

WILLIAM MADDOCK BAYLISS'S THERAPY FOR WOUND SHOCK

by

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During World War I, military surgeons discovered that patients die from wound shock because their blood pressure falls catastrophically. William Maddock Bayliss produced experimental shock by bleeding anaesthetized cats, which lowers their blood pressure. He restored pressure by infusing salt solution containing enough gum acacia to generate the colloid osmotic pressure ordinarily contributed by the plasma proteins. Ernest Henry Starling had demonstrated that as plasma flows through the capillaries the colloid osmotic pressure of its proteins retains water. From 1917 to 1919 Bayliss and Starling served on the Special Investigation Committee on Surgical Shock and Allied Conditions of the Medical Research Committee. Both gum-saline and blood transfusions were used successfully on wound-shocked soldiers, but we do not know how many were treated, and the effectiveness of whole blood in comparison with gum-saline was not ascertained. Today the colloid osmotic pressure in transfusion solutions is usually provided by dextran or human albumin. Vast quantities are used, but Bayliss's role in the development of this clever biophysical therapy has been almost forgotten.

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wound shock; World War I

Wound shock has been a major killer for as long as men have fought. The symptoms include an ashen skin (sometimes distinctly bluish), copious sweating, rapid pulse, dilated pupils, and lethargic, withdrawn behaviour. Military surgeons had no treatment to proffer and knew that it was hopeless to operate on such patients; they were triaged and nature was allowed to take its course.

In World War I, Captain Ernest Cowell (1886–1971) was a surgeon at Casualty Clearing Station (C.C.S.) No. 23.¹ Cowell had learned how to measure human blood pressure with a cuff around the upper arm. The sphygmomanometer was rarely used at the time; most physicians merely felt the pulse to measure heart rate and to judge the strength of the pulse wave. Cowell undertook a systematic investigation, teaming up with Captain John Fraser (1885–1947) from the nearby C.C.S. No. 33.² They measured soldiers' blood pressures. In camp, systolic pressures were 110–120 mmHg, typical of healthy men in

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their age group. At the front, many men's pressures were around 140 mmHg, which is unsurprising considering the stress they were under, although some stolid countrymen retained normal pressure. The investigators even measured pressures of troops guarding isolated outposts in no man's land at night, while the enemy were roaming nearby, reading their gauges by moonlight.^{3,4} Some wounded men had still higher pressures: up to 170–180 mmHg. Others, within 20–30 minutes after being hit, showed the classic symptoms of shock and their pressures had fallen to 90 mmHg or lower. They were said to have primary shock. Another group initially showed no signs of shock, but developed the symptoms a few hours later—by then their pressures were 70–90 mmHg. This was known as secondary shock. Some shocked men recovered in time and their blood pressure returned to normal, but in others pressures continued to decline; if they fell to 50–60 mmHg the men died because their pressure was too low to drive enough blood into the coronary circulation to sustain the heart. We shall see later how the medics tried to prevent secondary shock.

WOUND-SHOCK RESEARCH IN BRITAIN

The Medical Research Committee (MRC) was founded in 1913 to administer funds collected by the National Insurance Act of 1911. It was directed by a physiologist, Walter Morley Fletcher (1873–1933).⁵ In February 1917, the *British Medical Journal* published a statement from the MRC about shock in experimental animals.⁶ It pointed out that many investigators attributed shock to a decrease in the volume of circulating blood. The article described work by Henry H. Dale (1875–1968; Nobel laureate 1936)⁷ and Patrick P. Laidlaw (1881–1940)⁸ on the shock produced by injecting histamine into anaesthetized animals. A few weeks later they published a similar article in *The Lancet* in which they also solicited ideas from clinicians.⁹ Histamine had been discovered by Dale and George Barger (1878–1939) a decade before. It causes a profound decrease in blood pressure accompanied by an increase in the fraction of the blood occupied by red blood cells, showing that plasma has been lost from the circulation.¹⁰ The remaining plasma has a normal protein concentration, so proteins are lost from the circulation along with salts and water. The article did not point out that histamine shock differs profoundly from wound shock: adrenaline counters histamine shock and enhances wound shock. It suggested that shock might be treated by replacing the missing plasma with a solution that has the viscosity of blood, because resistance to the flow of a fluid through a pipe is inversely proportional to its viscosity.¹¹ Flow in a pipe is equal to the product of pressure divided by resistance. Therefore if the flow out of the heart was unchanged, a decrease in blood viscosity, by lessening resistance, would decrease blood pressure.

