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THE SECOND BAYLISS–STARLING MEMORIAL LECTURE

SOME ASPECTS OF THEIR SEPARATE AND COMBINED RESEARCH INTERESTS

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Delivered on 25 March 1966 at University College London

The invitation extended to me by the Physiological Society to deliver the second Bayliss–Starling Memorial Lecture is a singular honour and one I greatly appreciate. But my appreciation is tinged with misgivings for I am deeply conscious that to do justice to the memories of two such remarkable personalities is beyond my powers. I hope, however, to present certain aspects of their lives and works that may interest you.

My early memories of Bayliss and Starling cover the years 1919 to 1923 when Starling was replenishing his staff after the First World War, and when physiologists from abroad were once more able to visit his laboratory. In 1919 Bayliss was 59 and Starling 53 years old, and this year is the centenary of Starling's birth.

I came to work under Starling purely by chance. I had written to the Professor of Physiology at St Bartholomew's Hospital applying for the vacant post of Assistant in his Department. The Professor at that time was Professor Bainbridge. He replied, in addition to rejecting my application, on not unreasonable grounds, that he had mentioned my interest in clinical electrocardiography to Professor Starling who wished to carry out work on the electrical activity of the heart in the heart–lung preparation. Professor Starling was prepared to offer me the post of Sharpey Scholar; would I write to him and give him an answer? This indeed was manna in the wilderness. I wrote immediately, accepting.

Meeting Starling for the first time was an exciting experience. His enthusiasm readily put young people at their ease. At the interview he ranged over a wide field of cardiovascular problems, both physiological and clinical, and said he wanted me amongst other things to join him once a week in attending Sir John Rose Bradford's ward round at University College Hospital, so that we could keep our knowledge of clinical medicine up-to-date. Rose Bradford at that time was the senior Physician. Thirty-five years previously he had worked with Bayliss at University College on the electrical changes accompanying secretion. We attended Rose Brad-

ford's ward rounds on three or four occasions only; after that we fell by the wayside as the call of the laboratory was too strong. Starling appointed me an Assistant in the Department at a salary of £200 per annum with annual increments of £50. This had the advantage of being a permanent post but I regret having missed being on the Sharpey Scholar roll of honour.

Bayliss seemed to be the universal provider of knowledge of problems that arose in the laboratory. His charm and kindness were proverbial. I was fortunate to be his assistant in the General Physiology Class. In conversation his approach to a problem was interesting. He would skate about the perimeter of existing knowledge in ever-decreasing circles until he had reached, as far as was possible, the centre or core of the problem. In this way he was an excellent teacher, and his hearers picked up an enormous amount of collateral information. He always wore his brown overall, which had seen better days, in the laboratory, and as long as I knew him it did not seem to change. I imagine therefore that the memo to be found in one of his notebooks which runs 'Overalls, 35 inches, price 4*s*. 3*d*., post free' supplied by a firm in Newcastle, was a reminder in the event of an emergency which never emerged.

Starling spent a good deal of his time in his office but guided and took part in most of the research activities which included cardiovascular studies, the secretion of urine, and mechanisms of pancreatic secretion. A surgical operation in June 1920 and the convalescent period which followed kept him away for some time but he was back in the laboratory in January 1921. On the 21st of that month the Staff and their wives celebrated his return by entertaining him to dinner at the Comedy Restaurant in Panton Street. Starling seemed like his former self. It was a great occasion, seven courses at dinner, potentiated by appropriate libations (Pl. 1).

The personalities of Bayliss and Starling have been illuminated by those who grew up with them in the world of physiology; more especially by Charles Martin, Starling's life-long friend, by Charles Sherrington and Joseph Barcroft. The Bayliss–Starling partnership was described by Barcroft as an 'alliance of two men of complementary genius'. Perhaps the most penetrating assessment of the characters of Bayliss and Starling respectively came from Sherrington when he wrote 'a resolute but placid enthusiasm of the one met a high tension and impetuous enthusiasm of the other'. Their way of life was vividly narrated by Lovatt Evans in the First Bayliss–Starling Memorial Lecture he delivered 3 years ago. Little more can be said except to add that their friendliness, generosity and humour kindled a great flame of loyalty in all those who worked for them.

Particular mention should be made of the revealing biography of

Bayliss by his son, Leonard. Physiology has suffered a grievous loss by Leonard's death. To me he was a loyal friend and colleague, as he must have been to many of you here. In the course of years he became very like his father in mannerisms and in outlook, and he also achieved a similar encyclopaedic knowledge. I regard it as one of my greatest privileges to have learnt so much from both father and son.

By 1919, all the pre-war non-professorial staff had dispersed with the exception of Ruth Skelton. Early new appointments were D. T. Harris and the ill-fated Jack Drummond who was made Reader in Physiological Chemistry, and 3 years later appointed to the newly created Chair of Biochemistry at University College. In the four years preceding 1923 G. V. Anrep, Henrietta Bainbridge, Katherine Coward and E. B. Verney joined the staff. G. P. Crowden and Grace Palmer (Mrs Leonard Bayliss) were among a number of Demonstrators.

The visiting research workers included B. P. Bapkin, who with Anrep was on a second visit to the laboratory, S. de Boer from Amsterdam, Helene Conet, J. F. Donegan, N. B. Dreyer, K. Shellshear and a Japanese physiologist, R. Shoji. W. E. L. Brown, C. N. H. Long, H. Lupton and A. S. Parkes arrived towards the end of 1923.

