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LISTER AS PHYSIOLOGIST[1]

IN his article on Baron Lister in the eleventh edition of the Encyclopaedia Britannica, Sir Clifford Allbutt says that Lister, appraising his own work, once stated that he had done no more than seize upon the discoveries of the great French scientist, Louis Pasteur, and apply these discoveries to surgery. The writer of the article then goes on to say, "But though Lister saw the vast importance of the discoveries of Pasteur, he saw it because he was watching on the heights; and he was watching there alone." How are we to account for the unique preparedness of Lister to lay hold of the revolutionary work of Pasteur and to apply it with such momentous effect to the treatment of surgical wounds? How had he reached those heights on which he stood watching alone?

The various biographical accounts of Lister all contain references to the early physiological work that he carried out. They make plain that he approached his surgical problems with the peculiar experimental outlook that is acquired through physiological training. In his Huxley lecture delivered in 1900 before the Medical School of Charing Cross Hospital he gives a charming review of these introductory researches, and thus outlines the influences that were brought to bear upon him at the commencement of his career:

> As a student at University College I was greatly attracted by Dr. Sharpey's lectures, which inspired me with a love of physiology that has never left me. My father, whose labours had raised the compound microscope from little better than a scientific toy to the powerful engine for investigation which it then was, had equipped me with a first-rate instrument of that kind, and I employed it with keen interest in verifying the details of histology brought before us by our great master. When I afterwards became house surgeon under Mr. Erichsen, I applied the same means of observation to pathological objects.

In other words, through physiology and physiological investigation Lister became what we should now call an experimental pathologist.

Let me digress for a moment to speak of some of his teachers. He makes mention of his father's improvements on the microscope. The father, a London wine merchant, a skilled mathematician and a world-renowned expert on optics, was a fellow of the Royal Society and known to a large circle of scientific people, biologists and astronomers. He had once col-

[1] Lister Centenary address delivered in the Moyse Hall, McGill University, Montreal, April 5, 1927.

laborated with the physician Hodgkin in microscopic examination of the red cells of the blood. Those two men together first established the real shape of the red corpuscles, and described their peculiar aggregation in rouleaux (1827).

When the son at the age of twenty-one began his medical course at University College, London, he came under the influence of some unusually able teachers. One was the professor of chemistry, Thomas Graham, whose work on colloids and on diffusion of gases has made his name so famous. The influence of Graham may be detected in many of Lister's subsequent papers. The men, however, to whom he owed most in the way of direct inspiration were Wharton Jones, professor of ophthalmic medicine and surgery, and William Sharpey, professor of physiology.

Wharton Jones, a shy, retiring and somewhat eccentric man, little known to the world at large but held in high esteem by a circle of intimate acquaintances who understood his scientific quality, devoted all the leisure that he could spare from practice to physiological inquiry, working particularly on the blood and on the circulatory system. To him, the original discoverer of amoeboid movement in the blood leucocytes, we owe an elaborate and comprehensive survey of these cells, which he classified into two main varieties, hyaline and granular, distinguishable not only by their appearance and configuration but also by their behavior on a glass slide. This work, published in 1846, *i.e.*, when Lister was a student, forms the foundation of all our subsequent knowledge of these interesting and vitally important blood elements. His researches on inflammation were the direct means of inducing Lister subsequently to pursue the subject.

Lister's chief incitement to scientific investigation came from William Sharpey, to whom his country owes a lasting debt as the outstanding exponent of the experimental method in biology at a time when England lagged far behind her continental neighbors in such inquiries. By the unwonted clarity, by the stimulating quality of his lecture-room exposition, combined with a wide knowledge of the history of the subject down to its latest continental developments, Sharpey was able to inspire his listeners with a profound and often lifelong interest in physiological science. The Germans trace the great upgrowth of physiology in their country during the middle and latter half of the nineteenth century to Johannes Müller, of Berlin. The English trace the subsequent great rise of physiology in their country directly to Sharpey. He trained the physiologists, *e.g.*, Sir Michael Foster, Sir John Burdon Sanderson, Sir Edward Sharpey-Schafer, who, by their own work, by the schools they founded and the pupils they in turn sent out, established English physiology, and (through Newell Martin, Foster's pupil, who went to Johns Hopkins) created American experimental biology. Sharpey's influence was not limited to the aspirants to a career in physiology. Men in other branches of medicine, like the surgeon Lister, even men in other walks of life altogether, were profoundly affected by his teaching. One of the proudest boasts of our own Dean Moyse, in whose honor this beautiful hall is named, was that when a student at University College he took Sharpey's lectures on physiology.