Near its end the article mentioned some of Bayliss's work 'which may be valuable', without citing a reference. Almost a year before, on 25 March 1916, Bayliss had contributed a talk to the Physiological Society; his abstract was circulated before the meeting and was later published in the *Journal of Physiology*. Bayliss's presentation was on 'Viscosity and intra-venous injection of saline solutions'.¹² He reminded the meeting that after a substantial haemorrhage the low blood pressure is restored by the injection of salt solutions, but only transitorily. He suggested that the salt solution might decrease the viscosity of the blood. Therefore he injected salt solutions containing 5% gelatine or gum acacia into haemorrhaged animals (species not specified). These solutions restored blood



Figure 1. Bayliss and Fraser. (a) William M. Bayliss in his home laboratory (probably in 1890). He took the photograph himself; he was an ardent photographer.⁶² (Reproduced by courtesy of the Wellcome Library, London.) (b) Captain John Fraser (left) and Captain Walter B. Cannon (right) in 1917.⁶³ (From the Cannon Papers, Countway Library of Medicine, Boston.)

pressure and the recovery was sustained.¹³ He mentioned that gelatine or gum acacia increased viscosity but also were colloids ‘with a definite osmotic pressure’. Regardless of whether his solutions acted by viscosity or colloid osmotic pressure, Bayliss’s ‘valuable work’ suggested a biophysical treatment for wound shock. It could be tested on moribund patients, who had no other hope.

As we track the unhurried steps in the translation of idea to application, the pace will be more readily understood if we consider Bayliss himself (figure 1a). In 1917 he was 57 years old and was Professor of General Physiology at University College London (UCL). General physiologists study processes that are common to all living things; he was the author of an encyclopaedic, discursive textbook on the subject, which he ‘might almost have called an autobiography’.¹⁴ Latterly he had been investigating colloids. He also worked on mammalian physiology, often collaborating with his brother-in-law Ernest Henry Starling (1866–1927). For instance they discovered the first hormone, secretin, that is released from cells in the intestine and stimulates pancreatic secretion.¹⁵ Bayliss’s father was a Wolverhampton blacksmith who created a thriving iron works that was notable for ornamental gates. He had four wives but only one child. William inherited everything; he did science for love, not gain. He took fame as it might come. He did much of his general physiology in a laboratory built from corrugated iron in the garden of his four-acre estate on the edge of Hampstead Heath. His study was under the coachman’s flat, adjoining the stables. On Saturday afternoons the garden filled with friends and colleagues who had an open invitation for tea and tennis. His obituary for the Royal Society described him in the following terms. ‘His quiet generosity, his kindness, his self-effacing modesty and his simple goodness endeared him to all his fellow-physiologists.’¹⁶

His knowledge, though exhaustive, was never overbearing, and his genius was never frightening—probably because his mind did not work rapidly. He argued a point slowly, sometimes almost tediously, making quite sure of his ground as he went; and in many cases appreciating discrepancies in the argument which might easily be passed over by a less cautious thinker.¹⁷

A. V. Hill (1886–1977, Nobel laureate 1922), who knew Bayliss well, wrote: ‘No man more consistently esteemed others more highly than himself.’¹⁸

He seems to have made no effort to push his discovery. The lack of medical interest surely was partly due to the peculiarity of his reagents.¹⁹ Gelatin is a protein produced by treating collagen obtained from skin and bones. He could make warm 5% solutions, but they gelled as they cooled and were apt to clog his infusion cannula. Gum acacia (also called gum arabic) is a complex polymer of polysaccharides and glycoproteins. It is found in the sap of the trees *Acacia senegal* and *Acacia seyal* and is gathered by scraping hardened exudations from the bark. Most commercial supplies come from East Africa. Solutions had to be filtered to remove bits of bark caught in the gum. It has many uses, including in chewing gum, candies, water colours, the glue on postage stamps, and ink.

STARLING'S LAW OF THE HEART

In hindsight, it is easy to understand how gum-saline restores blood pressure in haemorrhaged animals. The keys are two of Starling's great discoveries, which now are known to every student of physiology but then were just entering physiologist's mindsets. The first is that the heart is a self-regulating pump, in which outflow automatically matches inflow; this is why it is so difficult to design a mechanical heart.²⁰ Starling and two co-workers worked on anaesthetized dogs.²¹ They cut all of the nerves to the heart, so the nervous system could not regulate output. They diverted the outflow from the left ventricle, except for the small fraction that enters the coronary arteries to sustain the heart muscle, into a thin rubber tube compressed by air pressure so that it mimicked the resistance to flow of the blood vessels. The blood emerging from the resistor was collected in a measuring cylinder. The blood was returned to the heart from an external reservoir whose height above the heart determined input pressure. They measured the pressures in the chambers of the heart, the volume of the ventricles, and output from the left ventricle. The pressure of the blood entering the right heart determines the volume that the relaxed ventricles reach as they fill between beats. They found that the amount of blood ejected by the contracting ventricle is directly proportional to its volume—hence the self-regulating pump.

A decrease in blood volume decreases input pressure, so there will be less ventricular filling, less output, and decreased blood pressure—as in shock.

