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HISTORY

Sydney Ringer (1834–1910) and Alexis Hartmann (1898–1964)

J. ALFRED LEE

Summary

This article outlines the careers and the achievements of Sydney Ringer (1834–1910) and Alexis Hartmann (1898–1964), both of whom gave their names to well-known solutions for intravenous infusions.

Key words

History: Ringer, Sydney; and Hartmann, Alexis.
Intravenous infusions; Ringer's solution; Hartmann's solution (Ringer-lactate)—compound sodium lactate solution BPC.

The administration of intravenous infusions is part of the everyday activity of the anaesthetist but most are unfamiliar with the originators of the solutions they use. It is 100 years since Sydney Ringer, an outstanding nineteenth-century physician, teacher and investigator, described his fluid, and 50 years since Alexis Hartmann, the distinguished American paediatrician and chemical pathologist, wrote a series of articles drawing attention to what he considered to be a new and improved balanced salt solution. The careers of both of these men whose names are so well known are therefore of great interest to anaesthetists.

Sydney Ringer (1834–1910)

Early life

Sydney Ringer was born in Norwich in 1834, one of the three sons of John and Harriet Ringer. The father was a tradesman of strong nonconformist principles, and Sydney was brought up in an environment in which great attention was paid to hard work, sobriety and good behaviour. John Ringer died young, leaving his wife with three growing sons to bring up and support financially during the years of their education.

Medical education

It was a struggle for them all but, at the age of 20, Sydney applied for and obtained a post as apprentice to a local doctor, as was the custom at that time, as a prelude to a career in medicine.

The next stage, the entrance to a medical school, presented the problem of obtaining the necessary fees for tuition and financial support as a medical student, but with the generous help of friends and relatives this was overcome. He was enrolled at University College and its hospital in London, an institution which, until the year of Ringer's birth, had been known as the North London Hospital and where a somewhat ostentatious non-sectarian atmosphere prevailed. His association with University College Hospital (UCH) was to last throughout his career. Ringer followed the family tradition of hard work and, in 1860 he obtained the Bachelor of Medicine (MB)

J. Alfred Lee, FFARCS, FFARCSI(Hon), Honorary Consulting Anaesthetist, Southend-on-Sea Hospital, Prittlewell Chase, Westcliff-on-Sea, Essex SS0 0RY.

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degree, 2 years after the publication of John Snow's book *On Chloroform and Other Anaesthetics*[1] and the premature death of its author. The year before, in 1859, the first examination for the Membership of the Royal College of Physicians of London took place, an examination which he took himself in 1863, together with the Doctor of Medicine (MD) of the University of London. He was elected Fellow of the Royal College of Physicians of London (FRCP) in 1870.

Medical career

His career proceeded along the usual lines, and after serving as house physician he became the Hospital's resident medical officer in 1861/62, 10 years after the post had been occupied by Joseph Clover (1825–82). He broadened his experience by working for short periods of time as clinical assistant at the Brompton Hospital for Diseases of the Chest, at hospitals in Paris and at the Hospital for Sick Children in Great Ormond Street. He was elected an honorary assistant physician to the last of these institutions as well as to University College Hospital. His senior colleague, supporter and preceptor Sir William Jenner, on hearing of these appointments told him that any young consultant in London who held two hospital posts was a fool, so Ringer, taking the advice, resigned from the staff of the Children's Hospital.

He became full physician to University College Hospital in 1866, about the same time that Joseph Lister (1827–1912), a former UCH man who took his Fellowship of the Royal College of Surgeons of England (FRCS) from there in 1852, was pioneering the antiseptic treatment of wounds, as professor of surgery in Glasgow.[2]

Ringer rapidly built up a sound practice and a reputation as a scientific physician and expert diagnostician and, in due course, he was elected to the posts of professor of materia medica and therapeutics, and later of medicine and clinical medicine in the University of London. His opposite number on the surgical side during the later years of his professorship was A.E. Barker (1850–1916), the pioneer of spinal analgesia in Britain.[3]

Ringer wrote a book of popular appeal in order to further his career and to bring his name to the notice of the profession, as others did before him and have done since. This was entitled *A Handbook of Therapeutics* and it was so successful that it eventually went into 14 editions and was translated into several foreign languages.

