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PROCEEDINGS OF THE HISTORY OF ANAESTHESIA SOCIETY

Volume 8a and b

PAPERS PRESENTED AT THE HUDDERSFIELD MEETING 8th-9th June 1990

HISTORY OF ANAESTHESIA SOCIETY

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EARLY BRITISH EXPERIENCES WITH KETAMINE
or
THE DISASTROUS INTRODUCTION OF KETAMINE IN BRITAIN

Professor J.W.Dundee

The alternative title of this paper recalls the first major clinical trial of ketamine in Britain[1] where an unacceptably, and more important an unexpectedly, high incidence of emergence sequelae were reported. These events were recalled at a symposium, recognising 25 years of clinical use of ketamine, held in Ann Arbor, Michigan in June 1989,[2] the findings of which appear in book form.[3] Ann Arbor was an appropriate setting for the meeting as Parke Davis & Co were based in this town and the University of Michigan Department of Pharmacology, and Dr Ed.Domino in particular, played a major part in its evaluation.[4]

Ketamine had been under clinical trial in America for several years before it became generally available. At a meeting of the American Society of Anesthesiologists in San Francisco about 1964 an 'in-house' television programme extolled its virtues. Several prominent American speakers urged viewers to put pressure on the FDA - the US drug regulatory body - through their elected congressmen or delegates. 'Why should your children be deprived of this valuable agent? ..... Do the public know what their children are missing?'

The British Committee on Safety of Medicines did not exist at that time and ketamine became available in Britain late in 1969, without any organised large scale trials of it in this country. The Belfast department had much experience in this field having been involved in the initial clinical studies of methohexitone and propanidid as well as a number of compounds that never reached clinical use. Our initial studies were usually carried out in unpremedicated patients undergoing minor gynaecological operations followed by use in a wider field and the involvement of several anaesthetists. Rather than being asked by Parke Davis to carry out a clinical study, several American colleagues urged us to contact the company, who provided us with ample supplies of the drug and a detailed investigations manual. This latter described it as a 'rapidly acting non-barbiturate general anesthetic'. A current American paper had described it as producing 'dissociative anesthesia' characterised by complete analgesia with only superficial sleep.

The literature supplement to clinical trialists in Britain included the following indications for its use:

- 'Sole anesthetic agent for diagnostic and surgical procedures. Although best suited for short procedures it can be used with additional doses, in procedures requiring anesthetic for periods of six hours or longer.'

- 'For the induction of anesthesia prior to the administration of other general anesthetic agents.'

- 'To supplement low potency agents such as nitrous oxide.'

Minor diagnostic procedures included cervical dilatation and uterine curettage, and these formed the bulk of our early cases.

While we were aware of the possibility of emergence delirium, we had not expected either the frequency or severity which we encountered. Patients were usually not aware of this delirium, but it upset the attendants; incoming patients heard the screams and the ward, to which the patients were returned directly, became a bedlam. It was not normal practice to use the recovery ward after short procedures at that time and if the patients receiving ketamine had been admitted then, it would have caused a major crisis. We persisted for up to 50 administrations[5] before involving others in the trial, and within 3 months we had data on 450 inductions.[1] Our ten author report embraced paediatrics, obstetrics and general surgery as well as major and minor gynaecology.

While the incidence of emergence sequelae was not as high after major as compared with minor procedures, it was still troublesome - particularly in unpremedicated or lightly medicated patients, particularly women. In Britain we regard a rapidly acting drug as thiopentone-like, i.e. adequate doses producing loss of consciousness in one arm-brain circulation time. Ketamine clearly did not fall into this category and those who tried to use it as they used intermittent thiopentone got into trouble. The 20-30 second delay in onset prevented it being titrated against the patients' needs. This caused problems with several other investigators who, like ourselves, took the manufacturer's literature at its face value.

Table. Factors leading to the initial ketamine fiasco in Great Britain

1. Pure studies - no premedication
   - avoidance of supplementary drugs
2. Choice of trial operation - dilatation and curettage
3. Brevity of short operations : 5-6 minutes
4. Rapid turnover: one per 10 minutes
5. Single anaesthetist for successive cases
6. Return of minor cases direct to ward

In retrospect, there appear to have been six reasons for our early disastrous results (Table). Our choice of operation, seemingly unfortunate at the time, was in retrospect a fortunate one, as others less well used to clinical trials would eventually have encountered the same problems. Furthermore, it led us to look at the importance of the sex of the patient, the premedication and the duration of operation as factors influencing the efficacy of ketamine[6] and to attempt to minimise sequelae while retaining its clearly beneficial effects. The short British operation contrasts with the 30-40 minutes taken for a similar procedure in most American teaching hospitals.

Ketamine has never fully 'recovered' from our initial adverse report. With a greater awareness by the drug company of how British anaesthesia and surgery differed from that practised in the United States this could probably have been avoided to some extent. Many British anaesthetists regarded it as a 'non-hypotensive thiopentone' and gave up its use before they had an opportunity of appreciating its unique advantages in selected patients. This incident is probably without parallel in the field of clinical trials in any medical discipline.

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THIOPENTONE, CHICAGO TO PEARL HARBOR

Dr F.E.Bennetts

German barbiturate origins

Barbituric acid was synthesised in Germany as long ago as 1863 and its structure was determined ten years later, but there was a surprising thirty year gap to 1903, before Fischer and von Mering applied for a German patent for the first pharmacologically active form - barbitone[1]. The discovery of this rather slowly acting substance proved the trigger for further research and it was soon found that the salts of barbiturates were relatively soluble and more rapidly acting.

Although barbitone and many similar compounds are oxy-barbiturates, research chemists quickly found that the sulphur analogues were convenient to prepare. Later in 1903, Fischer and Dilthey produced the first of these thiobarbiturates - not surprisingly, a substance that might have been called 'thiobarbitone'. Fischer and von Mering gave 1g of this by mouth to a dog. The dog died after 8 hours and the workers - on this basis - considered that the more lipid soluble thiobarbiturates must be highly toxic. It appears that for this reason they were virtually forgotten for a further twenty-five years[2].

By the start of the First World War in 1914, a number of useful barbiturates - including phenobarbitone - had been synthesised and marketed by German firms. They enjoyed a lucrative world monopoly.

Development in the USA

The United States entered the war in April 1917, and in the following September the Trading with the Enemy Act was passed by Congress. American manufacturers were then able to obtain Federal Trade Commission Licenses and produce their own versions of the German products, whether the original 17 year patents had expired or not. Qualifying companies could make certain German products under new names. Only a 5% royalty on sales had to be paid to the Alien Property Custodian, and they were away !

Barbitone, phenobarbitone and several similar products were quite soon produced in the States. A rapid fall in the price of barbiturates took place there and in the rest of the world and the German monopoly was shattered. There can be no doubt that these events were of great significance in the subsequent development of thiopentone.

Meanwhile, all was not lost in post-war Europe where the first intravenous barbiturate anaesthetic to be internationally used - Somnifen(e), a combination of salts of barbituric acid - gained popularity between 1924 and 1928. The French workers, Fredet and Perlis are mainly credited with its brief success[3]. In Germany, Dial (diallyl barbituric acid) and Pernocton (butylbetabromallyl barbituric acid) were introduced, as was sodium amytal from the Eli Lilly Company in 1929 in the USA. In that country, a year later, the use of intravenous pentobarbitone or Nembutal for anaesthesia was described by both Lundy at the Mayo Clinic and Waters and his colleagues at Madison, Wisconsin[4].

German workers had not been idle during the intense American activity of the 1920s, and with the first truly short acting intravenous anaesthetic agent, Evipan,(hexobarbitone or Evipal), introduced in 1932 by Weese and Scharpff, the Bayer Company might have had a long-term winner[5]. For two years it stood alone because of its rapid onset and short, predictable action. However, before Evipan had a chance to make real international headway, two thiobarbiturates, which animal studies had shown to be improvements in terms of brevity of action, were offered for trial by Abbott to workers at both the Mayo Clinic and in Madison, Wisconsin[6].

The new thiobarbiturates - one of which we now know as thiopentone, of course - resulted from a technique which is still standard practice in the pharmaceutical industry. Substances resulting from minor changes in the molecular structure of successful new drugs are tried out in an attempt to get even better versions.

Ernest H.Volwiler at Abbott, North Chicago, and his colleague, Donalee Tabern, who had been jointly responsible for the introduction of Nembutal (pentobarbitone) in 1929, made the fundamental decision to proceed with the preparation of the sulphur analogue, knowing that the Germans had unsuccessfully followed a similar path in 1903. The workers prepared what might be called 'thionembutal', and a number of similar substances.

Thiopentone

After a brief period of animal work, Waters and Lundy separately tried out the new agents in patients in 1934, and it was soon clear that 'thionembutal' was the preferred agent of each working group. Rapid, smooth induction occurred without the muscular activity so characteristic of other barbiturates. Unconsciousness lasted a few minutes rather than the hour or more found with its oxy-analogue - Nembutal. As with most new drugs, odd findings emerged during the early stages. Lundy,for example, noted an apparent resistance to the effects of what soon became known as thiopental, in people with red hair, those born in the Southern United States and of Jewish extraction. In a note to Tabern added to a technical report, he said 'I don't know why this should be, but I'd hate to have to administer the stuff to a red-headed rabbi born in New Orleans.'

Although Lundy is widely considered to have been the first to have administered thiopentone to a hospital patient, that honour undoubtedly belongs to Ralph Waters whose original case paper is dated, 8th March 1934. The patient lunched at 1pm and was anaesthetised at 3![7] The date is confirmed by the Madison workers' first paper - published in the American Journal of Surgery (!) in March 1936 (2 years later) which said that the drug - under the experimental number 8064 - had been used in 45 clinical cases since March 1934. Not exactly a hectic rate of research[8].

The first use of thiopentone in a Mayo Clinic patient occurred in June, three months after the one at Madison. It is quite possible that this particular administration was not in fact by Lundy's own hand. In the only reference I know to that date, Lundy says of pentothal sodium in his book 'Clinical Anesthesia'published in 1942, 'We began its use on June 18 1934'[9]. Corroborating evidence of a kind can be found. Lundy and his close but junior colleague Ralph M.Tovell read a joint paper on 'Some of the

newer local and general anesthetic agents' to the 13th Annual Meeting of the Pacific Northwest Medical Association held at Salt Lake City between Thursday and Saturday 21st-23rd June, only three or four days after their first administration. Bearing in mind that Salt Lake City is well over a thousand railway miles, and therefore two full days travel from Rochester Minnesota, it is not surprising that at this meeting the Mayo Clinic workers reported that '....as yet opportunity afforded us for clinical trial of this drug has been limited.'![10]

Perhaps supplies also were limited, at any rate Lundy and his co-workers only managed to administer thiopentone to 73 patients during the remaining six and a half months of 1934 - between two and three cases each week. However, the following year yielded far more extensive experience, and by August 1935 seven hundred patients had received the agent, resulting in fairly enthusiastic reports by the Mayo Clinic workers[11].

Early work in Britain

The London anaesthetist Ronald Jarman was a pioneer in the use of intravenous anaesthetics. His joint paper on Evipan in the Lancet in 1933 was one of the first in the world on that agent[12]. In a later edition of the same journal (also with the surgeon, Lawrence Abel), he was the first British worker to describe the use of Pentothal. In February 1936 he wrote that he had 'met' the agent in the United States sixteen months previously, i.e. in October 1934. At that time Waters would have used it only two or three times and Lundy ten or twelve[13].

Comparing the results from a series of over 1000 cases anaesthetised with Pentothal, (an experience only slightly less than that of the Mayo Clinic workers at the time), with those from Evipan, Jarman found that induction with the more potent Pentothal was a little smoother, twitching or jactitation (sometimes seen with Evipan) scarcely ever occurred, the fall of blood pressure was less noticeable and recovery was quicker. However Pentothal was more of a respiratory depressant and Jarman noted that a few patients had complained of a sulphurous taste or smell. He thought that Pentothal was 'a worthy addition to our list of safe and satisfactory intravenous anaesthetics.' At any rate, confidence in the future of Pentothal was sufficient for its launch on the American market in 1936 and for the construction of a European manufacturing plant in England during the following year.

In spite of the ardour of enthusiasts it seems that much suspicion of intravenous anaesthesia remained among anaesthetists during the late 1930s. One suspects that this was because they found it difficult to obtain both adequate anaesthesia and satisfactory spontaneous respiration when these agents - which lack analgesic properties - were given as the sole anaesthetic, which was the practice of the time. The concept of their use primarily for induction in longer cases (though advocated by both Lundy and Jarman) was yet to be generally accepted. By the beginning of the Second World War in 1939, intravenous barbiturates were being given in fewer than 10% of the 140,000 or so anaesthetics administered annually in the UK at that time, and thiopentone was being used in less than 50% of those cases. It seems likely that Evipan (hexobarbitone) was then at least equally regarded and, if anything, was slightly more in vogue in the UK. Not

surprisingly, the popularity of the home-product, thiopentone, proved greater in the Mayo Clinic and in the United States generally during the pre-war years.