STARLING'S PRINCIPLE

Starling also discovered the importance of the colloid osmotic pressure of the blood plasma. In the capillaries, water and salts are pushed out of the plasma because its hydrostatic pressure is higher than that of the fluid in the interstitial space. The capillary wall is a

filter that permits water and salts to pass through but retains proteins in the plasma because outflow is through extremely narrow channels between the cells. Normally the channels are too narrow for proteins to pass through. Hence the proteins retained in the plasma generate a colloid osmotic pressure, which draws fluid by osmosis out of the interstitial space into the plasma. The hydrostatic pressure declines as the blood is pushed through the capillary; in humans we now know that the mean force moving fluid out of the capillaries is 28.3 mmHg.²² The colloid osmotic force moving fluid from the interstitial space back into the blood is 28.0 mmHg. The 0.3 mmHg difference pushes water and small molecules from the blood into the interstitial fluid. In humans this outflow is about 2 ml min^{-1} . The 2 ml added to the interstitial fluid every minute drains into the narrow dead-end tubules of the lymphatic system, which also take up any escaped plasma proteins. The lymphatic branches merge stepwise—like a tree—into a large trunk. In the thorax the trunk returns the lymph into the large vein opening into the heart, the superior vena cava. A ligature that prevents lymph return kills an animal in a day. A 70 kg adult contains about 15 litres of interstitial fluid and about 3 litres of plasma.

The Starling capillary principle explains what happens when blood volume is increased by an infusion of saline. Expanded blood volume increases the output of the heart. However, the plasma is diluted and its colloid osmotic pressure is decreased, so the added fluid soon drains into the interstitial space and blood volume decreases. The increase in cardiac output is therefore transitory. The outflow into the interstitial space can be prevented by infusing fluid with the colloid osmotic pressure of plasma—hence the gelatine or gum. In his abstract, Bayliss referred to earlier work by Knowlton on the rate of urine formation.²³ Urine is formed from water and small molecules filtered out of the plasma as it passes through the tufts of capillaries in the glomeruli at the blind ends of the kidney tubules; fluid is pushed out by hydrostatic pressure but pulled back by colloid osmotic pressure. Injecting saline increases the rate of urine formation transitorily; sometimes a volume of urine equal to the fluid injected appears within 10 minutes. When Knowlton increased the colloid osmotic pressure of his injected solutions with gelatine or gum, urine formation did not increase. These solutions did not alter the rate of blood flow through the kidney, so their viscosity was unimportant. He also infused starch-saline, which increases viscosity but not colloid osmotic pressure. It acted like saline alone.²⁴

BAYLISS IN FRANCE

In July 1917 the MRC sent Bayliss to France. It was an exciting trip. Early on, he became separated from his minder and was arrested as a spy.²⁵ After liberation, he was taken to C.C.S. No. 23, where he saw Captain Cowell. Cowell surely knew Bayliss, because he had studied medicine at UCL, and Bayliss may have remembered such a bright, energetic student. C.C.Ss were outlandish locations for medical research. They were planned to accommodate 200 patients, but many had expanded to 1000 beds.²⁶ The British army was always sure that soon they would break through the German fortifications, so throughout the years of stalemate the C.C.Ss remained in tents, ready to move forwards. The wounded went first to a regimental aide post, then to an advanced aide station and from there to the C.C.S., where major surgery was done. For the seriously wounded the next step was a base hospital, which was permitted to be in a solid structure.

Next Bayliss went over to C.C.S. No. 33, where he met the commander, Colonel Cuthbert Wallace (1867–1944), Captain Fraser and Captain Walter B. Cannon (1871–1945) of the United States Army Medical Corps (USAMC) (figure 1*b*). (Bayliss and Cannon may have met in London that spring; on his way to France Cannon spent a week discussing wound shock with the MRC.)

WALTER B. CANNON

Cannon, aged 54 years, was the Higginson Professor of Physiology at the Harvard Medical School and was well known for his work on the body's reaction to emergencies.²⁷ In 1915 he published his book *Bodily changes in pain, hunger, fear and rage*.²⁸ He described in experimental animals the changes observed in warriors in the trenches: elevated blood pressure, faster pulse, dilated pupils, sweating and the rest. Similar nervous and hormonal reflexes are evoked by a decrease in blood pressure, as in wound shock. The decrease, detected by receptors on arteries and in the brain, evokes a reflex that constricts arteries and thereby raises blood pressure. The circulation is diverted away from non-essential regions such as the skin, which turns ashen or even blue. Nevertheless, cardiac output is low in shock because less blood is returning to the heart. In time, when the emergency reflex is exhausted, the arteries relax, so blood pressure begins the decline characterizing secondary shock.

Cannon was assertive, raring to go, self-confident: displaying in full measure traits many Europeans then associated with Americans. He had studied the shock literature before coming to France. If wound shock is caused by decreased blood volume, then where is the missing blood? Normally more than 60% of the blood is in the veins. Cannon thought that shock might be produced by blood stagnating in the massive veins in the abdomen. Veins are contracted by an extract of the pituitary gland. He had brought along vials of extract to test by infusing it into the abdominal cavity. While visiting Cowell at C.C.S. No. 23, he was given permission to try the extract on a shocked German with a massive chest wound.²⁹ The patient died. At autopsy, Cannon, a physician who had never practised medicine, was relieved to see that he had not pierced the intestines when he inserted a trocar for the infusion, but also saw that the abdominal veins were not engorged—not news to his hosts. They also knew that in wound shock the fraction of the blood occupied by red blood cells was increased, so plasma volume must have decreased. (This was confirmed a year later by dye dilution measurements of plasma volume, using vital red.) He would have to think again.

