesia and who attempted to interest a number of anaesthetists in its use.[42] One of those approached by Wright was Stuart Cullen in Iowa City. In his first paper on curare in 1943, he reported that he had tried an early preparation of the drug in dogs in 1940 and had noted salivation, extreme respiratory depression and asphyxial movements when the dose was adequate to produce abdominal relaxation.[43]

E.M. Papper, then a junior anaesthetist in Rovenstine's department at New York University and Bellevue Hospital, was also asked to study the preparation.[44] In Bellevue the common experimental animals were monkeys and cats. Monkeys were deemed to be too expensive so the preparation was given to two cats, both of which died from severe bronchospasm. Undeterred by these complications, Rovenstine suggested that Papper should try the drug in patients. The drug was given to two patients anaesthetized with ether, since this was the most popular agent at that time. Both patients developed a prolonged apnoea which required manual ventilation overnight. Since apnoea was not then regarded with the same equanimity as it is today, the trial was abandoned. It is, therefore, even more surprising that Griffith should have the courage to use the drug in humans without any preliminary experience in the experimental animal. However, it is fair to say that Griffith was one of the anaes-

thetists approached by Wright in 1940, that he had seen the film showing how Bennett had used it for convulsive therapy in psychiatric patients, and that he had given the matter much serious thought before embarking on the clinical trial in 1942. But of even greater importance was the fact that he was confident of his ability to cope with the main problem likely to arise from its use, namely respiratory paralysis. To quote Griffith's own words:[45]

> "I met Dr Wright again in 1941, and asked him how he was getting along with his idea. He said he still thought that curare might be of value to the anaesthetist but he hadn't been able to get anyone to try it in the Operating Room. I argued to myself that if it did not kill Dr Bennett's patients it could hardly do any harm to ours, because the major danger would be respiratory paralysis and even at that time anaesthetists were accustomed to maintaining controlled respiration over long periods so I asked Dr Wright to send me some Intocostrin."

The classical paper by Griffith and Johnson was published in Anesthesiology in July 1942[46] and I cannot resist quoting the introduction which reads as follows:

> "Every anesthetist has wished at times that he might be able to produce rapid and complete muscular relaxation in resistant patients under general anesthesia. This is a preliminary report on the clinical use of a drug which will give this kind of relaxation, temporarily and apparently quite harmlessly."

Would that other introductions to scientific papers were as simple, clear and welcoming to the reader!

Within a year of this first report Stuart Cullen had reported on the use of Intocostrin in 131 cases[43] and had pointed out that ether augmented its action.[47,48] Surprisingly, small quantities of Intocostrin also reached England. In an unassuming letter in the Lancet of 1943 Helen Barnes, of London, reported that she had asked two colleagues to give her 4cc of Intocostrin intravenously. After listing the rather dramatic consequences, she noted that her colleagues had been able to visualise her vocal cords with great ease, even though she was fully conscious at the time! As a result of these observations she recommended its use for laryngoscopy and reported that five patients had been intubated with the aid of the drug.[49] This letter evoked a rather pompous response from another anaesthetist[50] who wrote:

> "It would be regrettable if the less experienced anaesthetist were tempted to resort to what appears to be a dangerous drug to facilitate a manoeuvre that only extreme gentleness and patience, coupled with a thorough knowledge of the anatomy and physiology of the larynx, can encompass successfully without gross and unwanted damage to the patient."

Griffith and the first Professor at Oxford, Robert Macintosh, corresponded regularly during the war, for they were old friends and were each responsible for the anaesthetic services of the Air Forces of their respective countries. On April 12th 1943 Squadron-Leader Pask, later Professor at Newcastle, wrote to Macintosh concerning some proposed experiments designed to evaluate the efficiency of various methods of artificial ventilation. The proposal was that Pask should be rendered apnoeic and his tidal volume measured whilst different methods of artificial ventilation were applied. On April 17th Stuart Cowan, a physiologist working in the Nuffield Department wrote to Macintosh:

> "We (Pask and Cowan) discussed the relative advantages of producing respiratory arrest with ether and with Curarine Chloride. Whilst he leaves the final decision with you, he would prefer ether because the Curarine may not eliminate completely laryngeal reflexes, and because the insertion of a cuff tube while fully conscious, but under Curarine might be very unpleasant."