Patients receiving Thiopentone at the Mayo Clinic - 1934-41

1934	35	36	37	38	39	40	41	34-41
73	1333	2745	3810	4157	5874	6629	7310	31 931 cases

after Adams R. Intravenous Anesthesia. 1944. p513

For those concerned with military anaesthesia, improved intravenous anaesthetics held much promise, and some experience was gained during the Spanish Civil War. The advantages of simplicity of administration, portability, non-flammability and apparent lack of need for elaborate ancillary equipment suggested that anyone who could depress the plunger of a syringe in response to movement in a patient could give an anaesthetic.

Pearl Harbor

This, of course, was the background to the folk-tales surrounding the use of thiopentone at Pearl Harbor. I was exhorted during training in the '40s and '50s, to be cautious in dosage in shocked patients with sayings such as... 'more US servicemen were killed at Pearl Harbor by Pentothal than by the Japanese.....', and similar stories. Having been intrigued by these yarns for more than 30 years, I tried to find what truth lay behind them.

Firstly, the attack itself. On Sunday, 7th December 1941, prior to declaration of war, a succession of Japanese bombing raids was directed at the Hawaian island of Oahu; not solely at the US Pacific Naval Base at Pearl Harbor, as is often thought, but also on many other military installations there. Heavy casualties were sustained by naval personnel and also by the Army (the US Air Force at that time was part of the Army), and by civilians. Eighteen ships - including 8 battleships - were sunk and 188 planes destroyed. These events, of course, led to the entry of the United States into World War 2 and so to the eventual downfall of the Axis powers. The declaration of war meant an embargo for the duration of hostilities on casualty figures and on firm information about what really happened at and around Pearl Harbor.

The casualty figures set out in the accompanying table, speak for themselves. In the battleship Arizona alone, which was hit and capsized rapidly, 1,177 sailors and marines were trapped and killed. Between 1,000 and 2,000 casualties presented to the 13 or 14 military and civilian hospitals on Oahu during and immediately after the onslaught. A substantial proportion of the injured would have required anaesthesia. I must confess that I have not been able to find out how many of the injured were anaesthetised solely with thiopentone and therefore cannot quantify accurately the precise contribution this agent made to the surgical fatality rate.

Pearl Harbor (Oahu) Attack - 7 December 1941

	Killed, missing died of wounds		Wounded
US Navy	2008	(1227 died on USS Arizona & Utah)	710
Marines	109		69
Army (incl. Air Force)	218		364
Civilians	68		35
	2403		1178

We can learn something however, from the contemporary accounts.

First-hand accounts

The situation at an Army Hospital, North Sector General Hospital, Schofield Barracks, where about 160 wounded were admitted within two or three hours of the start of the attack, was described long after the war by one of the surgeons there at the time....'Anesthesia was a problem. Some of the debridements were done under local anesthesia. But general anesthesia was needed in many cases and the only nurse anesthetist was busy in the operating room. Captain Bob Hoagland of the Medical Service came over to help. We had just been issued with a new drug called pentothal which could be given I.V. for anesthesia. We got out a box, read the directions and Bob used it on many of my cases over the next 48 hours with excellent results.'

There seems no reason for this 1988 account by a Texas Professor of Surgery to be biased or lacking in critical data. No mention is made of any excess mortality or morbidity from Dr Hoagland's activities.

A truly contemporary account, 'Observations on the treatment of war wounds', published in the local Hawaii Medical Journal, was provided only a few weeks after the attack by Dr Strode, a civilian surgeon attached to the large Tripler Army hospital during the emergency. He fails to mention barbiturates but reports that 'Ether anesthesia, by the drop method, lends itself well to this type of surgery. It has the advantage of safety and, in addition, it may, when necessity demands, be given by those with little training.' Note the mention of 'safety'.

The Naval Hospital, being at the centre of the attack, received several hundred of the injured. (At midnight they had 960 patients in a hospital built to contain 506; the following day they received a further 100 who had been temporarily cared for elsewhere.) In his report on the treatment of acute surgical cases among the wounded, published in 1943 - a full year after the previous account - the Officer Commanding, Pearl Harbor Naval Hospital did not mention any problem arising, or mortality rate, from the use of thiopentone. He commented.... 'Most of our anesthesia was by drop ether. This lends itself well to this type of surgery and in addition, when necessity demands, it may be given by those with little training.' This

wording, from a different service and published in another journal, is surprisingly similar to that of the earlier paper. This author could have read the previous account, but why should he plagiarise ? Could this be wartime censorship in action, suppressing damaging information ?

The main 'scare-story'

Censorship seems unlikely in view of the rapid appearance of what is undoubtedly the main source of the 'problems with pentothal'legend - the paper 'A critique of intravenous anesthesia in war surgery' also published in 1943 by Halford, who was another civilian surgeon assigned to the Tripler Army hospital in the town of Honolulu on the day in question. Summarising the experience gained in dealing with the seriously wounded from the Japanese attack, he and his colleagues again testified that open drop ether was, in their opinion, the best anaesthetic for war surgery. Intravenous agents were,dangerous for shocked patients suffering from heavy blood loss.

Of the Pearl Harbor casualties, he said

> 'A number of patients were given evipal by competent anesthetists only to have respiratory failures, some of which ended in death. After several such fatalities, pentothal sodium was used, and again respiratory failures occurred, and, as in the case of evipal, death ensued in enough cases to cause us to abandon it as too dangerous.
>
> In several cases when as small an amount as 0.5Gm.of pentothal sodium had been administered, there suddenly appeared a "cyanosis decolletage" which was the inevitable and irremediable predecessor of death.'
>
> There was a definite lack of oxygen and equipment for administering continuous oxygen therapy.'

From all accounts, it is clear that facilities for fluid and blood replacement for overwhelming numbers of severely injured patients were understandably inadequate. Hurriedly enrolled and unskilled anaesthetists were pressed into giving intravenous anaesthesics, sometimes in relative overdosage, and often without adequate means of administering oxygen or providing ventilatory support. They had to learn - as we all do, even today - that sick and seriously injured patients need smaller dosage and careful support.

It cannot be doubted that several additional deaths did occur in the Tripler Army Hospital - and perhaps elsewhere, though I have found no record of this - as the direct result of barbiturate overdosage; thiopentone was not the only agent used. But in the context of more than 1,000 deaths directly due to enemy action on that one day, and a rather greater number of wounded - many of whom must have undergone successful anaesthesia, comments of workers on the spot strongly suggest that the Pearl Harbor barbiturate mortality horror story has - like so many war-time rumours - been grossly exaggerated.

Wartime censorship, which aimed at preventing publication of suggestions of medical mishandling at Pearl Harbor that might have been of comfort to the enemy - and discomfort to the allied troops, ended in 1945. Ten years later, Beecher - a respected authority - in his chapter on 'Anesthesia for men wounded in battle' which formed part of the official account 'Surgery in World War II', indicated that during the early stages of the war, inexperienced anaesthetists and unwise choices of agent were responsible for an excess mortality rate, of the order of 1 in 450 administrations, from barbiturate anaesthesia. This barbiturate mortality rate from the early North African campaigns ...'paralleled', Beecher said 'the experience reported from Pearl Harbor.' If this is so, the excess mortality at Pearl Harbor from this cause would have been of the order of 4 or 5 cases - unfortunate, but hardly a major disaster in itself.

Calming troubled waters

Although British service and civilian anaesthetists had learned these lessons the hard way, disquiet spread in the United States during 1942, fanned, I suspect, by tales of difficulties in other theatres of war. In January 1943 - more than a year after Pearl Harbor - Anesthesiology published not only Halford's paper but also a description by Charles Adams of the Mayo Clinic of 'how to do it properly'. He described how he injected 1-2ml doses of 2.5% thiopentone - (5%, and sometimes even 10% was customary at the time) - to induce a patient who was in shock due to severe gun-shot injuries. Oxygen and nitrous oxide were given via an endotracheal tube, plus further small doses of thiopentone totalling 400mg over 1½ hours. When another operation was required three weeks later, 400mg thiopentone were needed during the first 10 minutes alone.

The practical lessons were clear, and were hammered home by an editorial in the same edition. Henry S.Ruth was Editor at the time. The Associate Editors were Ralph Tovell (Lundy's former collaborator at the Mayo Clinic but seconded to the Army at the time,) and E.A.Rovenstine. I suspect that Tovell was responsible for the editorial which did much to rehabilitate thiopentone in the USA. It spelled out - small doses at long intervals, oxygen availability etc - how the agent should be used in shocked and ill patients and helped to lay the foundations which resulted in thiopentone's current remarkable 50 year record as the world's most popular induction agent.

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HAROLD KING - A NOTABLE CONTRIBUTOR TO ANAESTHESIA

Professor T.Cecil Gray

There are still important pioneers in the story of anaesthesia whose contributions are not as widely appreciated as they deserve. They are more likely to be scientists than clinicians. Perhaps their name is vaguely familiar but, generally, that is all. One such was Harold King. His contribution to our specialty was considerable.

Biographical details

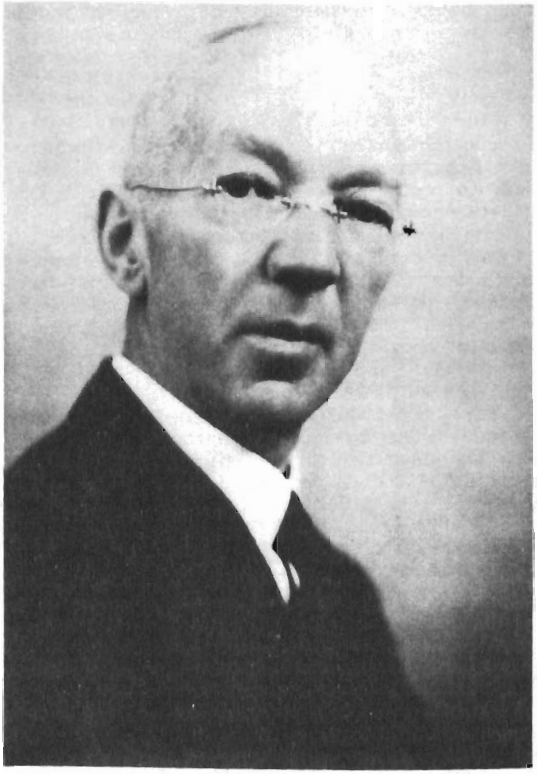
Although of Lancashire stock, King was born in Wales and graduated in chemistry with first class honours from University College, Bangor. He was appointed research analytical chemist in the London Gas, Light & Coke Co. (The name of that company will remind those of the writer's generation of a famous anaesthetic partnership, practising in London at 9a Upper Brook Street, telephone number Mayfair 0808, known as the 'Gas, Fight and Choke Co'. Among its directors was one who in the future was to become the first Professor of Anaesthesia in this country and another the second Dean of the Faculty of Anaesthetists in the Royal College of Surgeons.)

After a short time, King moved to the Wellcome Physiological Research Laboratory, where he made his first contact with biological research and with Henry Dale.

He spent the four years of World War I in the Wellcome Chemical Works at Dartford, synthesising drugs such as aspirin which could no longer be imported from Germany. After the armistice, King was taken on to the staff of the Medical Research Committee, a statutory body, which was to become the Medical Research Institute and eventually the Medical Research Council. There he was a member of a team led by Dale and he remained working in the Council's laboratories until he took early retirement in 1950. He died six years later, aged 69 years.

Early anaesthetic controversy

King's work covered a wide field. In the early twenties, inspired by Ehrlich's discovery of Salvarsan, he was synthesising prospective chemotherapeutic agents and doing constructive work on the arsenicals and antimalarial drugs which later paved the way for great advances in that field. But his work, even so early in his career, impinged on anaesthesia. A controversy was raging over the anaesthetic effect of ether. Was it due to the ether or to the impurities in it?[1] King, with Dale and a young anaesthetist on the staff of St Bartholomew's Hospital, C.F.Hadfield, in a classical paper concluded that their 'observations give no support to the statements that pure ether is devoid of anaesthetic action, that the activity in this direction of ordinary ether is due to impurities and that the removal of impurities improved the potency of the ether'.[2] Hewer, strangely enough, did not agree and



Harold King.