The atmosphere of the Department was light-hearted. There was a feeling that a new era of intellectual freedom had arrived following 'the war which was to end all wars'. We arrived at 9 a.m., lunched in the old Refectory, had tea in the room on the mezzanine floor around Sharpey's table as in pre-war days, and left between 5 and 6 p.m. Some of us stayed to work during the night, especially those using galvanometers, because the electrical installation of the Department left much to be desired. During the day violent galvanometer deflexions of unknown origin would suddenly appear. Overloading of the electrical installation, leaks to earth, and even the starting of the trains in the Underground were all suspect. Whatever the reason, the Department late at night was free from these hazards.

I would like now to go back to the earlier days of Bayliss and Starling and trace how their separate research activities interdigitated with what may be called their 'combined operations'. In Table 1 Bayliss's academic life-line is shown on the left and Starling's on the right. Their combined operations in research, starting in 1890, follows the double line in the centre of the table. The initials in square brackets in the centre indicate the holders of the Jodrell Chair. John Burdon-Sanderson who had occupied the Chair since 1874 when he moved to Oxford to become Waynfleete Professor of Physiology was succeeded by Sharpey-Schafer. In 1890 Schafer took the Chair of Physiology at Edinburgh University and Starling, moving from Guy's Hospital, became Jodrell Professor.

TABLE 1. The academic life-lines of Bayliss and Starling showing their separate (left- and right-hand columns) and combined researches (centre column) up to 1905, mainly carried out at University College London. The enclosures within the broken lines show the years spent by Bayliss at Oxford and Starling's career at King's College School and Guy's Hospital (see text).

J. B-S, E. S-S and E.H.S. denote John Burdon-Sanderson, Edward Sharpey-Schafer and Ernest Henry Starling respectively, holders of the Jodrell Chair; (a), attendance as guests of the Physiological Society; (el), elected as a member of the Society; R.S. = Royal Society; R.C.P., Royal College of Physicians; R.C.S., Royal College of Surgeons

	W. M. BAYLISS, b. 1860		E. H. STARLING, b. 1866	
1880	Univ. Coll. London		King's Coll. School	1880
1881	|	[J. B-S.]	|	1881
1882	B.Sc.		Guy's Hospital	1882
1883	Electrical changes of			1883
1884	secretory glands	[E. S-S.]		1884
1885	(a) Wadham Coll.			1885
1886	Oxford			1886
1887	|		Dem. Physiology	1887
1888	(a) |		Lect. M.B.	1888
1889	|			(a) 1889
1890	(el) |		M.D.	(el) 1890
1891	|	E.M.F. mammalian heart.		1891
1892	Depressor nerve	Heart innervation.		1892
1893	B.v. innervation;	Intravascular pressure	Lymph production	1893
	vascular reflexes.	changes at various sites.	Absorption of body fluids.	
to	Salivary glands.	Innervation, movements	Arris and Gale Lectures	to
	Intracranial pressure and	of intestines.	(R.C.S.)	
1899	cerebral circulation	Portal vein innervation		1899
1899	|	[E.H.S.]	Glomerular functions of kidney	1899
1900	Vasodilator fibres in posterior roots. Vascular reflexes.			1900
1901	Antidromic v.d. fibres. B.v. autoregulation			1901
1902	|	Mechanisms of pancreatic		1902
	Proteolytic activities	secretion.		
to	of pancreatic juice	Chemical regulation of the secretory process (Croonian		to
1904		Lecture, R.S.)		1904
1905		Enterokinase and trypsin	Chemical correlation of the functions of the body. (Croonian Lectures R.C.P.)	1905

Bayliss's first researches at University College were with John Rose Bradford on the electrical phenomena accompanying the processes of secretion of the salivary glands, and of the skin of the frog, toad, newt and salamander. He then followed his old chief to Oxford taking up residence in Wadham College. After 3 years he obtained a 1st class in Physiology. He then returned to University College as a Demonstrator in Physiology. The broken lines (Table 1) indicate the period of Bayliss's intellectual diversion to Oxford. Leonard Bayliss recalls that his father when at Wadham was affectionately known as 'father Bayliss' partly perhaps

because he was already wearing a beard (he never, in fact shaved during his life) and partly because he was a little older than most undergraduates.

Over the same period of time Starling had passed from King's College School to Guy's Hospital. His meteoric career was marked by a number of academic prizes, two exhibitions and several medals. He became a Demonstrator in Physiology at Guy's in the same year, 1887, as Bayliss became a Demonstrator at University College. The year 1890 was remarkable for several reasons. Both Bayliss and Starling were elected members of the Physiological Society, they started work together at University College whilst Starling was still at Guy's, and Starling took his M.D., and also published his first paper, in collaboration with Gowland Hopkins, entitled 'Note on the urine in a case of phosphorous poisoning.' There is no direct evidence that Bayliss and Starling met before 1890, although according to Schafer's History of the Society each had twice attended Society meetings as guests before 1890, but on separate occasions. Schafer, however, does not always record guests at the meetings.