Although the first experiments on the 26th and 28th of April 1943 were performed under ether we have a film in the department showing another artificial respiration experiment, carried out in 1945, in which curare was given to produce apnoea.[51]

In the next two years there was an enormous increase in the use of Intocostrin and by 1945 Squibb were manufacturing over 10,000 doses per month. Griffith continued to use it with caution, and in a paper in the Lancet in 1945, he reported that he had used it over 500 times but was still only administering it to some 38% of the patients undergoing abdominal operations.[52] He also commented that he had never had to use neostigmine to antagonise its effects. In the same paper he reported a personal communication from Macintosh stating that he was administering Intocostrin by infusion into the sternum! After further discussion of its merits Griffith concluded his paper with the warning "Curare should not be made the excuse for a poor anaesthetic sloppily administered."

Although Mallinson reported that he had used Intocostrin in seven patients in 1945,[53] and Forrester had compared Intocostrin with d-tubocurarine,[54] very little Intocostrin was available in the U.K. British anaesthetists therefore switched to d-tubocurarine, which had been made available by Wellcome in 1936.[32] In 1945 Mac-

intosh reported that he had used it in 100 cases without trouble, but warned that the dosage differed from Intocostrin.[55] In 1946 Prescott, Organe and Rowbotham described the effects of up to 30 mg of d-tubocurarine administered to the conscious Prescott and reported their experience of its use during 180 surgical operations.[56] In that year Gray and Halton[33] also described their initial experiences with d-tubocurarine but, whereas Griffith gave the intocostrin in small doses to augment the general anaesthesia and rarely had to control ventilation, Gray and Halton gave much larger doses which usually produced apnoea. This was, of course, the forerunner of the technique which is in widespread use today.

By 1954, when I went to Boston to spend a year at the Massachusetts General Hospital with H.K. Beecher, suxamethonium, gallamine and d-tubocurarine were in regular use in British hospitals, whilst ether was only used for children undergoing circumcision or for ear, nose and throat operations. Imagine my surprise, therefore, to find that most of the surgery in Boston was performed under ether, spinal or regional anaesthesia and that Beecher and Todd had just published a study showing that the use of muscle relaxants in ten major North American University hospitals was associated with an increase in the death rate from 1 in 2100 to 1 in 370 - a six-fold increase in mortality.[57] This study created an uproar in the anaesthetic community for it was published in a surgical journal and fuelled the antagonism that then existed between many surgeons and anaesthetists in the United States. However, the paper had many excellent sequelae. It made anaesthetists re-examine their practice when muscle relaxants were used, and it identified many of the problems of assessing anaesthetic risk with which we are still struggling today.

My attempts to introduce the British technique of controlled ventilation with muscle relaxants into the Department resulted in many friendly arguments with Beecher and, eventually, he challenged me to prove that the relaxant technique was safer and more satisfactory than ether. I, therefore, set up a randomised controlled trial of the use of ether versus the relaxants in upper abdominal surgery, and this was continued by colleagues after I returned to England. After studying some 693 cases over a period of three and a half years we concluded that there were no significant differences between the two techniques in terms of abdominal relaxation, surgical complications, length of surgery, duration of hospitalization or perioperative mortality. The only differences between the two techniques were that there was a higher incidence of circulatory depression and postoperative vomiting in the patients given ether, whilst there was a higher incidence of postoperative atelectasis in those given relaxants.[58] However, it must be noted that Beecher refused to let us use curare for this trial, because of the high mortality rate with curare in his study. We were, therefore, forced to use a suxamethonium drip for relaxation, a technique which would not now be considered the best choice for surgical procedures conducted by fairly junior surgeons and anaesthetists, and often lasting for six to eight hours!

So where does this leave us in 1992? In many countries of the world we have achieved a commendably low mortality rate associated with anaesthesia. We have developed academic standards which match or exceed those in other specialities. Anaesthetists are playing important roles in preoperative evaluation and postoperative care, intensive care and in acute and chronic pain relief. Anaesthetists are also prominent in the academic and medico-political arena. As a result, our status is now the equal of colleagues in other medical disciplines. For the first time in our history we are able to compete for the brightest medical students and we are at last able to offer them a challenging intellectual environment which matches or exceeds that of the majority of other disciplines. But we must not rest on our laurels, for the modern world changes quickly and we must keep ourselves ahead. I feel that we need to address three major issues.