Undeterred, on the following day Cannon began investigations with a Van Slyke blood gas analyser, a clever device of glass and tubing for measuring the volume of gases liberated from a small sample of blood or plasma. Cannon had learned how to use the apparatus in France, and it was one of the few items of laboratory equipment available. One of the protocols was to add acid to a plasma sample and then measure the volume of CO₂ released. This quantified the concentration of HCO₃⁻ in the plasma. Cannon found that the HCO₃⁻ concentration was substantially decreased in shocked patients, which showed that their plasma must have been acidic. The lower the patient's blood pressure was, the less plasma HCO₃⁻ was present.

Cannon told Wallace and Fraser excitedly of his discovery. If acid produced shock, neutralizing the acid with NaHCO₃—bicarbonate of soda—might be the cure. There was a

frustrating wait because a lull in the fighting left them with no shock cases. Finally, as he wrote to his wife:

Well, on Monday there was a patient with a blood pressure of 64 (the normal is about 120) millimetres of mercury and in a bad state. We gave him soda, a teaspoonful every two hours and the next morning the pressure was 130. And on Wednesday a fellow came in with his whole upper arm in a pulp. Fraser said such cases usually die. At the end of the operation he had the incredibly low pressure of 50; soda was started at once and the next morning the pressure was 112.³⁰

He had equally impressive results when he infused several patients with salt solutions containing NaHCO_3 . Colonel Wallace notified Headquarters of the breakthrough.

Bayliss, Charles G. L. Wolf, a Canadian biochemist working at Cambridge, and Lieutenant Colonel T. R. Elliott (1877–1961) of the Royal Army Medical Corps (RAMC) had been sent to C.C.S. No. 33 to evaluate Cannon's data.³¹ Elliott had been a promising Cambridge physiologist but did not obtain a fellowship, so he studied medicine at UCL and became a distinguished clinician.³² The visitors examined Cannon's data. When they finished, a reassured Cannon wrote home: 'They have seen my method and found nothing at fault, and they have discussed the suggestions which I have made and come to agree with them.'³³ After returning to London, on 9 August Bayliss wrote to tell Cannon that the MRC was forming a Special Committee on Shock and Allied Conditions, and invited him to become a member.

TREATING SHOCK AT THE FRONT

While in France, Bayliss also learned what Cowell, Fraser and like-minded medics were doing to counter shock. After a few days in the trenches the men were in poor condition. Anxiety, terror, poor and limited food, scant water rations, sometimes only 300 ml a day, wet and cold—even in winter greatcoats were not allowed in the front line—all took their toll. By this time stretchers were provided with blankets to maintain the victim's body temperature without shivering, because shivering diverted precious blood flow to the muscles. Cowell designed a blanket covered with a waterproof sheet to keep the wool from saturating with muddy water. Three blankets were provided, and bearers were drilled on how to wrap their patient, like stewards on ocean liners wrapping first-class travellers on their deckchairs in winter. Shocked patients who were kept warm had a better prospect of survival. One-quarter of a grain (16.2 mg) of morphia was given by mouth; higher doses depressed respiration. Broken legs were splinted at the aide posts, no longer waiting until they reached the C.C.S. As soon as possible the wounded were given hot drinks, to help keep them warm and to replenish lost fluid. Pathetic calls for 'water' are timeless features of battlefields. The men were then conveyed by relays of carriers back to the C.C.S., whose reception area was heated even in summer and where the stretchers of chilled patients were laid on frames above heat sources. If necessary, hot water bottles were provided and the patients were fed hot food as soon as possible. Operating tables were also warmed, and by the end of the war most ambulances were heated. After Cannon's breakthrough, sodium bicarbonate was often spooned into the tea of the helpless wounded.

During the Somme battles of 1916, many wound-shocked men were infused with salt solutions. As the animal experiments predicted, there was only a transitory increase in blood pressure (figure 2a).