Bayliss and Starling's first joint investigations were published in 1891 and 1892, on the electrical activity and nervous control of the mammalian heart. During the following 7 years or so they studied intravascular pressure changes following mechanical interference with the circulation at various sites. Whilst these joint researches were going on, mostly at University College, Bayliss was investigating the depressor nerve and vascular reflexes, whilst Starling at Guy's was working on lymph production and absorption of body fluids. Towards the end of this period (1898–99) they joined forces once more in a study on the nature of the control of intestinal movements by the autonomic nervous system. Whilst this was in progress Starling left Guy's to become Jodrell Professor. Their discovery of secretin and the evolution of the concept of the chemical regulation of the secretory process came later. The story, epitomized in a joint Croonian Lecture delivered before the Royal Society in 1904, was the peak of their combined operations. Some of their cardiovascular studies I shall refer to later in more detail.

There is much of interest of these early days in Bayliss's notebooks in the Thane Library. I am indebted to Mr Marmoy, the Librarian, for making these available. They record Bayliss's wide interests in biology, chemistry and physics. There are entries relating to a wide diversity of subjects such as photographic developers, photo-electric cells, fluorescent screens, Marconi transmitters, anaesthetics for earthworms and so forth. There is also a photograph of his room at Wadham (Pl. 2) on the back of which is written 'My room at Wadham, Autotype Sepia, Dirth Transfer'. The photograph was no doubt taken by himself as he was a skilled photographer.

The first 10 years or so of the Bayliss–Starling partnership were devoted

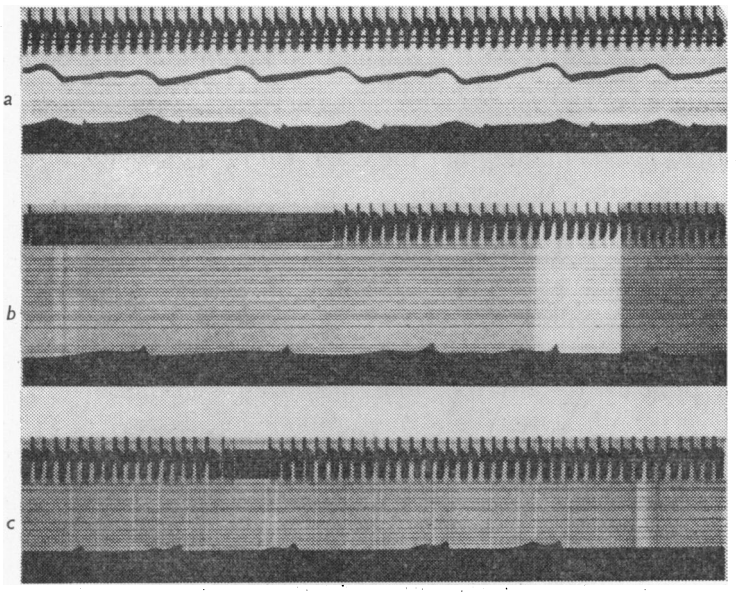
to cardiovascular studies. It is these studies and those of Starling, carried out much later on the heart–lung preparation, that I wish to mention in more detail. When they first started their first research together on the electrical activity of the mammalian heart, the direction of the excitation wave in the ventricles was in doubt. They used direct leads from the dog's heart, and recorded e.m.f. changes with a capillary electrometer.

They made four important observations: the first that contrary to previous views the base of the mammalian heart becomes negative before the apex, and that the direction of the wave could be reversed by respiring the animal with cold air; this was an important experimental detail; the second that the excitatory state of the base outlasts that of the apex; and the third that the previously observed tetanic nature of cardiac contraction, claimed by others, was an artifact due to the shaking of their apparatus; finally, and perhaps their most important observation, that the delay between auricular and ventricular contraction was of the order of 0·15 sec. They comment that this delay, coupled with the fact that transmission across the *a–v* junction is possible in either direction, points to a direct muscular continuity between auricles and ventricles. This prophecy was made two years before Stanley Kent (1892) published his discovery of the specialized tissue running through the auriculo-ventricular fibrous ring.

Waller was the first to record an electrocardiogram of the human heart. His records gave no certain indication of the direction of the excitation wave in the ventricles. Bayliss and Starling set to work to clarify the problem. For this purpose they visited Burdon-Sanderson's laboratory in Oxford, where a more sensitive electrometer was available and also an electric arc, so that a greater magnification was possible than with the lime-light that they used at University College. They again found that the base of the heart becomes negative before the apex (Text-fig. 1). In the same year Bayliss and Starling showed that stimulation of the cardio-sympathetic nerves caused positive chrono- and inotropic effects both on the auricles and on the ventricles. Vagal stimulation produced opposite effects except that it was not possible to demonstrate any direct inotropic effect on the ventricles.

More or less concurrently with these cardiac studies Starling, already interested in the relationship between capillary pressure and the processes of secretion and transudation, was joined by Bayliss to examine the problem more closely. They measured the arterial, systemic-venous and portal-venous pressures under a great variety of experimental conditions. They concluded it was fallacious to argue, as had been done hitherto, that a fall in arterial pressure necessarily implied a fall of pressure in all the capillary areas of the body. They drew attention to the importance of venous pressure in determining capillary pressures, and adumbrated the

role of capacity vessels in haemodynamics. Starling, armed with this knowledge, continued his studies at Guy's on lymph formation and fluid exchanges in the body. These culminated in the measurement of the osmotic pressure of serum proteins, and the concept that at any given moment there is a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids. These studies laid the foundation for present-day views as to the relative actions of the vasomotor system in controlling fluid exchange and excretion of electrolytes. It seemed an inevitable step that Starling whose



Text-fig. 1. (Taken from Bayliss & Starling, 1892*a*). Electrocardiograms recorded by a capillary electrometer of (*a*) E. H. Starling, (*b*) W. M. Bayliss and (*c*) a morphinized dog. To be read from right to left. The top and bottom tracings in (*a*), (*b*) and (*c*) are $\frac{1}{10}$th sec marker and the e.c.g. respectively. The middle tracing in (*a*) is the carotid pulse.

mind was still occupied with clinical problems, should attempt to weld these laboratory findings into a scheme which would explain the processes involved in chronic cardiac failure associated with dropsy. His masterly expositions in six Arris and Gale Lectures (1896, 1897) on this subject still remain the centre around which discussions abound. Starling's last paper published from Guy's concerned the glomerular function of the kidney. Some 20 years later he returned to studies of renal function in collaboration with E. B. Verney.