Harold King

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in the same issue of the Lancet suggested clinical evidence for his disagreement.*

From the start, King had an interest in the chemistry of alkaloids. He revealed the complicated stereochemistry of hyoscine[3] and in 1922 isolated muscarine.[4] It was in this field that he made his major contributions to our specialty.

King and curare

In the Medical Research Institute, Henry Dale had gathered around him a brilliant group of scientists. Vogt, Brown and Feldburg are familiar names. They were to become stars in the physiological firmament involved in fundamental work on neuromuscular transmission. So it was not surprising that King should turn his attention to curare. It was a useful tool in such investigations and a substance with great pharmacological potential, if only the component responsible for its paralysant activity could be identified, purified and administered with accurate posology. King's work on the alkaloids of curare has been described as 'a classical exercise in organic chemistry which led to results of far reaching importance in pharmacology and therapeutics'.[5]

In the thirteen years 1935-1948, King published no less than ten papers on the curare alkaloids. The two most important appeared in 1935. In the first of these, he described the isolation from tube curare of a crystalline alkaloid.[6] The German chemist Boehm had classified curares into pot, calabash and tube according to the container used for the curare by the Indians around the Amazon and Orinoco rivers[7] and, in 1897, he had separated an amorphous alkaloid from tube curare which he named 'tubocurarine'. Likewise, King named the dextro-rotatory crystalline alkaloid which he had isolated from tube curare, 'd-tubocurarine'. He established its structural molecular formula as a bis-benzyl isoquinoline derivative, so containing two quaternary ammonium groups.[9] This work of 55 years ago has only recently been challenged, to the extent that one of the nitrogens is probably tertiary.

It is interesting to find that King investigated the alkaloids present in samples of the chondodendron family of plants. However, none of his material yielded tubocurarine. It was left to Wintersteiner and Dutcher[10] eight years later, to be the first to extract crystalline tubocurarine from a known plant source. The writer is not aware of any plant source for tubocurarine, other than the chondodendron tomentosum: so, if that is correct, King must have isolated his crystalline alkaloid from the chondodendron, although he did not know it.

Bovet, the discoverer of the first synthetic non-depolarising relaxant, gallamine, acknowledged his indebtedness to King.[11]

* The story of Ethanesal and CPE was widely reviewed by Stetson in Vol.6a of the Proceedings of the History of Anaesthesia Society. Ed.

New muscle relaxants

After the second world war, working in the Research Institute was an Oxford and University College Hospital graduate pharmacologist, William Paton, later to become an Honorary Fellow of the Faculty of Anaesthetists of the Royal College of Surgeons. He has related to the writer how, in 1945-46, he was investigating various compounds for histamine release. One of these, a straight chain compound, had eight methyl groups separated by two quaternary ammonium radicals. When he injected this into a cat, the animal stopped breathing. He was completely astonished by this response. On investigation, he found that the apnoea was due to a curare-like action. He realised the importance of this observation but, as the octamethonium had effects which clinically would be undesirable, he consulted King. King suggested that a series of these straight chain compounds - C2 to C12 - should be synthesised in the hope of finding one with only a paralysant effect and asked a young Greek research pharmacological chemist, Eleanor Zaimis, who was working in the Institute, to do the synthesis. This she did and the compound with the two quaternary groups separated by ten methonium groups - decamethonium - was found to have powerful neuromuscular blocking activity and was otherwise pharmacologically inert. It was introduced into clinical practice by Organe.[12] The compound with five carbon atoms was found to reverse the decamethonium block. However, hypotension due to sympathetic block which followed its injection made it an unsuitable antagonist.

Paton and Zaimis published their discovery in Nature on March 16th, 1946[13]: the letter immediately preceding their's was one from Barlow and Ing[14] from the Department of Pharmacology at Oxford, also reporting the paralysing action of the straight chain methonium compounds and stating that the deca- compound was the most active and apparently had no other effects. Ing, who thought of himself as a 'chemical pharmacologist', had for long been interested in quaternary ammonium compounds other than the methonium group and had written a review of their neuromuscular blocking activity ten years previously.[15] Whereas Paton had stumbled upon the relaxant action of these compounds, Ing conceded that he had arrived at it through knowledge of King's work on the formula of tubocarine. He considered that the straight chain methonium compounds were likely to be less rigid molecules and more adaptable to the varying inter-receptor distances at the endplate than such weighty molecules as tubocurarine and that this accounted for their greater potency. He acknowledged that the first demonstration of the curariform activity of 'onium' compounds was by Crum Brown and Fraser in Edinburgh in 1868.[16]

Other pharmacological interests

In 1951, Scurr described the use of another of this series of compounds, pentamethonium (C5) for the production of controlled hypotension during operation.[17] This was the first attempt to lower blood pressure pharmacologically, and the C6 compound, hexamethonium was seen by physicians to open up a whole new era for patients suffering from high blood pressure - a development in which King clearly had a hand.
Despite these major contributions, it has been suggested that King will be best remembered for his work, purely theoretical, in collaboration with Rosenheim between 1932 and 1934, on the revamping of the formulae of

cholesterol and related steroids. This cleared the way for the synthesis of hormones which have transformed therapeutics - the steroids, adrenocorticaal hormones, sex hormones and also for narcotic and relaxant steroids, such as Althesin and pancuronium. There is little doubt that there will be others to follow. It has been claimed that 'this (work) will stand in the history of organic chemistry as one of those few ideas that have revolutionised a whole branch of the subject'.[7]

King was a shy, quiet and retiring man. He was essentially a backroom worker and appeared happiest when at his bench in the laboratory. He was ever ready to listen to those of less strictly scientific disciplines, especially to clinicians, to advise and propose plans for research. Apart from holidays in Ireland, it appears that he only left this country once and that was during the war, when he went to the States as Secretary of the Committee on the Synthesis of Pencillin. His work was recognised by his election as a Fellow of the Royal Society in 1933 and in 1959 he was awarded a CBE.

Ranyard West's contributions

One of the clinicians who contributed to the early curare story and whom King helped and encouraged was Dr Robert George Ranyard West. He was a lecturer in physiology at St Bartholomew's Hospital and later in pharmacology at Oxford. West made many attempts to use curare clinically in patients with spasticity and tetanus, always with frustrating results because of the unpredictability of crude curare and of his inability to control respiration and bronchial secretion. He consulted King and begged from him samples of various curares for clinical trial. He thought some gave relief of the muscular spasm without causing paralysis. He called this a 'lissive' effect. If such an effect were possible, it would certainly be very useful clinically. Among the samples King gave to West was crystalline tubocurarine and he delivered a paper on its effects to the Royal Society of Medicine in March 1935.[18] He described how he gave subcutaneous doses of from 5-50mg to a patient with spastic paraplegia and had carefully observed and recorded its effects. West was, therefore, the first to administer King's d-tubucurarine to a human patient. The lack of expertise in supporting respiration was his difficulty. He decided that tubocurarine did not have as good a 'lissive' effect as crude curare.

It is humbling to appreciate that tubocurarine could have been available to anaesthetists who, certainly since the advent of cyclopropane in the early thirties, had some skill in controlling pulmonary ventilation, yet it took Harold Griffith in 1942 to provide the stimulus[19] for so great an advance.

West's relationship with King is delicately described by West in the Journal of Medical History: 'Reviewing my correspondence with Harold King, I see that 1936 was a very busy year. I chivvying, he patient, if occasionally expostulatory! I had plenty of pharmacology to do on King's many fractions, but no new successes in treating human spasticities to report'. Rather plaintively, he continues: 'I think I overestimated the degree to which those in authority on the Medical Research Council staff shared my enthusiasm'.[20]

Harold King was a distinguished scientist. He contributed 129 papers between 1911 and 1956, many of them seminal and a good proportion having relevance to anaesthesia.

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BRODIE'S BELL-GLASS

Dr D.D.C.Howat

After Sir Astley Cooper's death in 1841, Sir Benjamin Brodie was the most famous surgeon in Britain, with a large and successful practice. Yet, in his autobiography, he acknowledged his regret that he had had to give up his interest in physiological experiment which he had been able to indulge as a younger man.[1] It seems that it was always understood that he would pursue a medical career, although he admitted that he had no great ambition in that direction.[2] He was educated privately at his home near Salisbury. In 1801 he went to London and attended lectures at Abernethy's School of Anatomy and at the Great Windmill Street School. In the same year he joined a so-called 'Academical Society' to which, in 1802, at the age of eighteen, he read what was probably his first paper, entitled 'An Essay on the Principles of Science and the Mode of conducting Scientific Enquiries'. He showed a surprisingly mature appreciation of the relationship of physiology to medicine and stressed the importance of reporting facts and always being ready to modify hypotheses in the light of those facts.

In 1803, Brodie entered St George's Hospital as one of Everard Home's pupils, qualified MRCS in 1805 at the age of twenty-three, worked as Home's assistant and was appointed assistant surgeon to the hospital in 1808, when he was only twenty-six. In spite of an increasing practice as a surgeon and of being much in demand as a lecturer, he began his experiments on animals in 1810, stimulated by the work of the French surgeon, anatomist and physiologist Xavier Bichat, who had published his 'Recherches physiologiques sur la vie et la mort' in 1800.[3]
In 1964, Bryn Thomas gave a fascinating account of the significance of Brodie's experiments, based largely on the manuscript notes of the lectures he gave at the Royal College of Surgeons. In the archives of St George's Hospital Medical School are the manuscript notes he made at the time he performed those experiments.[4] There are four books of notes: the first two, bound in leather, deal with experiments made in 1810 and 1811 and 1812 to 1816 respectively. They consist of nearly one thousand pages in all and include over two hundred and seventy experiments. The third and fourth are loose-leaf leather-bound note-books: one including eight experiments made between 1813 and 1826 and the other details of thirty-six experiments on guinea pigs and rabbits made in 1821 and 1822.[5] Some of them are of particular interest to our specialty.

Brodie's experiments

The first experiment on May 2nd 1810, was not very successful. Brodie injected warm water into the inguinal vein of a rabbit; about a third of the water was lost because of a leaky brass syringe. The animal was pithed, the abdomen was opened and the bladder was found to be very distended, but because some urine had escaped under pressure, the amount could not be measured. He noted that the respiration ceased as soon as the animal had been pithed, but that the circulation continued, the heart rate slowing after twelve minutes and ceasing after twenty minutes. He then divided the ureter and discovered that no urine had been secreted after the respirations had ceased.

The second experiment is of greater interest. Brodie pithed another rabbit and immediately afterwards exposed the trachea and tied a flexible gum tube into it. To this he attached a gum-elastic bottle with a brass pipe and inflated the lungs, removing the bottle to allow it to refill with fresh air while the lungs deflated. One of his assistants then continued this manoevre twelve times a minute. The abdomen was opened and it was noted that while the blood in the vena cava was dark coloured, that in the aorta was pink. A ligature was then tied round the neck above the tracheal opening and the animal was decapitated at the level of the second and third cervical vertebrae. The ligature slipped and Brodie made a note that 'a good deal of blood' was lost - for some reason he crossed out 'a considerable quantity'. Even so, the circulation continued for another twenty minutes. He then injected two ounces (60ml) of tepid water into the vena cava, but no urine was found in the bladder.

In March 1810, Brodie had already been admitted a Fellow of the Royal Society for a communication entitled 'The Dissection of a Foetus which had no Heart',[6] which he himself described as 'of little or rather of no value'. He continued his experiments, which led to two further papers given to the Royal Society in the winter of 1810-1811. The first, 'On the influence of the Brain on the Action of the Heart, and the Generation of Animal Heat',[7] was given as the Croonian Lecture in November 1810. For this, he selected from a great number of experiments eight in which, in rabbits and dogs with the spinal cord divided or after decapitation, he showed that the heart's action ceased only because respiration ceased, but that the circulation would continue if respiration was maintained artificially, when red blood appeared in the lungs, although urine was no longer secreted. He also showed that carbon dioxide was generated in considerable amounts while a decapitated animal was artificially respired.

In a second lecture, on 'The Effects produced by certain Vegetable Poisons',[8] he showed that, if the brain was poisoned by various different substances, the animal cooled if artificial respiration was applied, but recovered, if not allowed to cool too much, when the effect of the poison wore off, and might even recover consciousness. For these two papers, he was awarded the Society's Copley Medal. At twenty-eight he was the youngest man ever to have received it. He employed various vegetable substances, including oil of bitter almonds and 'Wourara', as he called curare; the latter was supplied by a colleague, -
Dr E.N.Bancroft, a physician at St George's Hospital, whose father had travelled in the interior of South America and brought it back with him. He also used other arrow poisons, from Mozambique and - shades of Sherlock Holmes - from the Andaman Islands, besides experimenting with some metallic agents.