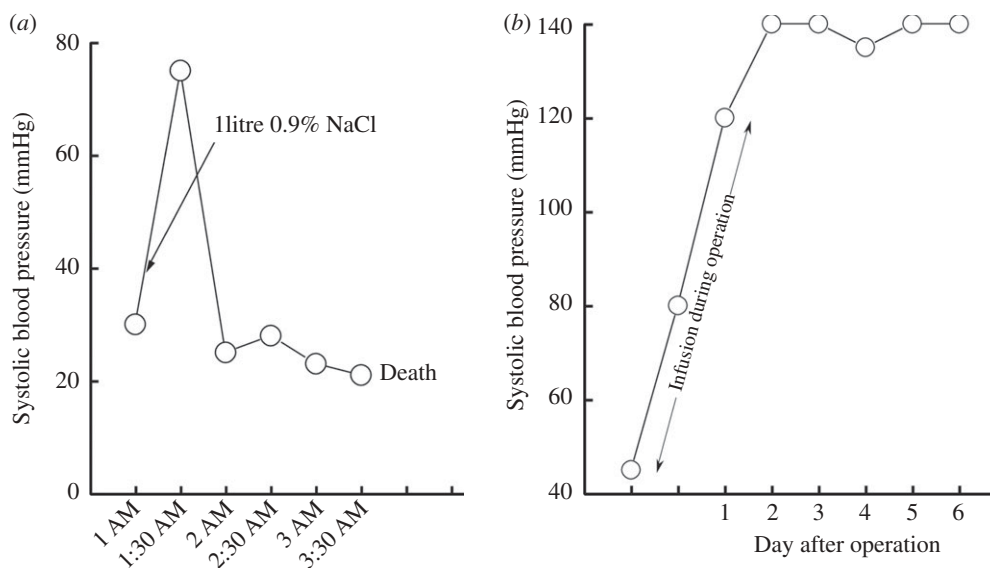


Figure 2. Blood pressure measurements by Captain Fraser and Captain Cowell. (a) Private C.M., with a severe shell wound, infused with NaCl solution. The increase in blood pressure is transitory. (b) Case 27, with an abdominal shell wound, apparently moribund on admission; during an operation to suture six intestinal perforations, 887 ml of 6% gum acacia in 0.9% NaCl was infused.⁶⁴

THE MRC SPECIAL INVESTIGATION COMMITTEE ON SURGICAL SHOCK AND ALLIED CONDITIONS

The committee first met on 17 August 1917, at the MRC offices on Buckingham Street. In the chair was Lieutenant Colonel Starling RAMC.³⁴ He had just returned to England after a year as the chemical warfare advisor to the British Army in Salonika. On the voyage home he stopped in Italy to inspect their preparations for chemical warfare.³⁵ He was about to be demobilized, having applied for a discharge on the basis that he was now over the age of 50 years. Other members present were Bayliss and Charles S. Sherrington (1857–1952, Nobel laureate 1932), Waynflete Professor of Physiology at Oxford. The secretary was Henry H. Dale, director of the MRC's Department of Biochemistry and Pharmacology. Bayliss reported on his visit to France and told them about Cannon's work. A report from Captain Fraser and Captain Cowell was circulated. They resolved to agree on a definition of wound shock at their next meeting. They decided that it should be 'a condition of circulatory failure due to deficient entry of blood into the heart'.

At the third meeting they were joined by two of Dale's collaborators, Francis A. Bainbridge (1874–1921), Professor of Physiology at St Bartholomew's Hospital and, as a guest, A. N. Richards (1876–1966), a pharmacologist from the University of Pennsylvania.³⁶ 'It was decided to ask Dr. Bayliss to resume his study of various transfusion fluids...'. Dale and his co-workers were asked to determine whether low blood pressure produces acidosis (it is now known that it does)—the converse of Cannon's hypothesis that acid produces shock. They had a letter from Captain Kenneth M. Walker (1882–1966)³⁷ reporting the investigations on shock conducted in the Third

Army. In his autobiography Walker revealed that he began to study shock as a ploy to avoid transfer to a base hospital, to remain with comrades near the front.³⁸

Seventeen days later Bayliss showed the committee his data on restoring blood pressure in anaesthetized cats with gum-saline or gum-bicarbonate. We can imagine him passing around the table tracings on smoked paper, fixed with shellac, of the blood pressures in his experiments, carefully explaining the squiggles. The Dale group reported that infusing acid did not produce shock. Colonel Wallace, from C.C.S. No. 33, attended the meeting as a new member.

The fifth meeting was fruitful. Cannon was there. Captain Walker was visiting; he had supposed that exultant wounded were predisposed to shock, but experience had convinced him that this was not so. Cannon was not so sure; he vividly described a shocked patient with a very low blood pressure who had to be held onto a stretcher. Walker agreed with Cowell that cold was a precipitating factor, and the committee decided to do animal experiments on the effects of cold. Starling and Bainbridge were investigating procedures to induce shock, and the Dale group presented their results with histamine. Dale was sure that wound shock was caused by the release of a histamine-like molecule from injured tissue and that it would be treated by a drug to block the receptor. Bayliss considered 5% gum acacia in 2.5–3% NaHCO₃ to be best and would now try to sterilize it.

The meeting on 29 November 1917 was a milestone. They learned that the infusion of 5% gum acacia in Ringer's solution had saved the lives of men in shock (figure 2*b*). Cannon argued that 2% NaHCO₃ would be much better than Ringer's. The committee agreed—it seemed a minor concession to an ally—and recommended infusing 500 ml, with a repeat after an interval if that did not suffice. At the following meeting they passed around bottles of sterilized gum-NaHCO₃ and gelatine-NaHCO₃ solutions and asked Bayliss to measure their viscosity. However, at their next meeting on 19 January 1918 they were informed that no gum solution had been dispatched to France, because the Burroughs Wellcome Company had been unable to keep gum dissolved in NaHCO₃ solution after sterilization. Dale had requested the company to produce the solutions; he had worked for them before moving to the MRC. Cannon argued that NaHCO₃ was essential, because he and Bayliss had put cats anaesthetized with urethane into shock by infusing them with 0.5 M HCl at 5.2 ml kg⁻¹—somewhat more acid than the Dale group had used.