Immediately after his return to University College from Oxford, Bayliss

started a series of investigations on vascular reflexes, which were to continue over the next 10 years, although he and Starling worked together over that same period. He showed that depressor nerve stimulation reflexly dilated the blood vessels of the head and neck as well as those of the skin and muscles. Previously the vasodilator response was thought to be confined to the region supplied by the splanchnic nerves. He then investigated the nature of the vasodilator response in the limbs following dorsal-root nerve stimulation. He noted that the responses lasted several minutes and were easily obtained by mechanical, thermal and chemical stimulation of the nerves. He showed that the fibres concerned were afferent, and named them antidromic fibres. In his 1901 paper Bayliss considered four possibilities as to the nature of the response to antidromic fibre stimulation. The first, that impulses reached muscle spindles and set up changes, chemical or other, which somehow affected the blood vessels. He discarded this view on finding that the chief seat of the vasodilatation was in the skin. The second, that an axon-reflex of the Langley-type was involved. This he regarded as unlikely because of the long latent period between the start of stimulation and the beginning of the response. The third, that if sensory and motor fibres end in a common periarterial plexus, it may happen that antidromic impulses may spread in the plexus, and so excite the motor fibres. The fourth, which to his mind presented the fewest inherent difficulties, that the same nerve-terminations in the vascular muscle serve both sensory and motor function. Today, the commonly accepted view is one, which Bayliss originally discarded, but in later years accepted, namely that an axon-reflex is involved. It seems now possible that the antidromic vasodilatation may be due to the liberation of a chemical substance in the tissues, possibly ATP.

Bayliss also studied the reaction of blood vessels to alterations in their internal pressure. He was the first to show in denervated limbs that a passive distension of the blood vessels leads to their active constriction, and a passive collapse to their active relaxation. These effects are now regarded as taking part in the auto-regulation of blood flow. At a recent symposium on the subject the variability of results obtained on different vascular territories was stressed. Hypotheses presented to explain the underlying processes concerned included the influence of metabolites, a local reflex, and perivascular pressure changes due to variations in the amount of transudate from adjacent capillaries. Recent experiments on isolated vessels suggested that the resting length, the rate of stretch, and the electrolyte and catecholamine content of the surrounding fluid determined the response. In summarizing some forty papers presented at the symposium the chairman dryly remarked that the question as to 'how' autoregulation came about had generated the most heat.

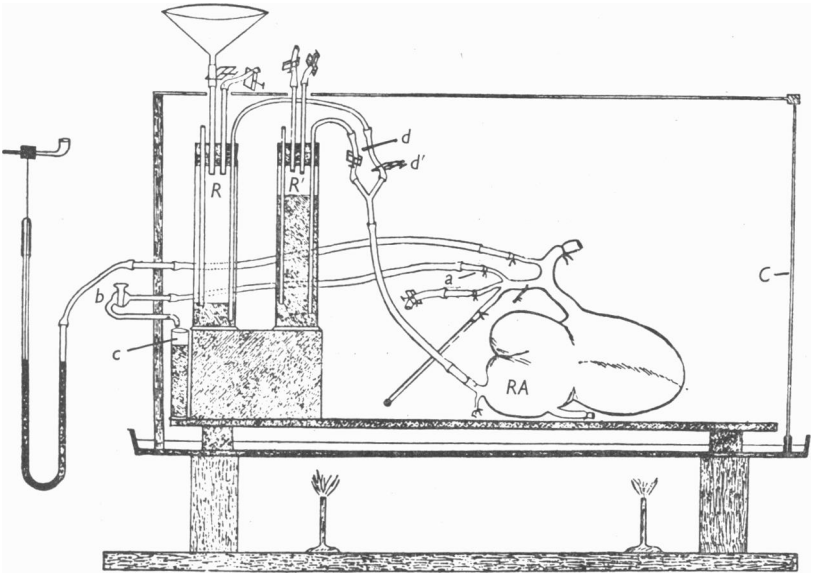
After their work on pancreatic secretion Bayliss & Starling's research interests diverged, and Bayliss devoted himself largely to the study of enzyme action and to writing. By 1915 it might be supposed his scientific reputation could reach no higher. In that year the full realization of his knowledge and scientific achievements burst upon the scientific world when he published his monumental book—*Principles of General Physiology*, dedicated to Starling, his fellow worker. There was only one criticism if it might be so-called. There appeared in *The Times Literary Supplement* a comment which today faintly echoes throughout the academic world. It ran 'Latin, for better for worse, is no longer current among men of science, or Professor Bayliss would have called this mighty book "*Principia Physiologica*". As Starling wrote later, the book 'not only treats of the science, but it is at the same time a revelation of the personality of the writer... and is indeed the history of a mind and its achievements'.