The bell-jar - carbon dioxide experiments

On February 27th, 1812, in a third lecture, Brodie described his 'Bell-glass'. (Figure) This was designed to measure the amount of carbon dioxide produced by his animals.[9,10] It consisted of a glass jar B, whose rim stood on a wooden stand A, in a circular groove ¼" (2cm) deep. In its upper part was an opening, admitting a tube attached to a bladder C. A silver tube F had a gum-elastic bag or bottle D attached to it by a stopcock E. The other end of the tube F made a right angle and projected into the bell-glass and made another right-angled turn, tapering to its end. In the side of the vertical part of the tube was an opening G. The whole was made airtight and the groove in which the bell-glass rested was filled with mercury. Before use, the bladder C was emptied by pressure and the gum-elastic bag was distended with atmospheric air. By squeezing the elastic bag D, the air in it was expressed into the bell-glass. The bladder C dilated to prevent air being forced through the mercury under the bell-glass. The bag D filled with air again when the pressure was released.

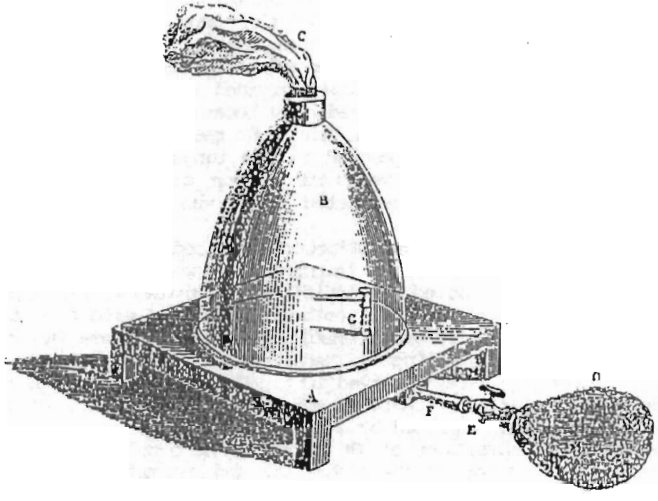

Figure Brodie's bell-glass
(from 'Physiological Researches'1851)

In those animals which had stopped breathing as a result of injury or poisoning of the brain or paralysis due to curare or other agents, the narrow end of the tube F was inserted sometimes into the nostril, sometimes into a tracheostomy, and the lungs were inflated at regular intervals by pressure on the gum-elastic bag. The tube did not make an airtight fit with the nostril or the trachea, so that most of the expired air escaped into the bell-glass, whence the gum-elastic bag filled with air through the opening G. At the end of the experiment, the bag D was completely emptied by pressure and allowed to fill with air from the bell-glass two or three times. The air in the bag was then preserved for examination. The quantity of carbon dioxide was estimated by agitating it in a graduated measure over mercury with an aqueous solution of potash. No allowance was made for carbon dioxide in the atmosphere. On the basis of work reported by Allan and Pepys to the Royal Society in 1808 and 1809,[11,12] the animal's oxygen consumption was assumed to be the same as its CO_2 production, that is, the respiratory quotient was assumed to be 1.0.

In the first three experiments with the bell-glass, three intact rabbits were each kept in it for half an hour. In the first experiment, the respired air was found to contain 1 in 20 or 5% CO_2. The space occupied by the rabbit, the capacity of the bell-glass, the gum-bottle and the tubes and bladder being known, a simple sum showed that the total amount of CO_2 produced in one hour was 50.6 cubic inches (830ml). (Table) Similar figures were obtained for the other two rabbits. The ambient temperature and the animals' rectal temperatures were also recorded, but no fall in temperature occurred as it did in those with destroyed or poisoned brains.

Table. Estimation of carbon dioxide in Brodie's bell-glass

Capacity of bell-glass	502 cu.in.
Capacity of gum-bottle	52 cu.in.
Air in tubes and bladder (emptied)	2 cu.in.
Space occupied by rabbit	50 cu.in.

Respired air contained 1 in 20 CO_2 after half an hour.

$$\therefore \text{ Total amount of } CO_2 \text{ produced} = \frac{502 + 52 + 2 + 50}{20}$$

$$= 25.3 \text{ cu.in. in } \tfrac{1}{2} \text{ hour}$$
$$= 50.6 \text{ cu.in. in 1 hour}$$

The carbon dioxide estimations were carried out by William Brande, whom Brodie had met at the 'Society for the Promotion of Animal Chemistry', or 'Animal Chemistry Club', which also had Humphry Davy as a member. Brande was the son of a German apothecary who had accompanied George III's Queen Charlotte to England. He was a popular and highly regarded lecturer in chemistry and followed Davy as Professor of Chemistry at the Royal Institution. Incidentally, Brodie's comment on Brande's illustrious predecessor is interesting: 'Davy, who in general society was generally over-anxious to display himself to advantage and thought too much of what others would think of him, with us retained his original simplicity and was

quite at ease. Whatever the subject of conversation, he had something to offer and something to suggest, which showed in how remarkable a degree he combined within himself a highly poetical imagination with a strict, cautious and accurate judgement'.[13]

Brodie's main interest was in the action of the brain on the respiration and circulation and on the preservation of 'animal heat' or body temperature. Therefore, many of his experiments were performed on animals whose central nervous system had been destroyed by decapitation, pithing or poisoning. However, in some cases the animals were allowed to survive, especially when curare or essential oil of almonds were used, and some of these experiments are of particular interest.

Self-poisoning - essential oil of almonds

On July 3rd 1810, after applying some oil of bitter almonds to the tongue of one cat and the rectum of another, he wrote: 'I dipped the blunt end of a probe into some thick emulsion which came over in the distillation of the almond oil, and from which the oil had not yet separated. The quantity was so small that it did not form a drop on the end of the probe. I applied it to my tongue and in about a second after the application felt a sensation in my chest as if from a strong shock of electricity, but without any sensation in the joints as in the later case.' This refers to two days later, when he wrote: 'I applied to my own tongue a drop of essential oil of almonds (a larger quantity than in the former experiment). In almost one or two seconds afterwards I experienced a remarkable sensation in the chest, such as I had formerly felt but more severe. I spit out the poison and wiped my tongue with my handkerchief, but in two or three seconds afterwards I experienced another similar attack; and in three or four minutes after this I had a third attack but not so severe as the two first. In the intervals between the shocks I felt giddy in a slight degree.'[5]

Essential oil of bitter almonds contains amygdalin, benzaldehyde and between 2 and 4% hydrocyanic acid. A brilliant career might well have been cut short.

Curare in 1812

On January 12th, 1812, Brodie wrote: 'At 5 m. after 9 pm a small quantity of wourara was inserted into a wound in the thigh of a young cat. She gradually became drowsy; at 35 m. after she rose and attempted to walk but appeared giddy and stumbled repeatedly, and lay down again drowsy and half sensible. At 20 m. after 10 a small quantity of wourara was inserted into a second wound. At 34 m. she became convulsed, breathing ceased, and the animal was apparently dead but the heart was still acting through the ribs 140 in a minute. A tube was introduced into the nostril and the lungs were artificially inflated about 40 times a minute, and she was placed in a temperature of 98. She lay perfectly motionless and insensible, and there was no evidence of life except the heart being felt through the ribs.'[5] Two hours after the first application of wourara, Brodie noticed that the pupils began to react to light and fifteen minutes later there was some salivation and lacrimation. After three hours there were convulsive movements of the limbs and occasional efforts to breathe, which became regular within half an hour. The cat was then allowed to breathe

spontaneously and seemed to be in a deep sleep for about another hour, when it suddenly got up and walked away. The drowsiness and convulsions may have been the effect of hypoxia, but the crude preparation of curare probably contained other alkaloids. In a note in his 'Physiological Researches' published in 1851, Brodie stated that the cat appeared slightly indisposed on the following day, but gradually recovered and lived for some years.[14] He then added: 'Not long after this experiment was made, I repeated it on an ass, with the assistance of Professor Sewell, at the Veterinary College. The animal lay in a state of total insensibility (the lungs being inflated by means of a pair of bellows and a tube introduced into the trachea) for more than an hour. She then recovered, and seemed to suffer no inconvenience afterwards. The poison used on this occasion had been given to me by Mr Waterton, who had himself brought it from America.' This was the famous she-ass 'Wouralia' but, as Bryn Thomas pointed out in his book on curare, no mention is made of this assistance by Charles Waterton in his account.[15]

In May 1812, another group of experiments included one in which two rabbits were given wourara: one was artificially ventilated, the other was allowed to die. Brodie noted that the living animal cooled more rapidly than the dead one. On the same day the experiment was repeated and the CO_2 production of the living animal was measured. On the next day, the experiment was repeated using oxygen instead of air.

Carbon dioxide 'anaesthesia'

Nine years later, in January 1821, a guinea pig was placed in the bell-glass in an atmosphere of carbon dioxide and was artificially ventilated when it stopped breathing; the animal was allowed to die after a thoracotomy had shown that the heart was still beating vigorously. In a second experiment on the same day, the supply of CO_2 ran out while the animal was still breathing. After five minutes the animal was taken out; it then began to breathe regularly and eventually recovered completely. Unfortunately, Brodie did not recognise the significance of this fact, as Henry Hill Hickman did three years later.

In 1962, Bryn Thomas described how, on February 5th 1821, Brodie placed a guinea pig in the bell-glass in an atmosphere of ether vapour and, when the animal stopped breathing, opened the trachea, intubated it and carried out artificial ventilation until it recovered.[16] In 1851 Brodie commented that this was of interest in view of the recent introduction of ether as an anaesthetic,[17] but he did not appear to be impressed by it[18] and did not make much use of anaesthesia, although he had certainly witnessed the first public demonstration at St George's Hospital in January 1847.[19]

In summary, it can be said that Brodie was more concerned with facts than theories and perhaps because of this, many of his experiments were repeated many times, but little attempt was made to interpret his results or to produce a theory of the brain's control of the vital functions. Yet undoubtedly he was ahead of his time in that, as early as 1810, he made practical use of tracheostomy and artificial ventilation.

Brodie, Brunel and a sovereign

Finally, Brodie's experience of tracheostomy came in useful in 1843. The saga of the foreign body inhaled by Isambard Kingdom Brunel and of the efforts made to extract it, has been recounted in various biographies of Brunel; by his son Isambard[20] and by his granddaughter, Celia Brunel Noble,[21] and by two novelists, John Pudney[22] and Laurence Meynell.[23] Brodie's own account, which he published in his 'Notes on Lithotrity' as an addendum and which he read to the Royal Medical and Chirurgical Society on June 27th 1843, is probably the most trustworthy:[24]

'On the 3rd April, 1843, Mr.B., being engaged immediately after dinner in amusing some children, placed a half sovereign in his mouth. By accident it slipped behind the tongue, and a violent fit of coughing, in which he had the appearance of being nearly choked, was the consequence. This was immediately followed by vomiting, the contents of the stomach being ejected with considerable force. He strained two or three times afterwards, and did not again vomit'.

Brunel had some soreness of the throat for twenty-four hours, but suffered little inconvenience until he had to spend some cold nights in the West Country on the construction of the Great Western Railway, when he began to cough and have pain in his right chest, which was relieved after vomiting. Being the engineer that he was, he discovered that if he bent over a chair with his head and neck lower than his body, he felt something run into his trachea and fall back into his chest when he stood up again. He then designed a tilting table on which he could be strapped in the prone position, 80° head down, while his right chest was hit smartly by the hand. However, this caused such severe spasm and choking that it had to be abandoned. Eventually, over three weeks after the coin had disappeared, and after several consultations with five other distinguished colleagues, Brodie, assisted by two surgeons, Aston Key of Guy's and Charles Hawkins of St George's, performed a tracheostomy without anaesthetic or antisepsis. On two separate occasions, Brodie attempted to grasp the coin with a long pair of forceps, but the spasms were so alarming that their use was abandoned. They were called Brodie's forceps, although Brunel's family state that the engineer designed them.[20,21] The forceps illustrated in Pudney's book, which are in the Royal College of Surgeons' museum, were actually designed by a surgeon called Bond some years later to remove a foreign body from the oesophagus.[25] Sixty years ago, Brodie's forceps were said to be in the museum of St George's Hospital; so, once, was the half sovereign, but that had already gone.[26] No one knows where the forceps are now.

Brunel was given a rest for ten days, the tracheostomy being kept open by occasional probing. On the 13th May, nearly six weeks after the original mishap, Brunel was strapped to his table, his chest was struck by hand, and after several coughs, the coin hit his upper incisor teeth and dropped out of his mouth, with no spasm or distress. He recovered completely and the tracheostomy healed in a fortnight.