It was on Sharpey's advice that Lister, intent on the pursuit of surgery, proceeded to Edinburgh after receiving his London degree, in order to study under Syme. The story of Lister's rapid promotion there is known perhaps to most of us. What I wish to speak of this morning is the astonishingly original and important physiological work that he proceeded to carry out in Edinburgh before he was led to the final and greater discovery that has made his name live forever. When referring in his Huxley lecture of 1900 to this preliminary work, he speaks of it—not without a whimsical touch of regret—as being "probably little known to the present generation." One of the curious enigmas of scientific history is the slight attention that has hitherto been paid, even by professional physiologists, not to speak of his numerous clinical biographers, to the quality and importance of his investigations in pure physiology. Undertaken mainly in order that he might be able to speak to his students at first hand of the complicated processes involved, he had to make a strenuous effort simply to find the time for these wholly self-imposed researches. Much of the work was done with the help of his wife, in the back kitchen of the dwelling in Rutland Street in which they started housekeeping. When these early investigations, unexcelled in their experimental quality and in the depth of insight they display, have been properly appraised—and it is beyond the capacity of any one to do so in a brief memorial lecture—we shall be able to see Joseph Lister for the first time in his real greatness. Wide as was the range of these researches—they include the structure of plain muscle, the structure of nerve fibers, the flow of the lacteal fluid in the mesentery, nervous regulation of the arteries, function of the visceral nerves, inflammation, coagulation of the blood, the cutaneous pigmentary system of the frog—wide as was their range, hardly one of his conclusions requires alteration or amendment to-day. Some of his results that I might readily name still await exploitation, having remained untouched and undeveloped at the point where he then left them.

In order to give a conception of Lister's experimental power and insight, one might select at random almost any aspect of these neglected researches and, by analysis of the contribution thus chosen, demonstrate the high place he achieved for himself in that particular field. I propose to adopt this method and to take his work on blood coagulation on the simple ground that I happen to be rather familiar with all its various antecedents, with its history up to the time of Lister, and after.

The problem of blood coagulation occupies a central position in medicine. It interests not only the physiologist and the pathologist but the practising physician, the surgeon, the obstetrician, and all in equal degree. Having extensive ramifications, it is also far from being a simple problem. In reporting on the question before the Royal Society of London in 1863 Lister says: "My difficulty on the present occasion does not depend so much on the lack of materials as on the complicated relations of the subject, which makes me almost despair of being able, in the short time that can be devoted to a lecture, to give, in anything like an intelligible form, even an adequate selection of the facts at my disposal."

When Lister came to the blood coagulation problem, the outstanding point of interest in the question was, "What induces the blood to clot when it comes out of the body? What first pulls the trigger, as it were, and sets in play the chain of events by which it inevitably changes from a fluid to a solid?" You may seek an answer to this apparently simple question in any of our modern text-books of physiology. Either the issue is avoided, or, if it is handled, you will be put off with carefully guarded answers, full of caveats and qualifications. The books are so anxious to describe the complex composition of the gunpowder that they forget about the percussion cap that is necessary to touch it off. We shall see with what result Lister worked at the question—but then, as I said, Lister's contribution to the subject is forgotten.

The problem, as presented to him, had taken scientific shape some ninety years before (between 1770 and 1776) at the hands of a brilliant investigator, William Hewson, whose untimely death at the age of thirty-six was a great loss to English physiology. Let us throw our minds backwards and picture the problem as it presented itself to the medical men of Hewson's time.

The blood comes out of the vessels. It is exposed to the *air*. What more simple than to suppose that the air acts on it?

Or, if you like, it *cools down*. We know that a solution of gelatine tends to set when it cools.

Again, the blood has come to a standstill. Whipped up in the circulation and kept in constant motion, one part gliding over another, it may have no opportunity, as it were, to stiffen. It might be that the simple condition of *rest* induces coagulation.

All these hypotheses—exposure to air, cooling, rest—had by one person or another been advanced as explanations. It was the merit of Hewson, along with other fundamental work on blood coagulation, first to devise and execute definite experiments to test these several hypotheses. He showed that cooling, instead of hastening, actually retards coagulation. He rapidly froze the blood, thawed it, froze it again, thawed it; it stayed fluid. He warmed it up; it clotted. A different matter this from any solution of gelatine.

In order to test the effect of rest, Hewson ligatured veins in two places, thus bringing the intervening column of blood to a standstill. Often enough no coagulation, but the results were variable and his conclusions indefinite. On the other hand, he could get no valid evidence that mere exposure of the blood to air has the slightest effect upon it. John Hunter made this matter still more definite. He received blood directly from a vessel into a Torricellian vacuum, where it clotted with particular prompitude.