In 1910 Starling once more returned to problems of cardiac function. He recognized the urgency for a more complete understanding of cardiac regulation in the absence of nervous and humoral influences, and started experiments with the heart–lung preparation. In that year C. Lovatt Evans (Pl. 3) became the Sharpey Scholar; he was to take a major part in the investigations. He later demonstrated a parallel between cardiac work and cardiac volume, and also a parallel between O_2 usage of the heart and cardiac volume. He also found that for any given increase in the work of the heart more O_2 was used by raising the aortic pressure at a constant cardiac output than by raising the output at a constant aortic pressure. All these results have been confirmed.

It is interesting to trace the history of heart–lung preparations. In 1881 Newell Martin, at Johns Hopkins University, made the first mammalian heart–lung preparation. This is diagrammatically represented in Text-fig. 2. The whole animal (cat or dog) was placed in a large warm chamber (*C*). Only the heart of the animal is shown in the diagram. Two 700 c.c. constant pressure blood reservoirs (*R*, R^1) alternatively supplied the right atrium (*RA*) via the superior vena cava. The peripheral output of the left ventricle passed via a cannulated aortic branch (*a*) and stopcock resistance (*b*) to a graduated cylinder (*c*) for measurement of the peripheral flow. The aortic pressure was measured by a mercury manometer. As the blood from one reservoir emptied into the heart the blood collected in the cylinder was transferred by hand to the other reservoir, which when full was switched over, by manipulation of the clamps (*d*, d^1), to supply the heart in place of the first reservoir.

Considering the complexity of the manipulations required it was a remarkable achievement to get the animal switched over from the natural to the artificial circulation. The apparatus, however, had limitations for

the measurement of cardiac performance. A uniform series of consecutive observations with large flows were limited by the time required for changing over the venous reservoirs. Moreover, 2 l. of calves defibrinated blood were necessary to start off the experiment. Again, the control of the systemic resistance by means of an adjustable stop-cock was unsatisfactory. Nevertheless, Newell Martin and, later, Howell & Donaldson made important observations. They found that the heart rate, which increased with the temperature of the blood, depended more on the temperature of the coronary blood than that of the right atrium or right

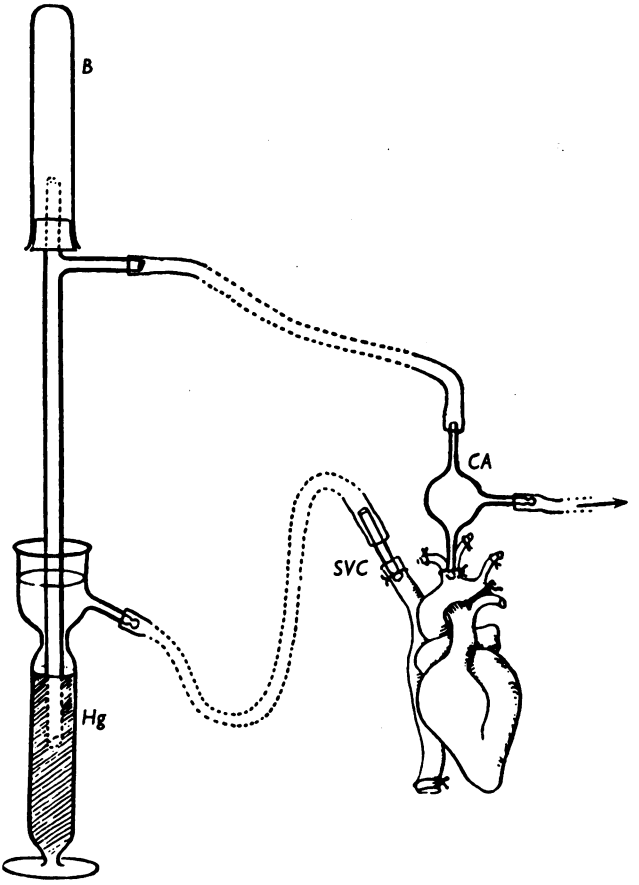


Text-fig. 2. Heart–lung preparation (taken from Martin, 1881). The various parts of the apparatus are lettered in great detail in the original diagram. A short description is given in the text. *C*, warm chamber; *R*, R^1, reservoirs alternatively delivering blood at a constant pressure to the right atrium (*RA*); *a*, aortic branch connexion carrying peripheral blood flow via stopcock resistance (*b*) to graduated cylinder (*c*); *d*, d^1, clamps for changing blood inflow from one reservoir to the other.

ventricle and was not dependent upon variations in flow or in aortic pressure. It was also shown within limits that the left ventricle could overcome a resistance to systemic outflow, and that raising the venous pressure increased the peripheral outflow.

Some 25 years later Jerusalem & Starling attempted to make a more workable heart–lung preparation on cats (Text-fig. 3). It too was not regarded as very successful because the mercury column resistance they used in the systemic circuit for adjusting the arterial pressure proved unsatisfactory. They made, however, considerable advances in the tech-

nique in other directions. A smaller volume of homologous blood was required and there was a continuous flow of blood through the external circuit into a single reservoir and thence back to the heart. The total heart output was measured by a cardiometer.