Brunel was at the height of his fame, all London was relieved at the news. On the same day, Macaulay, the historian, having called at the Brunel's

house and learnt the news, ran into his club, the Athenaeum, shouting: 'It's out!' and everyone knew what was out and from whom. On the same day, too, Brunel wrote to a friend:

'My dear Claxton,

At four ½, I was safely delivered of my little coin: with hardly an effort it dropped out, as many another has, and I hope will, drop from my fingers. I am perfectly well, and expect to be at Bristol by the end of the week.

Yours, I.K.B.'[20]

He sent a letter of gratitude to Brodie - and paid the bill - on which Brodie replied as follows:

'1A, Savile Row,
May 22nd, 1843

My dear Sir,

I thank you for the kind expression in your note, and its contents. I assure you that I have never been more gratified in the course of my professional life than by finding your case brought to a successful termination, but the credit does not belong only to those under whose professional care you were placed. I assure you that we feel ourselves deeply indebted to yourself and Mrs.Brunel, and the friends immediately about you for the unhesitating confidence which you reposed in us, and for the steady assistance which you gave us from the beginning to the end of our attendance on you, and we are quite satisfied that under no other circumstances could we have succeeded in the object, the accomplishment of which we had so much at heart.

May God grant that no more such trials await you, and that so valuable a life as yours is may be spared to the world.

Always, my dear Sir,

Yours, B.C.Brodie'

The incident is enshrined in R.H.Barham's 'Ingoldsby Legends', at the end of 'House Warming':

All conjuring's bad! They may get in a scrape
Before they're aware, and, whatever its shape,
They may find it no easy affair to escape.
It's not everybody that comes off so well
From 'leger de main' tricks as Mr.Brunel.

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A HISTORICAL REVIEW OF THE METHODS OF PRONE POSITION FOR OPERATIVE SURGERY

Dr J.M.Anderton

Until the mid 1930's the simple prone position with a pillow situated under the chest and another under the pelvis would have sufficed for the vast majority of surgical operations on the posterior surface of the body. Even in 1950, Professor Andrew Hunter writing on 'Anaesthesia for spinal cord tumours' could find no reference in the literature to this subject.[1] Surgical excursions into the spinal column must have been a rare event and were probably carried out only in a small number of international centres.

There are two important dates and papers relevant to this review. In 1934 the neurosurgeon, William J Mixter and the orthopaedic surgeon, Joseph S Barr, wrote their paper establishing the degenerative aetiology of intervertebral disc herniation and its relation to sciatic pain. It is regarded as the classic in this field and it was read at the New England Surgical Society in 1933 at Boston and published in the New England Journal of Medicine in 1934.[2] The second date relates to the importance of the Toronto orthopaedic department extending spinal axis surgery to thoracic levels in patients with gross skeletal abnormalities. Relton and Hall (1967) described an operation frame suitable for the support of patients with severe scoliosis undergoing corrective surgery utilising the Harrington Rod.[3]

Early American experience

Following Mixter and Barr's paper, Alan Deforrest-Smith (1944)[4] described 100 cases of lumbar disc surgery performed between 1937 and 1944. He stated that the patient was on a special operating table which placed the patient in the kneeling position with the hips flexed at 90°. There was no illustration in the article but it was probably rather like the 'Georgia prone position' which I will deal with later.

Early British experience

Mr Deforrest-Smith's special operating table had clearly not yet crossed the Atlantic! Both Lipton[5] and Hunter[1] (1950) state that it was not unusual for the surgeon to request the patient be positioned with the abdomen transversely across a metal bar, 'to undo the normal anterior curvature of a lumbar spine', and to make access to the disc space easier. I am not quite sure of the exact location of the transverse bar, whether it was directly under the abdomen or beneath the iliac crests. Either way, one shudders to think about the catastrophic effect that it must have had on venous back pressure and aortic occlusion. However, it must be remembered that at this time muscle relaxant anaesthesia was still not being used widely. The anatomical connections in the lumbar and epidural venous plexes had been well documented even in the last century, so that any pressure effects on the abdomen could have been reasonably predicted. I would also mention at this stage the prone jack-knife position; but only to dismiss it. It was probably

used on both sides of the Atlantic but was condemned strongly as early as 1947 by Slocum[6] (from Texas), for its adverse effects on the cardiovascular system. Interestingly, it still appeared in Brigdon's 1969 'Textbook of Operating Theatre Technique'!

Almost identical positions were next published, one from each side of the Atlantic. Ecker[7] in 1949 showed the use of lithotomy poles to hold a sling supporting the chest, with the patient kneeling. However, in his article he does acknowledge that he copied the method from a surgeon who had seen it previously used in Bristol and Norwich. Lipton[5] in the UK described the 'Mohammedan praying position' (Fig.1) which was almost identical to it.

The important advance in both of these techniques was that the thighs were separated so that the abdomen could hang freely without pressure on the inferior vena cava. Surgically, the lumbar spine was flexed, allowing good access. Unfortunately, gross congestion of the lower limbs occurred with this position and there were reports of renal failure from the release of myoglobin from anoxic and ischaemic lower limb muscles.

The next important advance came from the USA when Moore and Edmunds in 1950[8] wrote their article in Anesthesiology which was the first description of a frame that I have been able to find in the literature. This was adjustable for width but not for length, it was easy to store and easily moved, and could be made in any hospital workshop.

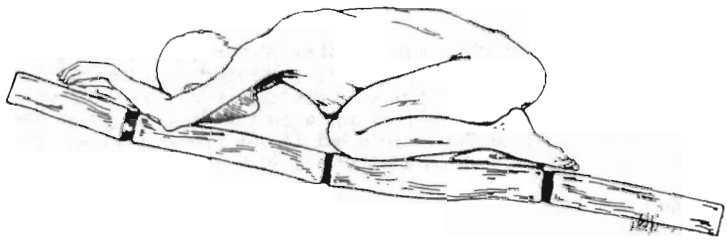

Fig.1. The Mohammedan prayer position as described by Lipton 1950

Meanwhile, the United Kingdom was moving in a different direction. In 1956 Taylor et al.[9] described a prop for supporting the iliac crests, this could be placed on the operating table and the patient placed over it so that the two vertical posts supported each iliac crest. The chest could be separately supported either by a foam block or by pillows. An important feature of this prop was that the medial margin of the top of each prop was lower than the lateral edge so that the patient did not have any tendency to slip laterally off the prop. Some later copies of this prop did not have this modification and were quite dangerous because the patient could slip sideways. Then, one prop inevitably occluded the femoral neurovascular bundle in the groin with

catastrophic effects in terms of surgical haemorrhage from venous back pressure.

The first venous pressure measurements made in prone patients

The first publication of recordings of IVC pressure from patients in the prone position appeared in the Proceedings of the Royal Society of Medicine in 1957.[10] This was, at least, a UK 'first'. The paper was the result of a Registrar's Prize essay: it showed that either tight abdominal muscles or raised abdominal pressure can cause the IVC pressure to rise from below zero to between 60 and 100mm H_2O, and when the pressure or muscle relaxation was released a fall to minus 80mm H_2O occurred. Incidentally, these patients were supported on a system of props very similar to that described by Taylor et al.[9]

Back to the USA

No review would be complete without mentioning the contribution of R.H. Smith.[11] Firstly, his 'Georgia prone position' required the patient to have a prop inserted beneath each iliac crest. These were attached to the rails on each side of the operating table. The thighs were flexed at 90° over the end of the table and the knees were supported by a special adaption to the end of the operating table. It was therefore a combination of the kneeling and iliac crest propped position. He also did some interesting X-ray studies of the lumbar curvature with different degrees of femoral flexion and showed that femoral flexion can abolish the lumbar curve, thereby improving surgical access to the posterior part of the intervertebral disc spaces. His comments on the study of the prone position in some conscious volunteers are well worth reading and give some interesting information concerning patient comfort. However, by 1974[12] he seemed to have abandoned the prone position in favour of ajdustable props similar to those of Taylor and Pearce.

Tarlov's contribution

The 'knee-chest' position as described by Tarlov[12] or, as I prefer to call it, the 'seated-prone' position was described in 1967. It was a very simple but brilliant advance on the Ecker or Lipton 'Mohammedan prayer' position. The weight is taken almost entirely on the ischial tuberosities and although the knees appear to be weight bearing, (Fig.2) I have yet to see any adverse skin pressure effects from this. Dinmore in 1977,[14] i.e. ten years later, published exactly the same position in Anaesthesia, and Foulds from Salford thought that he had also invented this position at about the same time as Dinmore. It is important to note that the seat should swivel about the position at the top of its support rather than have any fixed ratchet arrangement.

This Tarlov seated position is undoubtedly my own personal first choice for all patients having lumbar disc surgery, it has all the advantages of allowing the abdomen to hang freely without pressure on the epigastrium or in the groins, and it seems to be stable for the vast majority of patients.

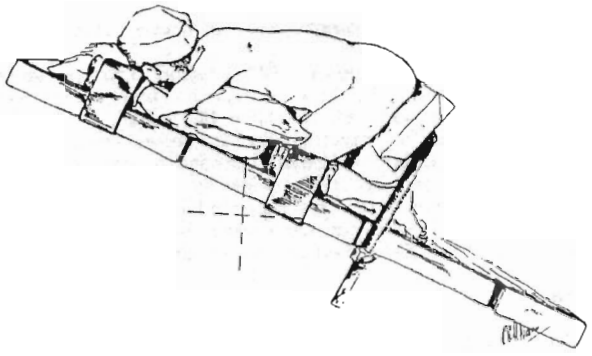

Fig.2. Tarlov (1967) described this as the 'knee-chest position' However, the use of the term 'seated-prone' distinguishes it from similar less satisfactory versions (vide Lipton and Ecker).[13,5,7].

The orthopaedic contribution

In 1963 Relton and Conn[15] from Toronto critically reviewed the current methods of supporting the grossly deformed patients who were presenting for Harrington rod scoliosis surgery. They found the current methods unsatisfactory and three years later in 1967 Relton and Hall[3] published details of their frame. This was adjustable for length and width. At both chest and pelvic level it had individually adjustable prop supports. It can be used also for adults having thoracic disc surgery or even for cervical and posterior fossa explorations. With the latter, it is probably best to put the patient's head in the Mayfield clamp. Although it was not, at first, advocated for lumbar disc surgery, it is quite satisfactory for this if the lower blocks are removed from the rails and placed on a separate base plate.[16] The chest can then be supported by a foam pad or pillows.

The work of Dr V.I.Young[16] of the London Hospital

Finally, I would like to mention one last totally different concept. All the previous methods concentrate on weightbearing over small areas where bone is relatively superficial. There is therefore some risk of pressure damage to the skin. The following spreads the load evenly over the entire body surface. I first heard of Dr Young's use of the 'Evac M' or evacuatable mattress at a neurosurgical travelling club lecture given in approximately 1982. I suppose it could be described as a new version of the old fashioned bean-bag. Currently available mattresses either contain polystyrene or Terylene granules and when the mattress is evacuated they set to a hard consistency and support all the contours of

the body. They have the added advantage of extremely good heat retaining properties and patients do not cool as quickly on these mattresses as with more conventional methods. They were first described for the management of injured patients needing transport from isolated areas of the countryside, e.g. for mountain rescue.

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PAIN IN CHILDBIRTH BEFORE SIMPSON: PERCEPTIONS AND RESPONSES

Dr Audrey Eccles

In the pre-Simpson period, pain in childbirth was viewed as an inevitable part of childbearing, and indeed occasionally (but very occasionally) specifically referred to as 'the curse of Eve'. All denominations of the Christian church accepted the interpretation of Genesis Simpson was later so concerned to refute, but it does not seem that before his time this led to any proscription of pain relief, though it may have favoured approaches other than the medical. Some of these earlier approaches persisted alongside the medical anaesthetic model and have indeed been re-emphasized in competition with it in recent times.

Until very recently however pain was labour; and even though authors from the 17th century onwards explained that the muscular movements of the uterus caused the pains, they nevertheless universally referred to them as 'pains'. So early as the 'Birth of Mankind' in 1540 midwives were urged to distinguish between colicky pains, which called for treatment, and the pains of true labour, which did not, and also to distinguish between the pains before the head was visible, which simply had to be endured, and those after, when bearing down was called for.

However, authors were aware that pain in childbirth was very variable, and that even in normal labours it was much more severe for some women than for others. The French surgeon Jacques Guillemeau (1612) noted that all women had pain, but referred to Aristotle's statement that the women of Ligustria 'doe bring forth without paine, and that they return to their businesse as soone as they are delivered'.[1] This idea that barbarians have less pain than civilised races was to be curiously long-lived and was frequently prayed in aid to condemn 'unnatural' and luxurious behaviour.