Private life

Ringer had a quiet and rather introverted temperament but he became a successful teacher of both undergraduate and postgraduate students. He and his wife (born Ann Darley from Yorkshire) lived a placid but immensely busy life at 15 Cavendish Place, in what was becoming a fashionable district of residence for London consultants. They had little time for social activities but enjoyed attending the Sunday afternoon orchestral concerts held in the Queen's Hall in Langham Place—then, and for many years afterwards, the centre of London's musical life until it was destroyed by enemy action during the 1939–45 war. His life-style was 'early to bed and early to rise' and much of his scientific work, which he continued throughout his life, was done in the laboratories of the hospital and college in the hours between an early breakfast and the commencement of his clinical duties.

Honours, retirement and death

Ringer received many honours during his career. The greatest of these was his election to the Fellowship of the Royal Society (FRS) in 1889—an honour not unique among the staff of UCH then as now.

He retired from the staff of his hospital in 1900 and he became physician emeritus, honourably discharged from the performance of public duty, 40 years after qualifying there.

The family eventually left London for Lastingham on the North Yorkshire moors, and here he died in 1910 at the age of 75 from a cerebrovascular lesion, having been attended in his last illness by his old friends Batty Shaw and John Rose Bradford, the latter of whom was later to become President of the Royal College of Physicians of London. His obituarists wrote of him and his achievements in terms which, even for obituaries of that time, were unusually enthusiastic.[4–6]

Research

Ringer, in addition to being an outstanding physician, was one of the first scientific clinical pharmacologists, and throughout his career was engaged in physiological and pharmacological

investigations. It was said of him that, while clinical medicine was his profession and his livelihood, science was his hobby, and it is probable that his devotion to the latter prevented him from achieving the highest success as a consulting physician.

The pitch of sound. He read a paper before the Royal Society while he was still a medical student on the alterations of the pitch of sound conduction through different media. This was an early demonstration of a somewhat similar physical principle recently employed as a whistle discriminator test for nitrous oxide and oxygen, in which a whistle inserted into the expiratory port of an anaesthetic system has a characteristic pitch, depending on the gas issuing from it; a test used to prevent the wrong gas being given.[7]

The effect of electrolytes on cardiac and involuntary muscle. Ringer became interested in the actions of various inorganic salts on the behaviour of the heart and involuntary muscle early in his career.[8–11]

His curiosity concerning the effects of electrolytes on the circulation is said to have been aroused because his laboratory assistant mistakenly substituted tap water (supplied by the New River Water Co.) for distilled water in the experiments they were performing on the frog's heart, and he noticed the difference when it was injected into the circulation. His astute recognition of this difference showed his careful observation and close attention to detail.

He was able to show that the salts of sodium, potassium, calcium and chloride in definite concentrations and in precise proportions are necessary for protoplasmic activity. He demonstrated that the members of one group of electrolytes tend to produce antagonistic effects to those of another group; this phenomenon is especially illustrated in his studies of potassium and calcium.

Ringer's solution was formulated as a result of these experiments. It can for a time replace blood and provide a medium in which many tissues and organisms can function normally, so that they can be studied. He showed for the first time that inorganic salts have the greatest importance for the organism as illustrated by the fact that even minute quantities of river water are sufficient to keep fishes, which would have died very quickly in distilled water, alive for weeks.[12–14]

This work was eventually recognised to have great physiological importance, although the conclusions reached did not attract either attention or praise for 20 years after it was published. It was ahead of its time, as knowledge of diffusion and of dissociation of ions had not then found its way into biological thinking. One hundred years later, however, the solution of salts introduced by Ringer is known everywhere as Ringer's solution.

The exact constitution of Ringer's solution used now varies slightly from laboratory to laboratory and from country to country but it is essentially an isotonic solution of the chlorides of sodium, potassium and calcium and contains 8 mg of sodium chloride, 0·3 g of potassium chloride, and 0·33 g of calcium chloride in 1 litre of distilled water. Many modifications have been suggested, each with a specific purpose in mind. The Ringer–Locke solution contains sodium bicarbonate and glucose, Tyrode's solution is similar but also contains a small proportion of magnesium chloride and of the acid and sodium phosphates, and Darrow's solution consists of sodium and potassium chlorides and sodium lactate.[15] Hartmann's solution is considered below.