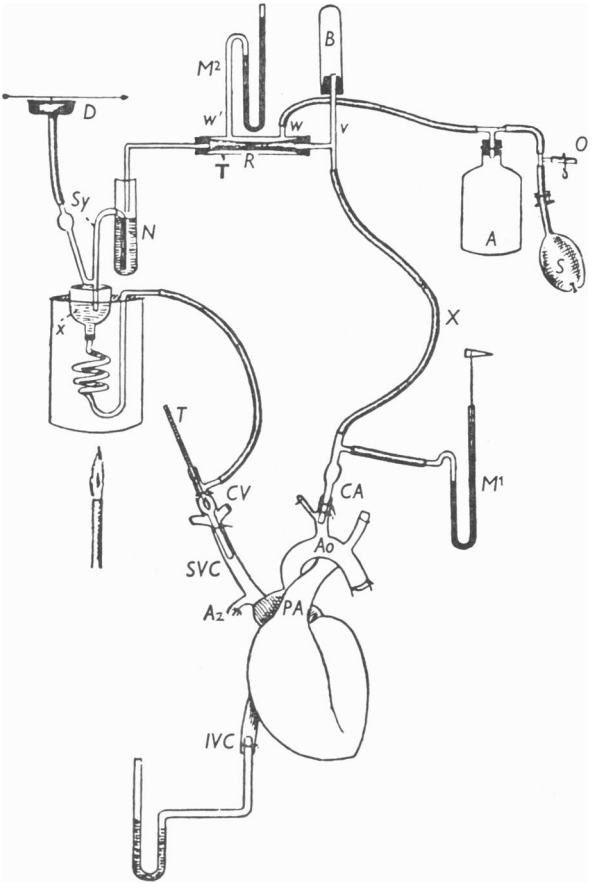


Text-fig. 3. Heart–lung preparation of Jerusalem & Starling (1910). *B*, bottle partly filled with air serving as an elastic resistance; *CA*, arterial cannula; *Hg*, resistance to peripheral blood adjustable by the depth of tube in the mercury: the blood bubbles up through the mercury to fill the wider tube portion to the outflow tube and thence to the superior vena cava (*SVC*).

The next important advance was made 2 years later when Knowlton & Starling replaced the mercury resistance by a thin-walled rubber tube through which the arterial blood flowed. Means were provided for varying its resistance to flow by adjusting the air pressure on its outer surface—the well-known 'Starling resistance' (Text-fig. 4). A further refinement was

the measurement of coronary blood flow by Markwalder & Starling and by Lovatt Evans & Starling.

Finally, Patterson and Starling fitted much wider bore tubing throughout the circuit in order to diminish the resistance to blood flow exerted by the viscosity of the blood. In this way they were able to obtain much

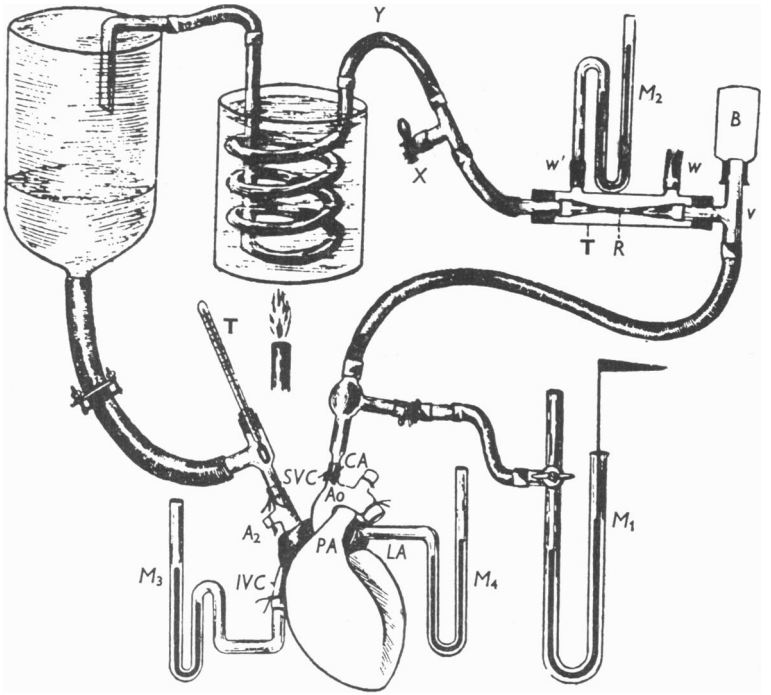


Text-fig. 4. Heart–lung preparation (Knowlton & Starling, 1912). *Ao*, aorta; *Az*, azygos vein; *B*, elastic resistance; *CA*, arterial cannula; *CV*, cannula with thermometer (*T*), inserted into the superior vena cava (*SVC*); *IVC*, inferior vena cava; M^1, M^2, mercury manometers; (*N*, *Sy*, *D*, siphon system recording peripheral outflow); *PA*, pulmonary artery; *R*, finger-stall resistance within glass tube **T**; *S*, pressure bulb connected with pressure bottle (*A*) for adjusting pressure bulb connected with pressure bottle (*A*) for adjusting pressure within **T**.

higher cardiac outputs than previously. They further improved the potentialities of the preparation by using optical methods for simultaneously recording the left ventricular pressure together with the left atrial pressure

or cardiac volume. The familiar diagram shown in Text-fig. 5 is included as a reminder that in some experiments the left atrial pressure was recorded; this is sometimes forgotten.