The first is our performance as anaesthetists. Although we now have some idea of the mortality associated with anaesthesia this measure is influenced by innumerable local factors which vary with the population served. Mortality is an extremely crude indicator of performance where anaesthesia is concerned and there is a pressing need to develop better methods of assessing the quality of care we provide. There is, therefore, a need to develop quality assurance programmes which not only take into account the major effects of anaesthesia in terms of overt damage to the patient, but also evaluate the effects of anaesthesia on the less obvious facets such as the ability to concentrate, sleep patterns and other physical and psychological effects. This seems, at first sight, to be a simple problem, but it is one which will take much time and effort to solve.

The second issue is the quality of our teaching in anaesthesia. Postgraduate teaching in anaesthesia is a relatively recent development and most programmes have been assembled without considering the ultimate aim i.e., what kind of anaesthetist do we want? We recognise that teaching which is suitable for a doctor is often not suitable for a nurse or technician and we try to adapt our teaching to the group we are addressing. I question, however, whether we are giving enough thought to the kind of product we are trying to generate in anaesthesia, and whether we are analysing critically the content of our courses and the method of teaching. A few centres are exploring new techniques such as the use of patient sim-

ulators or computer-assisted learning but I suspect that, for a given expenditure of energy, a critical analysis of our standard methods of teaching and the content of our courses would produce much more benefit.

There is a natural tendency for trainees to be swamped with detail whilst underlying principles are ignored because it is assumed that they already know them. I believe that we need to define the core knowledge in each subject and then to ensure that our trainees know how to apply this knowledge to the clinical situation. In that way we would eliminate what I call "cook-book anaesthesia" which, to my mind, is a major problem in Europe and many other parts of the world.

The third issue is that of research. Despite the large research effort of many departments we have to admit that most of the major advances in anaesthesia have come about either because the surgeons presented us with a new problem (such as the open thorax), or because basic scientists have taken an interest in our subject. We must question whether we can continue along these lines and we must ask ourselves whether we should be seeking to tackle the fundamental problems ourselves. This is a very difficult question. During the past half century those of us who have attempted to do research have had many difficulties to contend with. Most of us had little or no training, few facilities and very little time or money. However, we did have the big advantage that our laboratory-based research utilised similar techniques and tackled similar questions to those we were dealing with in the operating room. With the increasing sophistication of research it is becoming progressively more difficult to investigate basic problems as we did in the past. Many mechanisms have to be tackled at molecular level using highly sophisticated techniques which can often only be learned in years rather than months. Furthermore, the whole laboratory environment has a very different ethos from that existing in the operating theatre and intensive care unit. Even if an anaesthetist completes a training in basic research it is difficult to maintain skills in both the research and clinical disciplines. This is a problem which is intimately connected with the pattern of training, for with the increasing duration of such programmes the productive life of the worker is severely limited.

I have, perhaps, been guilty of attributing too much to the influence of Harold Randall Griffith on the development of our specialty: this is the common fault of everyone who is asked to give such a prestigious lecture and who, inevitably, becomes steeped in his subject. However, such an occasion does give us a chance to stand back, away from the hurly-burly of our busy lives, and to recognize just how far we have come in the last fifty years. In 1942 half the world was at war, there was very little non-emergency surgery and most of that was very restricted in scope, and there were very few dedicated anaesthetists even in the developed countries of the world. Now, our technical skills, our knowledge of medicine and basic sciences, and the enormous increase in our numbers have spawned a whole new range of operative interventions. We need to grasp this new-found glory and ensure that it spreads to all the countries of the earth. That is what Harold Griffith would have wanted.

References

1 *Maltby JR, Shephard DAE.* Harold Griffith: His Life and Legacy. Can J Anaesth 1992; 39 Supplement (January): 1–145.

2 *Bodman R, Gillies D.* Harold Griffith. The evolution of modern anaesthesia. Toronto and Oxford: Dundern Press Ltd, 1992.