The effect of anaesthetics on involuntary and cardiac muscle. Ringer was one of the earliest investigators of the effects of anaesthetics on involuntary and cardiac muscle and on the circulation.[16] He was associated in this work at one time with Dudley Wilmot Buxton (1855–1931), a young colleague who later became an anaesthetist on the staff of UCH. Buxton was one of the founders of the specialty; he was President of the Society of Anaesthetists in 1907/08, and the author of a widely read textbook.[17] Ringer and Buxton showed that the vitality of involuntary muscle in the frog persists longer following ether than after chloroform.[18]

Buxton was also associated with Ringer in work which investigated the effects of electrolytes on the vitality and function of contractile tissue in fishes.[14]

Other work which produced results which later became of interest to anaesthetists dealt with the action of pilocarpine and atropine on the frog's heart,[18] and on the antagonism between pilocarpine and muscarine.[19]

Colleagues and contemporaries

Sydney Ringer, like most of us, was influenced by his seniors and in his turn guided the activities of some of his junior colleagues, a number of whom bear interesting names.

Sir William Jenner (1815–98), a fellow East Anglian, pathologist, physician and courtier, was amongst his teachers on the staff of University College Hospital who gave him encouragement and support in his early days. As a pathologist Jenner published the first description of emphysema of the lungs;[20] as a physician his description of relapsing fevers, then much more common than now, was a classic which led to the clinical separation of typhoid and typhus fevers;[21] and as a courtier he became Queen Victoria's personal doctor in succession to Sir James Clark. Jenner was also one of the team of medical men who looked after the Prince Consort in his fatal attack of typhoid fever in 1861. He came to hold considerable personal and political influence over the Queen.

John Burdon Sanderson was one of the heads of the physiology department at UCH in Ringer's time. His distinction and fame attracted the young William Osler to his department when he was in London studying for the diploma of Membership of the Royal College of Physicians of London (MRCP) in 1878. Osler attended many of Ringer's ward rounds and out-patient clinics, and mentioned in a letter that he learnt from Ringer how attractive out-patient teaching could be made. 'Ringer,' he wrote, 'I always feel missed his generation and suffered from living in advance of it.'[22] Osler succeeded Burdon Sanderson as Regius Professor of Medicine at Oxford in 1905.

William Murrell (1853–1912), a physiologist, later to achieve fame as a physician at the Westminster Hospital, collaborated with Ringer in a paper on muscarine.[19] Murrell became the first to advocate nitroglycerin as a remedy for angina pectoris.[23]

Samuel Gee (1839–1911), later to become physician to St Bartholomew's Hospital, was a pupil of Ringer's. He was the first to describe coeliac disease[24] and his name has come down to posterity on a linctus label.

The Sydney Ringer Lecture

Ringer's only surviving daughter, Mrs Kayler, endowed a biennial lecture to be given at UCH in 1912 so that her father's name should not be forgotten. The condition was that some suitable topic of research in medical science, carried out in the laboratories of the College or Hospital, was to be the subject of the lectures; among medical scientists who have been honoured as Sydney Ringer lecturers have been T.R. Elliott, William Bayliss, Thomas Lewis, Charles Harrington, Peter Medawar, Bernard Katz and C. Dent.

Alexis Frank Hartmann (1898–1964)

Alexis Hartmann was an American paediatrician and clinical biochemist who, in 1932, modified Ringer's solution by adding sodium lactate to it with the idea of combating acidosis in his young patients.

Origin and education

Alexis Frank Hartmann was born in St Louis, Missouri, in 1898, the grandson, son and father of distinguished physicians. The Hartmann family were descended from German immigrants and his mother and his wife were also of German origin. His father was a general practitioner. Alexis Hartmann chose to follow the family tradition and enrolled at the Washington University School of Medicine in St Louis. He took his MD degree there in 1921 at the age of 23.

Medical career

Hartmann was influenced as a student and marked out as a young man of outstanding ability by Philip Anderson Shaffer, the biochemist; early in his career in the hospital he was also attracted to and befriended by William McKim Marriott (1886–1936) whose original contributions to medicine, largely concerned with the biochemistry of diseases of children, were many, and who is better known to paediatricians than to anaesthetists.

Hartmann decided to devote himself to the two disciplines of clinical paediatrics and biochemistry simultaneously, similar interests to those of Sydney Ringer 50 years earlier. It was said of him that he brought the laboratory to the child's bedside. He did his internship at the St Louis Children's Hospital and spent the whole of his professional life in the hospitals of his native city.

Hartmann was given certification by the American Board of Pediatrics and joined the faculty of his *alma mater*, and soon his name and influence became widely known. He excelled as a researcher and a clinician, while his ability as a teacher is shown by the fact that over 20 of his old pupils were to become professors of paediatrics in the USA and other countries. Hartmann succeeded

as physician-in-chief to the St Louis Children's Hospital and professor of paediatrics in the University when Marriott left for the University of California in 1936.