William Sermon in 'The Ladies' Companion' 1671 recounted a personal observation of what appeared to be a painless labour as follows: 'it would be almost a miracle to see a woman delivered without pain; though I am apt to believe, that the wife of Thomas James did enjoy that happiness, whom I saw delivered of a lusty Child in a Wood by her self, which presently after she took the Child and put it into her apron with some Oaken leaves, and marched stoutly with it almost half a mile, to an Uncles house of mine .... and within two hours, her Child and her self being refreshed .... took her journey a long mile further, not in the least discouraged, and the next day came and returned hearty thanks. This accident happened as she was walking homeward from a Market Town, in the year 1644, the manner of which I saw, being accidentally placed under a hedge (purposely) to shoot a Hare that I knew frequented the very place where she was delivered'.[2]

An even more heroic episode was recounted by William Harvey who heard it from Lord George Carew, formerly President of Munster in Ireland: 'There was a Woman bigge with Child, which followed her Husband, who was a Souldier in the Army; and the Army being daily in motion, was it seemes forced to make a Halt, by reason of a litle River that run cross the place whether they intended to March: wherupon the poor woman finding

her labour come upon her, retired to the next thicket, and alone by her self, without any Midwife, or other preparation, brought forth Twins: which she presently carried to the River, and there washed both her self and them: which done, she wrapt her Infants into a course cloth, and tied them to her back, and that very day, marched along with the Army twelve mile together, bare-footed: and was never the worse for the matter'.[3]

There seemed to be general agreement however that not only were painless births a great rarity, but they only happened to the poor and labouring classes. Sometimes the hardy Scots, sometimes the wild Irish, were mentioned as having painless labours; sometimes it was said that whores and doxies had less pain than others - Defoe made Moll Flanders comment after one of her numerous labours that she was 'as well as I always am on these occasions'. It was a fact, and generally known, that women who had concealed illegitimate pregnancies often seemed able to give birth without any screaming or groaning, quietly smothering the child and returning to work immediately as if nothing had happened.

Read was expressing a widely accepted view in 1687 that: 'poor Women, Hirelings, Rusticks, and others us'd to hard Labours, also Viragoes and Whores, who are clandestinely delivered, bring forth without great difficulty, and in a short time after, rising from their Bed, return to their wonted Labours: but Women that are rich, tender and beautiful, and many living a sedentary Life, bring forth in Pain, and presently after their delivery lye in an uneasie and dangerous condition'.[4] Hence painful and difficult labours were a sign of social status, and much solicitous attendance by men-midwives plainly became essential for upper class women. Dionis indeed declared that a quick painless birth might cause gossip: 'An easy and sudden Delivery is not so much for a Woman's Reputation, especially in her first Child; for People are apt to conclude, that the Parts have been open'd and relax'd before, and therefore most Women are proud of being long in Labour'.[5]

Thus, cultural and religious influences fostered the idea that childbirth, especially for those above the lowest social ranks, was always painful. Abnormal labour was usually even more so. This perception did not mean that nothing could be done about the pain of childbirth however, and several strategies were employed to cope with it. These could be divided into two types, the religious, psychological and cultural in one group, which for convenience we may call social, and the practical, medical and surgical in the other, though these approaches were in practice by no means mutually exclusive and any combination or all might be adopted in a single case.

The social approaches, like the various natural childbirth schools of our day, addressed the woman's frame of mind, whereas the medical approaches, like the anaesthetic approach pioneered by Simpson, addressed the body. In contrast with Simpson's solution of removing the pain by obliterating consciousness, the medical approach before his time was essentially to get the labour over as soon as possible, since pain and labour were the same thing.

Religious approaches to dealing with pain did not feature prominently in the textbooks for midwives and surgeons, although penitential and devotional literature exemplifies this approach. The Book of Common Prayer referred in the service for the churching of women to 'the great perils and dangers' of childbirth, and the fear of death was a powerful component in the mental suffering of women, not unreasonably when maternal mortality might reach some 25 per 1000 births.[6]

Especially where the labour seemed likely to be difficult, recourse to prayer might be explicitly advised. The anonymous author of 'A rich closet of physical secrets' 1652 wrote: 'Therefore when there appeareth difficulty in bringing forth the Child, Jesus Christ, the only preserver and saver in danger, is heartily to be called upon'. The seventeenth century man-midwife Percivall Willughby more than once consulted ministers of religion, who were apparently present, on the ethics of destroying a living child with the crochet to save the mother, and it seems to have been normal for women thought likely to die in childbirth to put their affairs in order and make spiritual preparation, as it was for those dying of illness.

Midwives were urged to maintain a godly atmosphere in the lying-in room rather than tell gossips' tales, and the chief rationale for the licensing of midwives by the bishops, instituted in the 16th century, was to ensure proper Christian conduct and to avoid superstition and witchcraft.

Superstition and witchcraft were of course other possible strategies for coping with pain and danger in childbirth, and in some social groups, especially earlier in the period, may have been very commonly resorted to. Superstitious means in use in medieval times included birth-girdles and amulets. Even in the seventeenth century much faith was placed in the eagle stone to draw forth the birth, although by then a 'scientific' explanation was given that the stone worked by 'magnetic virtue'.

Histories of anaesthesia often refer to the execution of Eufame McCalzane in 1591 in terms that suggest her crime, and that of her midwife Agnes Sampson, was the avoiding of pain in childbirth, but I think it much more probable that it was the use of witchcraft for the purpose that led to their execution. The accusation was that Eufame caused her 'naturall kindelie payne' to be transferred to a cat and a dog by witchcraft. Certainly the numerous clauses of the midwife's oath in the extant versions include several against witchcraft but none at all against pain relief. It would not seem, therefore, that the Church was particularly opposed to the relief of pain in childbirth by means other than witchcraft in the 16th and 17th centuries.

Psychological aspects of labour were well recognised at a very early date. The 'Birth of Mankind' mentions a fearful or unruly temperament in the mother among factors causing difficult labour, and advises the midwife to support the labouring woman with 'swete wordes, geuynge her good hope of a spedefull delyueraunce, encouragyng and enstomacking her to pacience and tolleraunce'. Guillemeau suggests the midwife should promise her a quick delivery and a fair son or goodly daughter, whichever she knows the mother would prefer, and several authors caution

against tactless reference to bad labours by the women present, although this advice never seems to have been much heeded.

It was customary until quite late in the 18th century for large numbers of female friends and relatives to be present at labours, and although some feminist historians portray this as a support system of great benefit to the mother, it seems equally possible that not only the noise and crowding, but often the conflicting advice and tales of woe that surrounded the mother might have been the reverse of constructive.

It may however be true that the relatively public way in which childbirth was conducted, with certain expectations as to behaviour, may have helped the labouring woman support the ordeal, much as anthropologists tell us the candidate in painful initiation ceremonies and suchlike rites of passage is supported by having definite cultural expectations and an assigned role to play. Several authors recounting difficult cases comment on the fortitude shown by the women, and in the Victorian period comparisons were made between the woman going into labour and a soldier going into battle, suggesting that it was seen as a personal moral test.

Medical approaches to pain in childbirth on the other hand were directed at expediting the labour rather than enabling the woman to tolerate the pain. Some direct attempts at alleviating pain were also made however. The 'Birth of Mankind' for example, has a recipe for: 'certayne pylles the which make the labour easye and without payne' (68v) containing myrrh and opium. The advertisement in 'Dr Chamberlain's midwives practice' (1668) for 'An excellent powder to procure easie delivery in Childe-bearing women, being a secret of the Authors to be had of Mr Thomas Rooks at the Holy Lamb at the east end of St Pauls' might equally well be an analgesic, or something similar to the well-known 'pulvis parturiens' 'the midwife's powder', in common use for stirring up ineffective pains. Indeed, a staggering array of medicines, fumigations, poultices and so forth features in the midwifery textbooks up to the end of the seventeenth century, when they seem to have been largely given up. The administration of these substances satisfied the need of both patient and attendants for some action to be taken, and authors frequently assert that these remedies produced the looked-for effect.

Many of these medicines were administered in alcohol, and a woman in labour for several days, which was not uncommon, might be much under the influence by then. Although no textbook proposes the deliberate use of alcohol as an analgesic, it is possible that midwives' alleged over-use of cordials[7] was partly an attempt to dull pain.

Charles White of Manchester remarked that alcohol was often freely given by the women: 'If the woman's pains are not strong enough, her friends are generally pouring into her large quantities of strong liquors, mixed with warm water, and if her pains are very strong, the same kind of remedy is made use of to support her'.[8] William Giffard commented on a case he attended: 'What in some measure occasioned the difficulty, was the Woman's being stupified and senseless from the quantity of strong liquors that was given her, and her smoaking Tobacco, so that she was .

very drunk, and no ways capable of pursuing directions, nor of assisting me by bearing down at the time of my extracting the Child'.[9]

Giffard, however, almost alone among authors before 1750, favoured opiates in labour, which he declared did more good than all the forcing medicines generally recommended. Other authors, however, although they prescribed laudanum for after-pains, and for numerous other conditions from hysteria to cancer, seem to have felt opiates inappropriate during labour because they concentrated on expediting the delivery rather than on relieving the pain directly.

Practical manual methods of hurrying on the birth advised by the earlier authors from the 'Birth of Mankind' to the end of the 17th century included greasing the passages, manually dilating and stretching the vagina and cervix, and pressing down externally on the belly. Many midwives followed this advice, and later 17th and 18th century authors devoted much attention to pointing out the ill consequences of such efforts to hurry the birth. Harvey wrote: 'Therefore the younger, more giddy, and officious Midwives are to be rebuked; which, when they hear the woman in travaile, cry out for paine, and call for help; lest they should seem unskilful in their trade and less busie then comes to their share, by daubing over their hands with oyles, and distending the parts of the Uterus, do mightily bestirre themselves, and provoke the expulsive faculty by medicinal potions: so that ... by their desire to hasten and provoke the Birth, they do rather retard and pervert it... and bring them in danger of their lives'.[10]

The men-midwives who became increasingly prominent in obstetrics from the early 17th century onwards, used surgical means to shorten the labour, at first only destructive operations in cases of danger, later podalic version for malpresentations and such emergencies as ante-partum haemorrhage, and from the 1730's the forceps for normal presentations which proved tedious or obstructed. The same pressures to show their skill and to rescue the woman from her pain often tempted them to over-use these techniques, and much debate about the improper use of the forceps ensued. It is however not unreasonable to suppose that both the meddlesome midwifery of the 17th century and the frequent recourse to the forceps of the 18th were not only responses to obstetric difficulties, but responses to the appeals of women in pain and their friends and relatives.

Interestingly, it seems that (except for witchcraft early in the period) the only one of the approaches outlined in this paper which provoked much moral or religious opposition was the use of the forceps. It is significant that surgical texts of the pre-anaesthetic era reveal the same approach to pain as do texts on midwifery; pain is noted and deplored, but the answer is sought in shortening the procedure by the fastest possible technique.

Direct attack on the phenomenon of pain itself by the adoption of anaesthesia required not only the discovery of certain technical facts but a real revolution in philosophy, and it is for this leap of imagination even more than the technical discovery of anaesthesia that Simpson and the other pioneers of anaesthesia are to be honoured.

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SPINAL ANALGESIA FROM BIER TO BARKER

Dr M.Bembridge

The development of spinal analgesia to date has had a course punctuated with plenty of ups and downs. It had a very inauspicious start when in 1885 in New York, J.L.Corning reported on 'a procedure in therapy which possessed the merit of novelty'. The syringe and hollow needle had been available for some time and when the local analgesic properties of cocaine became apparent it was only a matter of time before someone reported on the injection of the drug into the region of the spinal cord.

Corning's report of 1885[1] described the deposition of around 1.8ml of cocaine solution between the spinous processes of two of the inferior dorsal vertebrae, firstly in a dog and then in a patient suffering from 'spinal weakness'. He took two attempts to attain an alteration in sensation. It has to be assumed that the cocaine was deposited into the CSF. Corning's hypothesis on the mechanism of action was that the drug would be absorbed into the blood and thence carried to the spinal cord. Although this is false he did observe that 'whether the method will ever find an application as a substitute for etherization in genito-urinary or other branches of surgery, further experience alone can show'.

Lumbar puncture

The technique of lumbar puncture was described in 1891 by Quinke from Keil, but the first description in English of 'Paracentesis of the Theca Vertebralis' was written in the Lancet on 2nd May of the same year by Dr W.Essex Wynter, then a Medical Registrar at the Middlesex Hospital.[2] He reported four cases of children with tubercular meningitis giving rise to coma. In two patients a Southey's tube connected to a trochar was used to cannulate the CSF, but in the other two a cut-down was performed. All four patients who had CSF drawn off died some hours after the procedure, presumably having coned. His final comment was that further experience would no doubt enable a better selection of patients to be made and the treatment to be carried out more effectively, though a mortality of 100% must have put others off the technique!