Twenty days later Dale reported that they had infused the larger quantity of HCl used by Bayliss and Cannon into cats anaesthetized with ether. The cats did not go into shock. The committee agreed that the decisive test was to infuse acid into conscious animals, which was done the next morning at Dale's laboratory with Bayliss and Cannon also there. A local anaesthetic, cocaine, was injected into the skin of the cat's elbow. They all were good at reassuring laboratory subjects and the cat did not struggle as they exposed the vein and infused the acid. The small wound was sutured and bandaged, and the cat was set free to wander about the room. The cat breathed rapidly at first because the acid stimulated its respiratory centre, but before long it seemed quite normal. After waiting for an hour or so the scientists adjourned for lunch. They returned to measure the cat's blood pressure. It was normal for a cat: 180–190 mmHg. Dale was sure 'they were ready to throw up the sponge'.³⁹ He later gleefully recalled that in the committee: 'The free interchange of ideas and the challenging conflict of experimental findings among this group were not without dramatic and even humorous incident...'⁴⁰

The committee met next on 13 March 1918. Starling resigned the chair because of the pressure of other duties: he was scientific advisor to the Ministry of Food and was about

to go to teach the Italian Army how to train their troops to use the box respirators purchased from the British to protect their troops from poison gas.⁴¹ Bayliss was elected as his successor. The committee decided that because of the difficulties in preparing gum-NaHCO₃ solution they would settle on gum-saline and set up their own production facility. It was now 104 days since they had learned of the success with wounded men and two years after Bayliss had announced his discovery. To appreciate the consequences of the delay, on an average wartime day 1282 British soldiers were wounded, of whom 106 died.⁴² Cannon was gone; he had been ordered back to France. On 25 March the committee issued a memo recommending 6% gum acacia in 0.9% NaCl. The best gum was sold as 'Turkey elect', and the bottles used for selling sterilized milk were suitable.

Colonel Elliott and Captain Walker were at the meeting on 6 June 1918. They reported that gum-saline succeeded if given promptly after shocked men arrived at the C.C.S., but if treatment was delayed for more than 8 hours a blood transfusion was better. Naturally, the committee had been interested in treating shock with blood transfusions, and had asked Captain Oswald H. Robertson (1886–1966) USAMC for a progress report.⁴³ Robertson had been at the Rockefeller Institute before the war. Karl Landsteiner (1868–1943, Nobel laureate 1930) had made transfusions feasible by discovering the blood groups in 1901. Healing with blood seemed the safest and most natural of remedies. Canadian and American physicians brought the technique to France, where it was taken up by adventurous British counterparts. An enthusiastic report had appeared in *The Lancet* in May 1917: 'We have seen patients who were blanched and shocked and with a pulse hardly perceptible brought back to life in the most astonishing way...'.⁴⁴ It was like watching Lazarus rising. They transfused from donor's artery to recipient's vein, and described how to prevent coagulation in the connecting tube. The trials were performed on 16 moribund patients, of whom 5 survived, which was not bad when one considers, as the report stated, 'We have not considered it necessary to examine the compatibility of donor and receiver...'. They also cited two successes by Fraser, who blood-typed his donors and recipients. A year later *The Lancet* published a paper on the use of sodium citrate to chelate the Ca²⁺ in the plasma that is required for coagulation, so that blood can be collected in a bottle and then transfused.⁴⁵ This technique also let them know how much blood had been given. Then Robertson found that citrated blood could be safely stored in his refrigerator for a few days and used when needed. Walker urged them to collect blood in Britain and bank it; it would get the ball rolling if the King would donate. The RAF had agreed to fly the refrigerated blood to the C.C.Ss.

Bayliss reported on his recent experiments. Lowering body temperature did not put cats into shock but made them more vulnerable to haemorrhage. He could no longer produce shock by injecting acid; he thought that the cats used earlier may have been unhealthy to start with.

The committee spent much of their time evaluating ideas and results from correspondents, which often showed that the writers did not grasp the rationale for gum-saline. For example, Joseph Erlanger and Herbert Gasser (1874–1965 and 1888–1963, respectively; joint Nobel laureates 1944), at the Rockefeller Institute in New York, produced shock by constricting the veins returning blood to the heart. They failed to counteract it with small infusions of 25% gum acacia; the committee suggested they try a lower concentration and larger volumes—after all, the goal was to expand blood volume. One of their colleagues at the Rockefeller, Peyton Rous (1879–1970, Nobel laureate 1966), found that 7% gum acacia in saline worked.⁴⁶ Robertson spun down red blood cells and resuspended them in glucose

solution; they kept for many days in his refrigerator. But his suspension was ineffective against shock because it did not have the colloid osmotic pressure of plasma. The effectiveness of gum-saline showed that, in shock, enough red cells remain to transport all needed oxygen.