In Patterson & Starling's studies on the mechanical factors which determine the output of the ventricles they concluded that so long as the functional condition of the heart remains constant, stroke volume varies directly with diastolic filling. They also found that at inflow rates which keep pace with ventricular relaxation the venous pressure undergoes very



Text-fig. 5. Heart–lung preparation (Patterson & Starling, 1914). M_3, M_4, water manometers the upper ends of which are connected to piston recorders. *LA*, left atrium. For the meaning of other abbreviations see Fig. 4.

little change. When, however, the inflow exceeds the rate at which it can keep pace with ventricular relaxation the venous pressure rises and exerts an active distending effect on the ventricular walls and so further quickens the rate of their cavities. Attention was then concentrated upon the problem as to whether the initial tension within the ventricle or the initial length of its fibres determined the energy evolved at each contraction. In this connexion they recall that in Frank's experiments on the frog's heart the initial length was proportioned to the initial tension, so that the augmentation of energy set free on contraction might have been due either

to the increased tension or to the increased length. In the heart–lung preparation they recorded simultaneously, left intraventricular pressure and cardiac volume changes in response to an increase in venous inflow, or in systemic arterial resistance, and found that the only factor which constantly varies with the response of the ventricles is the volume of the heart, i.e. the length of the muscle fibres. They found no constant connexion between the diastolic tension and the succeeding contraction, though as a rule these two quantities will be altered together. These experimental results were the justification for the formulation of Starling's 'law of the heart'—that the energy of contraction is a function of the length of the muscle fibres. In these investigations they recognized that changes in venous pressure must not be taken as implying corresponding changes in ventricular diastolic pressure.

They were particularly impressed with their observation that the ventricular pressure rises more rapidly when the arterial pressure is high than when it is low. This phenomenon is associated with a more rapid state of reduction of systolic volume which they were inclined to ascribe to a more rapid setting up of tensile stress in the contracting muscle fibre. They state that still more important as regards the mechanical effect of the ventricular contraction in driving blood into the aorta was their finding that an increase in arterial resistance prolongs the duration of contractile stress of the heart, i.e. the duration of the excitatory state.

Several observations were made in Starling's laboratory on the nature and conditions governing cardiac 'tone' which has special interest in relation to present-day conceptions of cardiac muscle 'contractility'. Starling used the term cardiac 'tone' to denote the energy set free per unit length of muscle fibre. Knowlton & Starling had observed that a sudden rise in aortic pressure leads to an increase in the volume of the heart, followed after a short time by a partial recovery towards its initial volume. This late increase in 'tone' was attributed to an improved coronary circulation. This interpretation is now known only to relate to a heart in which the coronary blood flow is deficient. Their alternative suggestion that the increase in ventricular tension due to the aortic pressure rise might improve cardiac performance is more in line with views held at the present time. Anrep, at Starling's suggestion, examined the problem more closely. He found that the late increase in ventricular 'tone' following an aortic pressure rise was accompanied by a diminution in systolic and diastolic volumes of the heart, an effect which was potentiated by the administration of adrenaline or by splanchnic nerve stimulation. By further experiments he showed that, in the presence of adrenaline, an imposed fall in aortic pressure caused first a decrease then an increase in the volume of the heart. Anrep made the interesting comment that the

heart tends to maintain its volume constant, but that the power of the heart to react in this way to changes in arterial resistance is dependent upon adrenaline as a constituent of the circulating blood or of the heart muscle itself.

It is as well to remember that Starling and his school obtained their results with recording instruments having distinct limitations. With the exception of the optical manometers used by Patterson, Piper and Starling, the available instruments were mercury and water manometers, a cardiometer and piston recorders. Today there are transducers galore for measuring pressures, blood flows, volume changes and movements in various parts of the body. Sensing probes of various types are inserted in every available orifice, natural or hand-made, to gather the required information. Cardiac volume changes are calculated from the results obtained by X-ray techniques for delineating the outline of the heart in two planes, or the outline of a ventricular chamber by the injection of a radio-opaque substance. There are various electronic devices for measuring in the beating heart, changes in its circumference, in the internal diameter of a ventricle, and in the length of a myocardial segment. With all these new skills and techniques the simultaneous measurement and recording of a large number of parameters has become possible, some of which can be simultaneously integrated or differentiated with the aid of computers, thus ensuring much saving of time. Of equal importance has been the information about the conditions governing cardiac performance gained from experiments on isolated cardiac papillary muscle preparations, on the isolated heart continually perfused with blood from a living donor, and on the heart *in situ* in which the volume inflow and output resistance are under separate control.

The term 'tone', as used by Starling, in relation to cardiac muscle has largely been replaced by the term 'contractility' which has a somewhat different meaning. It has been defined in terms of the relationship between ventricular end-diastolic pressure (or fibre length) and external stroke power. Thus, when from any given length of fibre the ventricle produces more external stroke work and more external stroke power (calculated as stroke work per systolic second), an increase in 'contractility' is said to have taken place. Defined in this way 'contractility' is increased by the infusion of noradrenaline and other catecholamines, sympathetic nerve stimulation and a sustained increase in heart rate. In each case the rate of rise of intraventricular tension is increased and therefore the stroke power is increased.

Another view expressed is based upon the finding that at any given left ventricular end-diastolic pressure (or initial length of fibre) stroke work is largely determined by the height of the blood pressure (after-load) whereas

stroke volume is relatively unaffected by the blood pressure. Thus stroke work can only be a reliable index of 'contractility' if the blood pressure is regarded as a determinant of 'contractility'. For this reason it has been suggested that 'contractility' is preferably described by the relation of stroke volume to left ventricular end-diastolic pressure.