Bier and Hildebrandt

Almost certainly, Bier, who was an assistant of Esmarch in Keil in 1889, was stimulated by the technique of Quinke who was his contemporary and in 1889, Bier used cocaine for spinal analgesia in six patients, describing his findings in his classic paper of 1899.[3]

After performing six cases Bier asked Hildebrandt to carry out lumbar puncture on him, but it was unsuccessful because the cocaine leaked from between the Pravaz syringe and needle. Hildebrandt then volunteered to have the technique performed on himself. The block was described in great detail in the original paper; for example, at 10 minutes a long needle was thrust all the way to the femur with no pain felt and at 23 minutes, hitting the tibia with an iron hammer was not perceived as

pain. They both ate, drank and smoked cigars after the experiment, but both had very severe headaches. Hildebrandt's lasted for 3 - 4 days and Bier was bedridden for 9 days.

Although Bier had no mortality as a result of spinal puncture he certainly had some problems. Preoperative problems occurred in 80% with a 33% incidence of tachycardia (and possibly hypotension), a 50% incidence of vomiting and a 75% incidence of headache. He also had one patient who came very close to having a total spinal - the child had no feeling in his entire body. There were several pertinent conclusions in Bier's paper - firstly, the needle should be very fine, secondly, one should try to avoid the loss of CSF and thirdly, one should enforce strict bed rest; but he also commented that as long as cocaine was the only drug available the problems seen with it would prevent the general adoption of spinal analgesia.

The introduction of Stovaine

Thankfully, this situation did not last for long and Stovaine, which was synthesized by Fourneau, was introduced by Chaput in France in 1904. The first paper published in England on the use of this drug appeared in 1906 in the British Medical Journal from Henry Percy Dean.[4] Dean was born in 1864 and was educated at University College, London, where he qualified in 1888 with a brilliant academic record. He passed his Fellowship in the same year, but had to wait until he was 25 before he could be admitted as a Fellow (RCS). He was an Assistant Surgeon at the London Hospital in 1892 and went on to become a Consultant Surgeon there in 1913. In 1906 he published details of six cases in whom he had used Stovaine by intraspinal injection. Only two of the six had uneventful surgery; one died post-operatively, two had poor analgesia or inadequate block and one, whose block was to T4, had a feeble pulse which improved at the end of surgery. Headache was mentioned in the discussion as occurring in many patients, coming on at the end of surgery and lasting for a few hours. Despite these problems Dean felt that the major advantage of spinal analgesia was that it protected the patient, especially the ill patient, from a surgical shock - a belief which does seem still to be prevalent among a few of today's surgeons.

Dean presented a paper to the 75th Annual Meeting of the British Medical Association in Exeter in 1907,[7] comparing the relative values of inhalation and injection methods for inducing anaesthesia. He said that the problems of the harmful systemic effects of the anaesthetic and the fact that surgical shock was not abolished with ether or chloroform were good reasons for employing spinal analgesia in patients who were prone to these two problems, but otherwise there was little to choose between the two methods.

Barker's contributions

Further support was given to spinal analgesia in this country by Arthur E.Barker, Professor of Surgery at University College Hospital who observed in his paper of March 1907 that: 'an addition to surgical resources may have been made'.[6] Barker was born in 1850 in Dublin and qualified LRCP in 1870 at the Medical School of the Royal College of

Surgeons of Ireland. He then spent five years in Germany to gain more surgical experience and returned briefly to Dublin. At the age of 25 years he was appointed Assistant Surgeon to UCH despite being without his Fellowship. He went on to found the Ear Department, but still found time to continue his general surgical practice. He wrote three papers in 1907 and 1908, each on a series of 100 patients in whom he had used spinal analgesia. Barker acknowledged Bier's contribution in his first paper by accepting that the use of spinal analgesia was due to Bier alone, and in fact, by this time, Bier had performed over 1,000 spinal blocks.

Barker's first paper described many aspects of the technique.[6] He used 3-5 centigrams of Stovaine solution which had been specially prepared in Paris. This was made 'heavy' by the addition of glucose, and he achieved blocks to T6 with the pelvis moderately elevated. The blocks lasted from 23 to 120 minutes with an average duration of 50-70 minutes. Imperfect analgesia and the need for general anaesthesia occurred in fewer patients in each series, perhaps indicating a learning curve. He failed to locate the dura in five of the 300 patients. Death occurred in four patients but was unrelated to the anaesthetic although later he does describe two deaths which were partly related to spinal analgesia. Faintness occurred sometimes and headache was often present - a figure of 20 out of 50 is quoted in his first paper. The incidence of headache is not very surprising as the needle being used had a one millimetre diameter stylet inserted through it and Barker drew off 5-10ml of CSF before injecting the local anaesthetic. In his first paper[6] he described three aspects of spinal block which puzzled him; firstly, how to explain why, in a few cases, no analgesia followed what seemed to be a normal puncture. Secondly, how to explain the variations in block height, the side of the block and the duration, and thirdly, how to avoid what he called 'by effects' which were not infrequently seen. In order to explain these phenomena he developed a model glass spine, and, using solutions of differing densities which had been specially prepared, he went on to show how gravity affected the spread of solutions. His own preparation had a specific gravity of 1.030 (10% Stovaine, 5% dextrose and 85% distilled water), and flowed in a cephalad direction with the pelvis raised by three inches.

There are other details in Barker's first paper which show how carefully he undertook the technique, such as the skin preparation. The skin was repeated washed with very hot water, soap and a brush. Compresses of antiseptics were then left on for some hours and at the moment of puncture the skin was washed again with normal saline to remove traces of antiseptic. A specially made sloping screen prevented the patient seeing the operators or operation, but allowed those present to observe the patient's expression.

Barker's second and third papers dealt mainly with the type of surgery for which spinal analgesia had been used and some of the problems encountered.[7,8] He disagreed strongly with Bier in his second paper, as Bier believed that the spread of the local anaesthetic solution was determined by CSF flowing out of the cranium when the patient was sitting and into the cranium when the patient was laid down again. Barker said that this is certainly not the best or only explanation and

his experience showed that gravity made a major contribution to the extent of block.

I think we must acknowledge the work of Bier and his clinic but we must accept that Barker's meticulous work with spinal analgesia was enough to ensure its continued use and success despite a rather shaky start.

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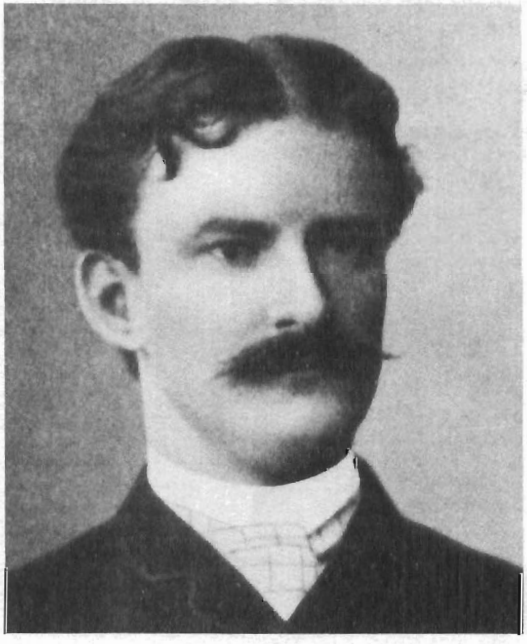
WHO WAS HILDEBRANDT?

Professor Ole Secher

When the history of spinal anaesthesia is discussed, two persons are usually mentioned together: the well-known August Bier (1861-1949) and the more elusive Doctor Hildebrandt. They both worked in Kiel in the Akademischer Krankenhaus where Bier was a Chief Surgeon and Hildebrandt his assistant. The Chief of the Department was Johann F.A.Esmarch (1823-1908).

Hildebrandt assisted Bier when he made his first trial of spinal anaesthesia on August 15th 1898, and he also did so for the next five cases. On August 24th they decided to give each other a spinal anaesthetic; each procedure was followed by unpleasant sequelae. When Bier wrote his first paper on spinal anaesthesia, published in 1889, he was the sole author and he only briefly mentioned the help he received from Hildebrandt. Hereafter, Hildebrandt disappears from history.

At the German Surgical Congress in Berlin in 1901, Bier gave a long paper on his experience of about 1200 cases of spinal anaesthetics. He had tried different new drugs because he considered cocaine too toxic, and causing too many complications. He made three suggestions for minimising its toxic effect (by toxic effect he meant the effect of high spinal anaesthesia): 1, by using new non-toxic drugs, 2, by using drugs in low concentrations and 3, by preventing drugs affecting the brain.



August Bier

(1861-1949)

at the time he

was working

in Kiel

The last proposal was realised in an interesting and peculiar way: he applied a tourniquet round the neck to increase intracranial pressure so the cerebral spinal fluid was forced down into the spinal canal! He used this method in 21 cases with no complication and, probably, with less toxicity. Fortunately, it never became a popular technique!

The other interesting part in this paper is at the very end, where Bier gave an explanation of how he got to know about James L.Corning's (1855-1925) experiments carried out in 1885. He found them mentioned later in French and American literature and had no prior knowledge of them when, in 1898, he made his own first attempts at spinal anaesthesia.[2]

There are good reasons to believe that Bier is right in this statement. In the paper which was published when he moved to Griefswald as Professor, Hildebrandt is only mentioned in connection with his own and Bier's mutual administrations of spinal anaesthesia. A third doctor, Fritz Engelmann (1873-?), a gynaecologist in Bonn, is also mentioned as one who tried spinal anaesthesia on himself.

But what became of Hildebrandt? Who was he?

From the little information I have found, his name was August Hildebrandt (1868-1954). He graduated in 1892 and, after his time as an assistant to Bier in Kiel, went on military service. As a military surgeon, he went to China during the Boxer Rising (1900) and to South Africa during the Boer War (1899-1902), on the Boer side. Coming back he had further surgical training with Professor Franz Konig (1882-1910) at the Carite Hospital in Berlin. Ultimately, he became Chief Surgeon in Eberswalde - 45 km north of Berlin - remaining until 1933. He also became Professor by title. He probably died in 1954.[4,8] What is more interesting is that Hildebrandt became one of Bier's ardent adversaries! One can only speculate why he turned against Bier.

August Hildebrandt should not be mistaken for the Professor of Surgery, Otto Hildebrand (1958-1927) at the Carite Hospital in Berlin from 1904. They both worked at that hospital.

Surprisingly enough, August Hildebrandt published an article in 1905 about spinal anaesthesia. He began the paper by praising Corning as the great inventor of spinal and epidural anaesthesia, who systematically studied and wrote several articles on the method. Bier, according to Hildebrandt, was the first to use the spinal method for operations; he mentioned that they gave each other spinal anaesthesia. The rest of the article is general information about the use of spinal anaesthesia.[6]

The following year (1906) another article (with a reference to a meeting of the Society of Carite doctors) appeared in March. It started with Herr Poul Lazarus who talked about 'Die Biersche Lumbalanaesthesie' and other methods for pain relief within internal medicine. Then came Herr Bosse (Poul Basse - 1881- ?) who had been asked by Professor Hildebrand to talk about experience with spinal anaesthesia in the surgical department. In the middle of his talk he took the opportunity to tell the audience that it was not Bier who had invented spinal anaesthesia, but Corning![5]

Priority to Corning or Bier?

This assertion meant that the Professor of Surgery at a most influential university agreed with that statement. Now it became serious. Remember, Hildebrandt (with a t) was also employed at the Carite.

Bier, now a Professor at Bonn, answered in May, when he explained his viewpoints, and in detail told what Corning and he had done. He also mentioned that a doctor named Philipp Boekenheimer (1875 - ?) also gave Corning priority credit. This doctor was employed in Professor Ernst von Bergmann's department (1836-1907) at the University Clinic in Berlin.[3] No doubt Bier felt unhappy about the situation and had the feeling that the 'big people' in Berlin would crush him.

The last paper came from Hildebrandt, who now gave his version of the history in a rather arrogant way, but he stuck to his opinion given earlier. He offered no explanation as to why he turned against Bier. Perhaps he felt offended that he had not been a co-author of Bier's first paper.[7]

Today, I think most historians will give Bier the credit for being the inventor of spinal anaesthesia. He understood the importance of his technique and popularised it. Bier became Professor of Surgery at the University Clinic in Berlin in 1907, when he followed von Bergmann, and the controversy was forgotten. To me, Corning is in some way in the same position as Crawford Long (1815-1878), who did not understand the importance of ether inhalation, and Bier's position may be compared to W.T.G.Morton's (1819-1868) who made it possible for everybody to give ether.