Here was a difficult impasse. As no condition that one could reasonably think of seemed to be the cause, the London surgeon, Sir Astley Cooper, then made a new suggestion: "What if blood, wheresoever it be, has a natural tendency to clot? The impulse to coagulation may not be communicated by any external influence. It may be inherent in the blood, being constantly held in check by the vital action of the vessels." Cooper, as you see, simply inverted the issue. On his supposition there was no need to search for any new condition that acts upon the extravasated blood. What we require to explain—if the matter be susceptible of explanation at all—is not so much the fact of coagulation as the process by which the vessels succeed in keeping the blood fluid.

Sir Astley Cooper carried out no experiments. He merely promulgated a new idea. However, a young graduate who had studied under Cooper, by name Turner Thackrah, decided to take up the whole question afresh. Thackrah's important connection with the problem, like that of Lister, is little known to writers on blood coagulation. He was stimulated partly by his interest in the subject, partly by the fact that a valuable prize, the Sir Astley Cooper Prize, had been offered for the best essay on the subject of blood coagulation. In his consulting room at Leeds, where he had set up in practice, Thackrah worked away at his chosen problem. Fighting against tuberculosis, he died at the age of twenty-eight, but not before he had won the prize and left a memoir on blood coagulation which reveals that he was an experimentalist of a very high order. After his work there could be no question of air, rest or cooling as causes of coagulation. In the end he was driven, one can see doubtfully and with no fervor of conviction, to the provisional conclusion that Astley Cooper's hypothesis best fitted the conflicting facts. Thackrah's essay was published in 1819.

In 1857 the subject set for the Astley Cooper Prize was again that of blood coagulation. Two essays were sent in, one by Dr. Richardson (later Sir Benjamin Ward Richardson, of public health fame), the other by Ernst von Brücke, professor of physiology in Vienna. The committee awarded the prize to Richardson, who advanced a new conception, viz., that the blood is kept fluid by a slight content of ammonia, the escape of which, when the blood is shed, allows the onset of coagulation. A somewhat analogous idea, involving, however, the gas carbon dioxide instead of ammonia, had been previously advocated with some apparent experimental support by Sir Charles Scudamore.

Brücke took his stand on Thackrah's work, which he greatly amplified and extended. In speaking of Thackrah's essay he says: "Surely no essay was ever more deserving of a prize." The final conclusion of Brücke, again hesitant, but adopted because he could see no other reasonable way out, was purposely phrased almost in Thackrah's own words: "The influence of the living heart and vessels is the source of the blood's fluidity, and its loss the cause of coagulation." Brücke's experimental findings, widely published and also incorporated in his own text-book of physiology, subsequently exercised much influence in Austria and in Germany.

At this stage, during the excitement of the Astley Cooper award, which caused rather an unusual flurry, enter Joseph Lister. He had read and studied Hewson and John Hunter: he had read Sir Charles Scudamore, Richardson and also Brücke. His first experiments were directed to an examination of Richardson's work, and it was some time before he was able to shake himself quite free of the ammonia theory. As usual, when he had to set aside an alluring and highly circumstantial hypothesis, he did so only after piling up overwhelming evidence against it. In order to preclude all escape of ammonia, a rubber tube, filled with a succession of short segments of glass tube, is looped and tied into a vein. The blood courses through. All the little glass sections are then separately ligated and the tube is removed. Confined in this way the blood clots just as quickly as when exposed to the air. Again, coagulation is known to be promoted when the blood is stirred with a rod. The stirring, according to Richardson, gives better opportunity for escape of ammonia. By means of an ingenious and complicated piece of apparatus Lister arranges to collect blood and to stir it without any possibility of ammonia escape. The mere stirring is found to accelerate coagulation. But I should weary you with those experiments on the ammonia hypothesis. Lister took much more than an hour to read his own paper. I have to be more brief.

Let us stop for a moment to picture him at work. As first assistant to Syme and later as full professor of surgery in Glasgow, he is subject to sudden call at any hour of the day or night. He has his own private patients. He has his lectures to prepare, constant infirmary duties, engagements of various kinds to keep. He must have gone from place to place, his mind constantly preoccupied with the particular research on hand; and we must also keep in mind the mere quantity of first-class physiological work that he turned out. The marvel is that he could find time to test his fructifying schemes and ideas. Fortunately, the slaughter-house is not far away. The veterinary college, where horses are killed, is also within easy walking distance. He goes to the slaughter-house, makes friends with the butchers. Sheep are being killed. He ties ligatures round their limbs, so as to cause venous congestion, and when the trotters are removed, he gathers them in his bag and hurries off to the back kitchen, where his wife has things ready for him. Or he learns that a horse is to be killed at the veterinary college. He goes there and secures the jugular veins filled with blood. Those who knew Lister tell us that his whole life was one endless succession of experiments. When later his attention was concentrated more upon wounds and upon dressings, he devoted infinite trouble to the selection of the best materials, trying and discarding scores of different things until he got the very best. He constantly went about with dressings and bandages on his own person. It may be news to some of the students of this audience that the introduction of all our routine surgical dressings—lint, gauze, absorbent wool, domet bandages, not to speak of the absorbable catgut to which he devoted so many years of patient labor—is due entirely to Lister's ceaseless experimentation.