3 *Griffith HR.* Some practical observations on general anaesthesia. Paper entered for McGill Medical Society Senior Prize Competition 1922. Awarded second prize. Published in The Boundless Realm of Anaesthesiology: A Collection of the Works of Harold Randall Griffith. Montreal: E.R. Squibb and Sons Ltd, 1963.

4 *Griffith HR.* Intratracheal ethylene-oxygen anaesthesia. Can Med Assoc J 1929; 21: 294–6.

5 *Griffith HR.* Intratracheal gas-oxygen anesthesia. Anesth Analg 1929; 8: 387–9.

6 *Griffith HR.* Further experiences with endotracheal gas-oxygen anesthesia. Anesth Analg 1932; 11: 206–9.

7 *Lucas GHW, Henderson VE.* New anaesthetic gas: cyclopropane – a preliminary report. Can Med Assoc J 1929; 21: 173–5.

8 *Griffith HR.* Cyclopropane anaesthesia: a clinical record of 350 administrations. Can Med Assoc J 1934; 31: 157–60.

9 *Edwards G, Morton HJV, Pask EA, Wylie WD.* Deaths associated with anaesthesia. A report on 1000 cases. Anaesthesia 1956; 11: 194–220.

10 *Griffith HR.* Anaesthesia from the patient's point of view. Can Med Assoc J 1937; 37: 361–3.

11 *Martyr PD'A.* De Orbe Novo (1516). Translated by MacNutt, F.A. vol 1, p75. New York: G.P. Putnam's Sons, 1912.

12 *De La Condamine M.* Relation abrégée d'un Voyage fait dans l'intérieur de l'Amérique méridionale, depuis la Côte de la Mer du Sud, jusques aux Côtes du Brésil et de la Guiane, en descendant la rivière des Amazones. Histoire de l'académie Royale des Sciences 1745; 391–492.

13 *Brocklesby R.* A letter to the President of the Royal Society concerning the Indian poison, sent over from M. de la Condamine. Philos Trans R Soc Lond 1747; 44(ii): 407–12.

14 *Herissant M.* Experiments made on a great number of living animals, with the poison of Lamas, and of Ticunas.

Translated from the French by Tho. Stack. Philos Trans R Soc Lond 1751–2; 47: 75–92.

15 *Bancroft E.* An essay on the natural history of Guiana and South America. London: T. Becket & P.A. De Hont, 1769.

16 *Fontana F.* An essay on the American poison called Ticunas. Philos Trans R Soc Lond 1780; 70(i): 163–220. (English translation: Appendix p 9–45).

17 *Brodie BC.* Experiments and observations on the different modes in which death is produced by certain vegetable poisons. Philos Trans R Lond 1811; 101: 178–208.

18 *Brodie BC.* Further experiments and observations on the action of poisons on the animal system. Philos Trans R Soc Lond 1812; 102: 205–27.

19 *Waterton C.* Wanderings in South America. London: MacMillan and Company, 1879.

20 *Bernard C.* On the effects of toxic and medicinal substances. 1857 (Translated from the French) *In:* Faulconer A. and Keys TE. Foundations of Anesthesiology Vol 2, p 1142–50, Springfield: Charles C. Thomas, 1965.

21 *Travers B.* A further inquiry regarding constitutional irritation. p 308. London: Longman, Rees, Orme, Brown and Green, 1835.

22 *Sayre LA, Burrall FA.* Two cases of traumatic tetanus. N Y J Med 1858; 4: 250–3.

23 *Wells TS.* Three cases of tetanus in which "woorara" was used. Proc R Med Chir Soc (Lond) 1859: 3: 142–57.

24 *Läwen A.* Ueber die verbindung der localanästhesie mit der narcose, über hohe extraduralanästhesie und epidurale injectionen anästhesierender lösungen bei tabischen magenkrisen. Beitr klin Chir 1912; 80: 168–89.

25 *Wilkinson DJ.* Dr. F.P. de Caux – the first user of curare for anaesthesia in England. Anaesthesia 1991; 46: 49–51.

26 *West R.* Curare in man. Proc R Soc Med 1932; 25: 1107–16.

27 *Cole LB.* Tetanus treated with curare. Lancet 1934; 2: 475–7.