Akademischer Krankenhaus shortly after it was built in 1860-1862.
It was in this building that Bier and Hildebrandt worked.

Acknowledgement

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THE MANCUNIAN WAY

Professor T.E.J.Healy *

Ether was used and demonstrated by William Morton, a dentist on the 16th October 1846.[1] The message reached Dr Francis Boott of Gower Street in London and he gave ether to Miss Lonsdale for the extraction of a molar tooth on the 19th December 1846[1] three days after the ship, 'Acadia', carrying the details to him in a letter from Dr Bigelow, docked in Liverpool.[2]

Charles Strange

The importance of the discovery of the anaesthetic effects of ether was confirmed by the haste with which the new knowledge spread[3,4] in a world in which communications were only just stirring. There was not long to wait for the first administration of anaesthesia in Manchester. The first account was published in the Manchester Guardian on the 14th January 1847.[5] Charles Strange had written to the Guardian on January 13th describing the self-administration of ether in order that an assistant might remove one of his teeth. At the time Charles Strange was 31 years old and was listed in Slater's street guide to Manchester as a druggist and chymist.[6] His listings in the street guide from 1845 to 1851-1852 continued to refer to him as druggist and chymist and as manufacturing chymist and wholesale druggist.[7-10]

However, in the street guides from 1855 onwards, of 1861, 1863 and 1869, his profession or occupation was listed as dentist.[11-16] This leads one to assume that he was already dabbling in dentistry in addition to his chymist and druggist activities and hence his, otherwise surprising, use of ether for the extraction of one of his own teeth. Unfortunately, he poisoned himself whilst in an unsound state of mind on 28th September 1870 and died. He was aged 54 and his occupation on his death certificate was given as dentist.[17,18] The inquest was held by E.Herferd, the Manchester Coroner, on 30th September 1870.[18] One must wonder if he had become addicted to the anaesthesia vapours and died as a result of one self-administration too many, just 23 years after his first self-administration of ether.

The first administration of anaesthesia by a doctor was also reported in the Manchester Guardian on Wednesday, February 3rd 1847 in a letter dated February 2nd 1847:[19] 'The patient, a lady of high respectability of this town, was the subject of a tumour, which her medical advisors Dr Bardsley and Mr Turner thought it prudent to have removed'.

It is interesting how times have changed for, in this letter, only limited comment was made about the surgery: 'At this point Dr Bardsley requested Mr Turner to commence which he did with great alacrity,

* Professor Healy would like to thank Dr E.N.Un for considerable assistance in the preparation of this paper.

removing the tumour with a few strokes of the knife'. In an appropriate recognition of the dangers of anaesthesia and of the importance of an appropriate training in its use, he wrote: '...I should wish to caution the public against submitting themselves to the influence of ether for the minor operations, without the approval and superintendence of properly educated medical men'. Most of the letter was given to describing the condition of the patient and her behaviour during and after the surgery with special consideration to the effects of the ether. A valuable comment, for our purposes, was made in the last paragraph: 'The apparatus used on this occasion was that invented by Dr Boott and Mr Robinson and appears to have accomplished its purpose very efficiently. It was furnished by Mr Wood, the surgical instrument maker, of King Street, who kindly attended with the instrument, and with the aid and superintendence of Mr Bowring, the house surgeon of the Infirmary regulated the inhalation of ether. I am informed by Dr Bardsley who consulted his watch at the time, that the effect of ether lasted four minutes and a half. He has since politely written to inform me that the lady is doing well. I have the honour to be Sir your obedient servant, Jas Bower Harrison, Surgeon'.

It is interesting that, in a letter dated 4th February 1847,[20] John Braithwaite, a surgeon at the Royal Infirmary, drew particular attention to the comment in Mr Harrison's letter in which the public were cautioned against submitting to the influence of so potent an agent without the advice and superintendence of properly educated medical men. Mr Braithwaite recommended clinical evaluation of ether: 'We want to know whether it has been supposed or found to interfere with the chance of recovery after the most important surgical operation in which it has been used. This is of the utmost importance to know but difficult to be known, and it were well if the progress and termination of each case could be given. Such trials as have yet been made in the Infirmary, in cases of important operations have been so incomplete and unsatisfactory in their nature, that it would be difficult to draw correct inference from them, as only one patient could be said to have been fairly under the influence,.....'.

We may be sure that the thoughts expressed by this surgeon in Manchester were little different from those expressed by others who were experimenting in the use of ether to provide pain free surgery in other parts of the country. The surgeons of the day recognised the need for appropriate clinical trials, they recognised that the administration of anaesthesia demanded special skills and that only those medical men who had these skills should administer ether.

Dr George Bowring

It appears that George Bowring could indeed have been the first doctor to administer general anaesthesia using ether in Manchester. John Braithwaite in his letter of the 4th February mentions: '...such trials as have yet been made at the Infirmary..'. Indeed, he goes on to refer to a patient who had died little more than a week after the removal of a leg under ether anaesthesia. He also referred to two other patients who were anaesthetised in the week of February 4th. One cannot imagine that the administration of anaesthesia by Mr Bowring, reported in the

'Guardian' on Sunday 31st January 1847, was the first occasion when Mr Bowring administered general anaesthesia. It would be surprising if he had been taken to a private house to anaesthetise a lady of high respectability if he had not already had good experience with the use of ether and gained the confidence of Dr Bardsley and Mr Turner. A note written by his son and retained in the Archives of the John Rylands Library of the Victoria University of Manchester records: 'He told us that he administered the first anaesthetic by a doctor in Manchester'.[21]

Certainly, the closeness of the dates (20 days) between the letters, i.e. those of Charles Strange and Jas Bower Harrison, and the recognised need to have skill suggests the need for appropriate practice and experience before being permitted to anaesthetise an important patient in her own home, and supports the view that George Bowring administered the first ether anaesthetic in Manchester.

It is fascinating that two of the medical men mentioned in Mr Jas Bower Harrison's letter, i.e. Dr Bardsley and Mr Turner, were particularly important in the development of medical education in Manchester. Dr Bardsley was regarded as one of the leading physicians in the country and was knighted for his special services.[21-25] Mr Turner founded the Pine Street Medical School (1825),[24] the first complete School of Medicine outside London. Mr Jas Bower Harrison became an anatomy demonstrator in Chatham Street School in 1850.[24] This school ultimately amalgamated with the Pine Street School in 1856 to form the Manchester Royal School of Medicine which itself later combined with Owens College to form the Victoria University of Manchester. George Bowring, a mere assistant house surgeon, administered this anaesthetic in illustrious company.

The important matter now is what do we know about Mr Bowring? George Bowring was born in Bradford on February 17th 1818 and died in Manchester of senile decay on March 3rd 1902.[26] He was the son of George and Sarah Bowring of Edensor, an old family tracing their origins back to 1700. He studied medicine at King's College in London qualifying MRCS in 1841 and LSA in 1843. He married Frances Walmsley of Stockport and they had three daughters and one son. George Bowring left King's College with glowing testimonials. We quote here two of them:[21]

'I have known Mr George Bowring intimately from the commencement of his studies in London till the present time, he was my private pupil and hence I can bear witness to his good principles and regular habits as well as to his professional industry and talents. Mr Bowring had devoted much more than the usual time to the acquisition of practical knowledge of the various branches of his profession and he has served successfully the offices of dresser, house surgeon, clinical clerk and physician's assistant in King's College Hospital as well as that of house surgeon to the Westminster Lying-In Hospital and in all these responsible situations he ably and honestly discharged his duties so as to merit and receive the approbation and esteem of all medical officers. I beg therefore earnestly and respectfully to recommend him to the subscribers to the Manchester Royal Infirmary as a candidate for the office of apothecary to that institution. Richard Partridge, Professor of Anatomy in King's College, London and Surgeon to King's College Hospital, London, March 1st 1844'.

Another referee wrote: 'This is to certify that Mr George Bowring diligently followed the prescribed course of instruction as a matriculated student in the medical department of this College during four years, that he was regular in his attendance to the College chapel and the divinity lectures and that his conduct, as far as it came under our observation, was uniformly good. J.Litchfield, late Principal of King's College and Richard Partridge, Dean of the Medical Department and John Allen, Chaplain'.

George Bowring left London on appointment to the post of House Apothecary at the Manchester Royal Infirmary on March 21st 1844. The Manchester Royal Infimary was then situated in Piccadilly Circus. At this time he lived at 186 Oxford Road. This house still stands and is a few hundred yards from the present Infirmary. On June 19th 1845, he was appointed Assistant Clerk to the Physicians and one year later reappointed Clerk to the Physicians. He was appointed House Surgeon on June 17th 1847 and reappointed on June 22nd 1848. He was appointed to the Salford and Pendleton Royal Hospital dispensary in July 1849.[28,29] In April 1855 he was appointed Surgeon to the Manchester Royal Infirmary and Dispensary Surgeon on June 14th 1855. The Chairman of the Board of Salford and Pendleton Royal Hospital and Dispensary wrote to Mr Bowring on June 14th 1855: 'Dear Sir, I have great pleasure in transmitting to you the following resolution passed at the meeting of the Board this morning. Resolved that this Board has great pleasure bearing testimoney to the abilities and kindnesses manifested by Mr Bowring in his attendance on the poor of this charity and to the great interest he has taken of the welfare of this institution since his appointment as Honorary Surgeon in July 1849. The Board of Management, Salford and Pendleton Royal Hospital and Dispensary. I remain, dear Sir, yours very truly, Mr Harvey, Chairman'.

Mr Bowring was appointed Casualty and Admitting Officer to the Manchester Workhouse and Hospital Surgeon on August 7th 1871. In due course he became Senior Surgeon at the Manchester Royal Infirmary. He was not noted to be a great surgeon. He was described as sometimes rash but extremely fast.

Early anaesthesia at Manchester Royal Infirmary

It is interesting to comment on the attitude towards the practice of anaesthesia at that time. Byelaw Number 8, of the Manchester Royal Infirmary, as late as 1879 and 1883, still required that assistant medical officers provide anaesthesia:[30] 'No.8. They shall on alternate days, administer chloroform when required to do so by members of the surgical staff.' 'New Byelaws 1883. No.8. They shall on Fridays and Saturdays and in special cases at other times administer chloroform when required to do so by members of the surgical staff.'

It was at a meeting of the Board in October 1886 that it was decided to advertise for a chloroformist. The Manchester Royal Infirmary Board on 29th November 1886, passed the following resolution: '5. Resolved that on the recommendation of the sub-committee allocated to examine applications of candidates for the appointment of administrator of anaesthetics, Alexander Wilson MRCS, LRCP, London, is thereby appointed

to that office for 12 months from the 1st December next at £75 per annum'.[31]

George Bowring lived a full and varied life and his interests spread beyond the Manchester Royal Infirmary. It is said that he had a very retiring disposition but a keen sense of humour. He was known to have a twinkle in his eye, and was a delightful personality who enjoyed a risque joke. He had a bald head and wore a monocle which never seemed to drop out. He was a member of the Board of Guardians and Medical Officer to the Lancashire and Yorkshire Railway. He was Church Warden of the Manchester Cathedral during the time of its restoration and listed in the book of Church Wardens. A small sculpted model of his head is to be seen over the archway leading into the Derby Chapel in the Cathedral. He was a member of John Shaw's Club and the Manchester Literary Club. He was a staunch conservative and a churchman. He must have been an opponent of the Corn Law because he was one of the chief guests and spoke at a great dinner for 3,800 persons on Wednesday 2nd February 1844 in the Free Trade Hall in Manchester in 1844.[32,33] His death certificate, certified by Dr A.B.Edge MD, stated his cause of death to be senile decay.[26] At the time of his death he was living in Melbourne Cottage on Platt Lane. A small block of flats now stands on this site and Sir Harry Platt lived in one of these, close to the present Manchester Royal Infirmary. The name Platt is in this case a coincidence.

Dentist and Surgeon, Strange and Bowring; we cannot yet be sure which of these two was the Manchester first. Yet the balance of likelihood, taking into consideration the need to practice the skill thoroughly before venturing to attempt anaesthesia for a respectable lady in her own home, makes it difficult to resist the suggestion that Bowring, who claimed the first anaesthetic by a doctor in Manchester, also administered the first ether anaesthetic in Manchester. On the other hand, a doubt will always persist. Strange may, if already a dentist, have previously used nitrous oxide, in which case it would have been a natural progression for him to use ether as soon as he heard of its effects. It is a mystery why the records of this momentous event are so scanty, but though this chapter in our history may have had a strange opening could Bowring, on the ceiling in the Cathedral, yet close it with the last word?

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