Having disposed of the ammonia hypothesis, Lister next turned his attention to Brücke's conclusion that the influence of the living heart and vessels is the cause of the blood's fluidity. He set himself to devise some method of withdrawing it from this influence and, if possible, still keeping it fluid. The blood in the ligated vein of a horse stays fluid. Suspend the ligated vein, open it carefully and look down. The blood remains unchanged. Thanks to the work of the German physiologist, Henle, Lister knew that all the vessels have an inner lining of extremely delicate flattened cells, which we now call endothelium. It might be possible to make cups of these large veins, and pour the blood from one to another through the air. He makes wire frames, sews the outer wall of the vein to these frames, turns down the top edge like a lip, and pours. In this passage through the air the blood is temporarily removed from the vital influence of the vessel—and he may go on pouring, alternately from one to the other—yet the blood does not clot. The evidence is still not conclusive, for the removal has been only temporary. The visceral cavity of the frog, with which blood does not ordinarily come in contact, is however lined with endothelium. He anesthetizes a frog, which is laid on its back; he opens the abdomen, pins the wall upwards and outwards, and makes a snip into the heart. The blood wells out into the endothelium-lined cavity. It does not clot. The same blood, pipetted out of the abdomen into a glass tube, coagulates. Plainly the issue narrows itself down to some difference between such a material as glass and endothelium.

Whenever coagulation had occurred one and the same condition had always been present. The blood had touched some foreign material.[2] He dips a solid rod into the fluid blood contained in an open vein. A crust of clot forms around the rod. He pushes needles into the veins of his sheep trotters; around the needle the blood coagulates, but not elsewhere. To make a long story short—and I can only refer you to his original paper for the wealth of detail and the ingenious variation of experiment by which he drives home the evidence—the cause of coagulation is neither more nor less than contact of the blood with extraneous foreign matter. The more effective the means taken to secure this contact, as by agitation or stirring, the more rapidly it clots. Here was some extraordinary influence, hard to explain on a physical basis, indubitably exerted by a mere touch with particular kinds of material. What this influence was he could only surmise. His training under Thomas Graham suggested some process of a catalytic nature. On the other hand, the absence of coagulation in the uninjured vessel shows merely that the endothelium is curiously and wholly neutral with regard to the process. It exerts no vital influence.

His next step was to demonstrate that the cells of the blood are implicated in the process, for in the absence of blood cells he could show that contact with foreign matter is powerless to cause coagulation. But at this critical and important stage he had to lay the matter aside. When he did return to it for a brief period in his later life, he proved that the influence which suffices to determine solid coagulation of the blood outside the body fails to act in the same way upon the circulating blood. The circulatory system contains some mechanism for protection against accidental intravascular coagulation. But I must not pursue the subsequent history of this fascinating subject. My object is to give some conception, however inadequate, of Lister's originality and amazing turn for experiment, in illustration of which I might equally well have selected almost any other of the physiological subjects that he handled at this commencing period of his career. Every touch of his work indicates the master hand.

Those of you who have visited Edinburgh may perhaps have wandered into the Library Hall of the old Arts Building of the university. There, close beside the octagonal table that Napoleon used at St. Helena, is another oblong table surmounted by a glass case containing the various distinctions and decorations that were eventually showered upon Lister by the world at large. Here are his medals; here the different orders conferred upon him by his own and by foreign countries; and here the beautiful casket that was presented to him when he was awarded the freedom of his native city of London. When at the end of his career he came to look back over the scenes of his struggles and of his hard-won victories, Lister decided that Edinburgh should be the repository of these unique tributes. There, under Syme, he had had his first full introduction to surgery; there he had courted and married Agnes Syme, the devoted companion of all his vicissitudes; there he had renounced his Quaker connection and joined the Church of England; from the University of Edinburgh had come William Sharpey and Wharton Jones, his London teachers; above all it was in Edinburgh that he had realized himself and learned to trust his own powers; there, experiencing all the alternating joy and disappointment, all the strong excitement of intensely interesting yet highly difficult scientific investigation, he had climbed those heights from which, without hesitation and with immediate comprehension he was in his turn to signal the beacon light that suddenly shone across from France. It is into his early struggles that a man puts, if not his best, at least his most significant effort; and just as Sir William Osler, looking back over his nomadic and meteoric career in three countries, decides that his ashes and his library, to the making of which he had devoted a lifetime, shall find a repository in McGill, where he had polished the weapons that carried him to his later triumphs, so did Lister feel that the scene of his scientific self-realization should retain those proud