Private life

Hartmann married a local St Louis lady, a librarian, in 1920. They had two sons, one of whom became, like his father, a professor of paediatrics. Hartmann was keenly interested in his garden and was an excellent tennis player.

Honours and early death

The Pediatric Section of the American Medical Association awarded him the first Abraham Jacobi Prize Award 'in recognition of outstanding advances in pediatrics' in 1963. He served for many years on the editorial board of the *Journal of Pediatrics* which dedicated the June 1964 issue to him as a 'festschrift'. He died of cancer, later in the same year, aged 66.

Clinical and scientific work

Hartmann became a life-long practitioner of the dualism of basic science and clinical medicine. Ninety papers were written during his active professional life, describing his work. Most of them dealt with problems of metabolism, biochemistry and such clinical paediatric subjects as infantile hypoxia, hypoglycaemia, chemotherapy and nephrosis. Of course, like most of us he sometimes got it wrong, as when he collaborated with his famous surgical colleague Evarts Graham on subtotal resection of the pancreas for hypoglycaemia, in 1934.[25] Graham was one of the founders of thoracic surgery who removed a lung in 1923[26,27] and introduced the technique of cholecystography into surgical practice.[28]

Diabetes. Hartmann was one of the earliest clinicians to use insulin in the treatment of diabetes in infants. This work was stimulated by his teacher Marriott's postgraduate sojourn in Toronto in 1922, who, on returning to St Louis, obtained an early sample of insulin and, with the biochemical help of Shaffer and the clinical help of Hartmann, saved a diabetic infant's life. This was in the same year very soon after the publication of the first paper on the use of insulin[29] which earned Banting and Macleod the Nobel Prize in 1923. Hartmann also wrote a paper with Shaffer on blood sugar estimation.[30]

Body fluids. Marriott and Hartmann were amongst the initiators of modern body fluid physiology. Their early introduction of the study of fluids into paediatrics was one of the reasons why that discipline antedated those of medicine, surgery and anaesthesia in making use of the new knowledge.

Hartmann's solution. Hartmann became the champion of the hydrogen ion and of the value of alkaline therapy in acidosis in children; this led him to advocate sodium lactate to achieve his end. He correctly saw the need for proportionately more sodium than chloride in parenteral solutions at a time when 'normal' or 'physiological' saline was usually prescribed. The three most important papers dealing with the metabolism of lactic acid were published in 1932 with M.J.C. Senn (who later became a paediatric psychiatrist) when he was 34 years old.[31–33]

Hartmann and Senn[31–33] were looking for an isotonic alkalinising solution which would enable them to maintain water and electrolyte balance with minimal distortion of the composition of the extracellular fluid. They found 1/6 molar sodium lactate solution to be isotonic and sterilisable by heat without decomposition, and they showed that the lactate was metabolised in the liver, making sodium available to combine with available anions; at the same time, by the use of the solution the amount of chloride was reduced. They described work in their papers which led them to believe that racemic sodium lactate was not only efficient for their purpose but also safe in normal children as well as in those with renal or hepatic damage.

One litre of 1/6 molar sodium lactate solution is potentially equivalent to 290 ml of 5% sodium bicarbonate in acid neutralising effect and to 600 ml of 5% dextrose in anti-ketogenic effect. The conversion of lactate normally takes up to 2 hours.

The official BP formulation of compound sodium lactate solution (Hartmann's solution) contains 131 mEq of sodium, 5 mEq of potassium, 4 mEq of calcium and 29 mEq of bicarbonate (as lactate) and 111 mEq of chloride per litre. The USP solution of lactated Ringer's solution is slightly different.

Ringer's work on parenteral fluids was ahead of its time, but the same cannot be said of Hartmann's investigations, and his advocacy of lactated Ringer's solution soon made his name internationally well known and the solution came

to be called Hartmann's solution by everyone but Hartmann himself.

It would seem that the great popularity of Hartmann's solution today as a parenteral fluid is partly due to to its advocacy by Professor Shires and his colleagues of Dallas, who have over the years influenced surgeons, and after them anaesthetists, in the treatment of various fluid and electrolyte problems and of haemorrhagic shock.[34–35] Fashions, however, change.[36–38]

Conclusion

Sydney Ringer and Alexis Hartmann were outstanding clinicians and scientific investigators of great prescience and unusual activity. They arrived at the exact constitution of their solutions only after numerous original experiments. It is important that we, who use these solutions, so painstakingly formulated, and the modifications which have been developed from them, should do so only after careful consideration of the real indications for their employment.

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