28 *West R.* The pharmacology and therapeutics of curare and its constituents. Proc R Soc Med 1935; 28: 565–78.

29 *West R.* Intravenous curarine in the treatment of tetanus. Lancet 1936; 1: 12–6.

30 *West R.* The action of curare on respiration. Lancet 1938; 1: 432–3.

31 *King H.* Curare alkaloids. Part 1. Tubocurarine. J Chem Soc 1935; 5: 1381–9.

32 *Kellaway CH.* Curare in anaesthesia. Lancet 1945; 2: 186.

33 *Gray TC, Halton J.* A milestone in anaesthesia? (d-tubocurarine chloride). Proc R Soc Med 1946; 39: 400–8.

34 *Gill Mrs RC.* Mrs. Robinson Crusoe in Equador. Nat Geog Mag 1934; 65: 133–72.

35 *Humble RM.* The Gill-Merrill expedition. Penultimate chapter in the curare story. Anesthesiology 1982; 57: 519–26.

36 *Burman MS.* Curare therapy for the release of muscle spasm and rigidity in spastic paralysis and dystonia musculorum deformans. J Bone Joint Surg 1938; 20: 754–6.

37 *Burman MS.* Therapeutic use of curare and erythroidine hydrochloride for spastic and dystonic states. Arch Neurol Psychiat 1939; 41: 307–27.

38 *Betcher AM.* The civilising of curare: a history of its development and introduction into anesthesiology. Anesth Analg 1977; 56: 305–19.

39 *Bennett AE.* Preventing traumatic complications in convulsive shock therapy by curare. JAMA 1940; 114: 322–4.

40 *Bennett BT, Fitzpatrick CP.* Fractures of the spine complicating metrazol therapy. JAMA 1939; 112: 2240–4.

41 *Bennett AE.* The history of the introduction of curare into medicine. Anesth Analg 1968; 47: 484–92.

42 *Bennett AE.* How "Indian arrow poison" became a useful drug. Anesthesiology 1967; 28: 446–52.

43 *Cullen SC.* The use of curare for the improvement of abdominal muscle relaxation during inhalation anesthesia. Report on one hundred and thirty one cases. Surgery 1943; 14: 261–6.

44 *Papper EM.* The friend of the young anaesthetist. Can J Anaesth 1992; 39 (Supplement, January): 9–10.

45 *Gillies D, Wynands JE.* Editorial: Harold Randall Griffith. Br J Anaesth 1986; 58: 943–5.

46 *Griffith HR, Johnson GE.* The use of curare in general anesthesia. Anesthesiology 1942; 3: 418–20.

47 *Cullen SC.* Clinical and laboratory observations on the use of curare during inhalation anesthesia. Anesthesiology 1944; 5: 166–73.

48 *Gross EG, Cullen SC.* The effect of anesthetic agents on muscular contraction. J Pharmacol Exp Ther 1943; 78: 358–65.

49 *Barnes H.* Use of curare for direct oral intubation. Lancet 1943; 1: 478.

50 *Barnes M.* Use of curare for direct oral intubation. Lancet 1943; 1: 600.

51 *Beinart J.* The history of the Nuffield Department of Anaesthetics 1937–87. Oxford: University Press, 1987, 52.

52 *Griffith HR.* Curare as an aid to the anaesthetist. Lancet 1945; 2: 74–5.

53 *Mallinson FB.* Curare in anaesthesia. Lancet 1945; 2: 75–6.

54 *Forrester AC.* Curare in anaesthesia: report on 100 cases. Glasg Med J 1946; 27: 211–9.

55 *Macintosh RR.* Curare in anaesthesia. Lancet 1945; 2: 124.

56 *Prescott F, Organe G, Rowbotham S.* Tubocurarine as an adjunct to anaesthesia. Report on 180 cases. Lancet 1946; 2: 80–4.

57 *Beecher HK, Todd DP.* A study of the deaths associated with anesthesia and surgery. Ann Surg 1954; 140: 2–34.

58 *Bunker JP, Bendixen HH, Sykes MK, Todd DP, Surtees AD.* A comparison of ether anesthesia with thiopental-nitrous oxide-succinylcholine for upper abdominal surgery. Anesthesiology 1959; 20: 745–52.