[2] This suggestion, first mooted by Thackrah, had been more elaborately handled by Brücke, who finally, but not without qualification, discarded it.

insignia of homage that the nations had vied with each other in conferring upon him.

As time goes on, we shall come more and more to recognize in Lister an experimental genius of the first order. His trouble was that, being in every instance years in advance of his time, among men of lesser mould he was apt to be misunderstood. He had no gift of brilliant exposition by which he could rivet the attention of an indifferent public, and, with his innate modesty of nature, he had to rely for his ultimate vindication simply upon strenuous application to the work of his choice. The young assistants who loyally banded themselves around him, perceiving his merit, his sterling honesty to fact and the astonishing success of his methods, could guess at but could scarcely analyze his mental processes. They called him "a great thinker." They saw the outward Lister; they could not quite see what Wordsworth calls "the very pulse of the machine." There was, however, one experienced eye that had followed Lister's career from stage to stage with unabating interest. There was one man who could appreciate and closely follow every single experimental step he took. That was Sharpey. It was to Sharpey that the eager young student had first come with his microscope, seeking to examine for himself the structures of which the teacher spoke. It was Sharpey who had encouraged, advised and stood by him from the beginning, and before this inspiring and trusted counsellor died in 1880, he had the quiet satisfaction of knowing that his brilliant pupil had made what would probably prove to be one of the world's greatest discoveries.

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CHANNELS, VALLEYS AND INTERMONT DETRITAL PLAINS

AN article in the March number of the *American Journal of Science* by O. F. Evans on the "Origin of Certain Stream Valleys . . ." describes a common type of valley in the interior-plains region as having "a broad flood plain with a deep narrow trench winding through it." Is not this "trench" simply the river channel, filled to overflowing at time of flood, and occupied only by a dwindling, channel-bed stream during the rest of the year? In arid regions the prevailingly empty river channels, the beds of which are either dry or are followed only by the small flow of their low-water streams, contrast strongly with the well-filled river channels of humid regions, where a relatively constant flow covers all the channel bed and rises well on the channel banks. The most striking case of the arid-region kind that I have seen is in the interior of South Africa, where a channel over 100 feet in width at the rim and perhaps 30 or 40 feet in depth had, at the dry-season time of my visit, every appearance of a young valley, new-cut in a plain in consequence of river juvenation by uplift or otherwise, so deep was the channel bed below the surface of the plain and so small was the trickling stream that ran along the bed. Yet residents there assured me that, at time of great floods, the little stream expands until it fills the whole valley-like channel and overflows on the plain in which the channel is incised. Such a channel is truly trench-like; but it is nothing more than a channel after all. Its impressively large dimensions result simply enough from the great difference in volume of its river in low-water and in flood stages. Hence, unless the typical valleys described in the above-cited article are peculiar in some unspecified respect, it seems undesirable to adopt a new name, like trench, for their river channels. It would be unnecessarily redundant to have two names for one thing.

It is, on the other hand, true that we seem sometimes to have only one name for two geographical things, and there the poverty of our language in respect to appropriate names for the two features is embarrassing. For example, those lop-sided ridges which mark the outcrop of gently inclined, hard formations between more worn-down, weaker formations were long without any one-word name, until Hill of Texas introduced the Spanish word "cuesta" to designate them. They had previously been unsatisfactorily called "escarpments" by British geographers, who thus gave to the whole form the same name that is applied to one of its parts; namely, to the steep outcrop face of the determining hard formation, in contrast to the arched upland of the crest and the long and gentle declivity of the back slope. Cuesta is now coming to be more and more generally accepted as the technical, generic name for such forms.

But the poverty of our geographical terminology is sometimes rather apparent than real. Such is the case when a single name is used for two unlike features, although separate names are really available for them. Thus it is to-day customary in the Great Basin province to call the broad intermont detrital areas "valleys," as if the simple name, "plains," were not applicable to them and as if the equally simple name, "valleys," were not already fully enough employed in designating linear depressions, excavated under the guidance of streams or rivers, which are, like rivers, arranged in systems, with twig joining branch and branch joining trunk in down-grade suc-