Many of their correspondents thought that shock was initiated by changes in the central nervous system, which they detected by finding degenerating neurons in various locales in the post-mortem brains of men who had died from shock. The committee argued that, like acidosis, the neurological changes were a consequence of shock.

August 1918 tried Bayliss's heart. The chief medical officer in Italy stopped gum infusions because of untoward reactions, and there were similar incidents in France. Cannon examined some of the batches giving problems and found that they were acidic, perhaps from the tapwater used to make them up. Neutralizing them solved the problem. No troubles were reported with the gum-saline produced for the MRC at the Boulogne Base Hygienic Laboratory. The committee recommended another try in Italy, using only 'Turkey elect' gum acacia. Bayliss thought that the toxic solutions had probably not been adequately sterilized.

AFTER THE WAR

Immediately after the armistice, on 15 November 1918, the RAMC convened a conference in Boulogne of surgeons and pathologists to evaluate treatments for shock and haemorrhage. Bayliss, Dale and Cannon represented the committee. Few examples of bad effects from gum-saline were reported, and none with the 4000 bottles prepared at the base. Frequently 1% or 2% gum-saline had been used ineffectually in C.C.Ss, presumably by physicians wary of the strange substance and unclear on the physiological rationale for its use. In the First Army they learned that it was prudent not to run the solution in too rapidly—it should take 15 minutes—and the solution should be at body temperature. Slower infusion permitted them to use a large-bore hypodermic needle rather than incising a vein to insert a cannula. At least 750 ml should be infused. Cowell infused patients at the front, easily done with gum-saline but difficult with blood, although he did bring up cold blood before a large raid. The other British reports were also positive, although often patients stabilized with gum-saline were later given a blood transfusion to get them out of the woods. A second gum-saline infusion was rarely tested, so the argument for the superiority of blood was weak.

The Americans had good results in July and August 1918: 200 cases were treated, with only minor side effects. They were short of prepared gum-saline, which was provided in cartons holding six bottles. The empties and cartons had to be returned before the next case was issued, and prepared solutions were available only to the advanced hospitals; the others requisitioned blocks of gum acacia and made their own.⁴⁷ But in September and October 1918 they considered stopping infusions because so many died that it seemed useless. Robertson investigated and concluded that many of the men infused were too far gone to be helped: the weather was cold and as the army pushed forward the trip to the C.C.S. was long; some wounded were on the road for 40 hours. A few transfused patients were poisoned by a bad batch of rubber tubing. From 1 July 1918 to the end the war, 66 175 Americans died of wounds.⁴⁸

The last meeting of the committee was on 24 March 1919. Starling was with them once again. They discussed the Boulogne conference with six guest surgeons and

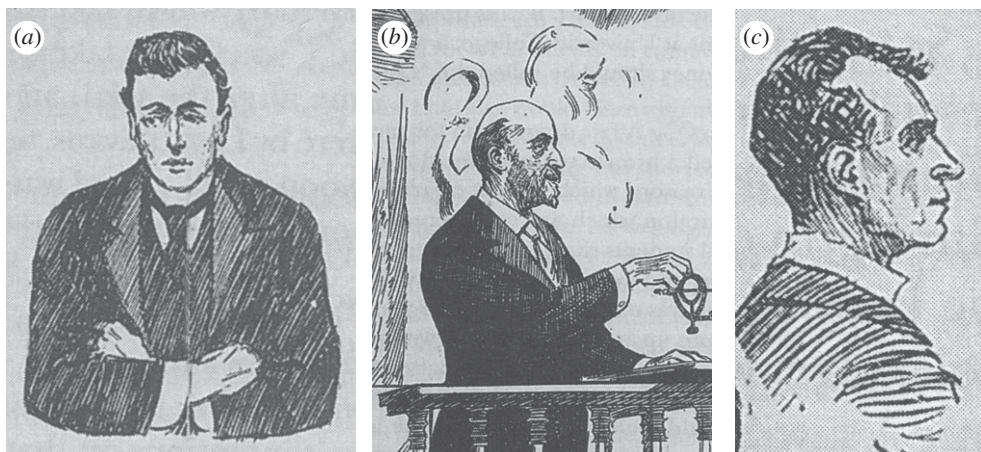


Figure 3. Physiologists in the public eye as sketched by Frank Gilbert for the *Daily Graphic* at the 'Brown Dog' trial in 1903: (a) Dale; (b) Bayliss; (c) Starling. The drawings are parts of a larger illustration, which Bayliss preserved in his files, showing the chief participants in the trial.⁶⁵

agreed that although blood was probably superior, gum-saline should be given further trials in civil practice. Understandably, but unfortunately, they did not have data on all patients transfused that noted the quantity infused, the recipient's blood pressure and the outcome.

BAYLISS IN THE LIMELIGHT

The hundreds or thousands of lives that Bayliss saved did not bring him into the public eye. He had transitory fame in 1903 after he, Starling and Dale demonstrated to the medical class the nervous control of salivary secretion in an anaesthetized small brown mongrel dog. In the audience were the joint secretaries of the Swedish Anti-Vivisection Society, one of whom was enrolled in a London medical school.⁴⁹ Weeks later the ladies told the director of the British Anti-Vivisection Society that the dog had not been properly anaesthetized. The director gave a vivid narration of their chilling account at a large public meeting; it made all of the newspapers. Bayliss asked for a retraction. This was refused, so he sued for libel. 'The Brown Dog Case' was tried before the Lord Chief Justice and was followed avidly by newspaper and periodical readers (figure 3). After four days of testimony the jury deliberated for 20 minutes and found for Bayliss, who was awarded £2000 in damages, a handsome sum that he donated to the UCL Physiology Department. If the dog had not been properly anaesthetized he would have committed a serious crime under the Vivisection Act of 1876. The notoriety did not end there. A statue of the brown dog was erected in Battersea Park. The Town Council removed it when they grew weary of protecting it from onslaughts by indignant, alcohol-fuelled medical students. The donor sued, but the judge ruled that the inscription was libellous. Bayliss's obituary for the Royal Society pointed out the irony that 'this kindest of men should have been the chosen butt of the anti-vivisection movement'.⁵⁰

AFTERWARDS

Bayliss published *Intravenous injection in wound shock*, illustrating his experiments with many blood pressure tracings and illustrating the clinical efficacy of gum with 13 brief case histories.⁵¹ He mentioned that a circular issued to German field hospitals in May 1918 stated that salt solutions, adrenaline and blood transfusions did little for patients with wound shock. The best treatment was transfusion of gum arabic in salt solution, as suggested by the physiologist Kestner from Hamburg, but caution was needed.⁵² The MRC issued a set of papers on wound shock by committee members and their consultants,⁵³ and some of the committee published their ideas elsewhere.⁵⁴ Dale gave a Harvey Lecture in New York in which he mentioned gum-saline in passing without giving the slightest indication of its biophysical logic.⁵⁵ He focused on the idea that further work would pinpoint the histamine-like molecule responsible for wound shock; this molecule has never been found.

Gum arabic transfusions were given a favourable write-up in the British official history, but without estimating how many patients were treated.⁵⁶ Nor are the numbers of blood or gum-saline transfusions recorded in the American or German medical histories.⁵⁷ Bayliss's son Leonard, another eminent physiologist, wrote that 5000 litres were provided;⁵⁸ another source gives a tenfold higher estimate.⁵⁹ Remember that solutions were also made at the C.C.Ss. It is noteworthy that the MRC committee had no exchanges about wound shock with French scientists, whereas, as we have seen, the British and Americans worked shoulder to shoulder.

Cowell became an eminent surgeon and in World War II he directed medicine in the Mediterranean theatre as a major general. Fraser became Professor of Surgery at Edinburgh, Wallace returned to St Thomas' Hospital as dean and surgeon, Elliott became Professor of Medicine at UCL, and Robertson became Professor of Medicine at the University of Chicago. Walker became a distinguished urologist and wrote more than 50 books. Over the years Bayliss, Dale, Elliott, Fletcher, Fraser, Sherrington and Wallace were knighted. Famously, Bayliss had to be persuaded not to decline to attend his investiture because it conflicted with a meeting of his beloved Physiological Society.

In 1940 Alfred Blalock published his influential *Principles of surgical care. Shock and other problems*. Bayliss is not mentioned, Starling has short shrift, and gum-saline is disparaged: 'Dr. Hugh Trout, in a personal communication, states that a number of fatalities resulted from its use in France in 1918.'⁶⁰ Blalock argued that if shock was due to a decrease in circulating blood volume, blood was the best remedy.

Gum arabic was replaced by dextran, a glucose polymer that is synthesized by certain bacteria. Changing their growth conditions alters the molecular mass of the polymer, so it can be tailored for restoring colloid osmotic pressure. Bayliss had tested dextran but had obtained no samples with a high enough molecular mass to work. Vast quantities of dextran-saline are now used in medicine, and the search continues for molecules to provide colloid osmotic pressure, including a renewed interest in gelatine. Blood transfusions reached their zenith in the decades of frequent blood drives and mammoth blood banks. Now there are far fewer blood transfusions, because the disasters produced by transfusing infected blood were followed by the realization that, even with the most careful matching of donor and recipient, blood transfusion is a transplant that triggers immunological reactions in the host. Expensive human albumin solution is used frequently and new blood substitutes are being developed. Arguments about best practice are ongoing.

It is regrettable that Bayliss's brilliant innovation has been largely forgotten. After all, as another great physiologist, A. V. Hill, perceptively put it: 'history is the cement that binds a crowd into a community'.⁶¹

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