Studies on cardiac papillary muscle strips have been largely influenced by A. V. Hill's work on the force–velocity of skeletal muscle. The tension–length curve of these strips resembles that obtained from a frog's gastrocnemius, and a force–velocity curve of the usual type is found, but unlike skeletal muscle, cardiac muscle possesses the ability to alter its maximal velocity of shortening. The maximal velocity of shortening is stated to be independent of changes in length in preload and in afterload but is increased by noradrenaline, by a raised frequency of contraction and by increasing the calcium content of the fluid in which it is immersed. The increase in maximal velocity of shortening is regarded as best defining 'contractility'. There is strong evidence that the fibres of the intact beating heart have characteristics similar to those of papillary strips. Thus A. V. Hill's speculation of 10 years ago that the heart may be able to change its intrinsic speed according to conditions and may become intrinsically quicker when the frequency of its beat rises is fully justified.

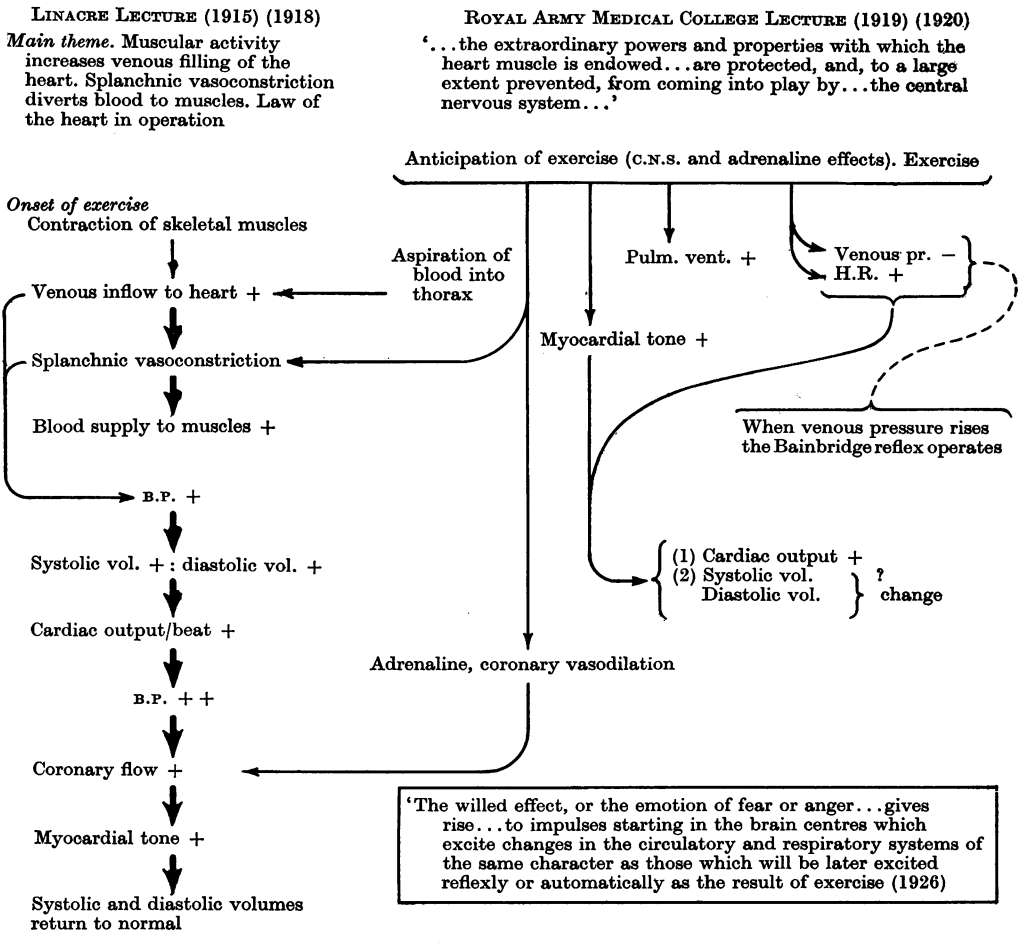
Apart from the power stroke of the cardiac engine the filling or suction stroke has been examined. It has been found that its efficiency depends upon the pressure gradient from the large veins to the right auricle, upon the booster effect of auricular contraction, upon the elastic recoil of the ventricles which lowers intraventricular pressure, and upon the mechanical impedance to relaxation which is diminished by an increase in the rate of diastolic filling and by noradrenaline.

Some comment should be made on Starling's views of the circulatory changes associated with exercise in man because they have not been fully recognized. They were epitomized in two lectures, the oft-quoted Linacre Lecture delivered in 1915, and a lecture, little known until quite recently, which he gave at the Royal Army Medical College 4 years later. In this last lecture he made it clear that he had modified his views. We owe a great debt to Dr Carleton B. Chapman who, last year, was responsible, together with Dr Jere H. Mitchell, for the reprinting in book form of Starling's more important publications on the heart, including both these lectures.

In the early Linacre Lecture, entitled 'The Law of the Heart', the successive train of events occurring during exercise which Starling described may be condensed into a few sentences. Splanchnic vasoconstriction is responsible for diverting blood to the muscles, which by their pumping action increase the venous inflow to the heart. The ensuing increase in

diastolic volume of the heart enables the heart to put out as much blood as it receives at a higher systemic arterial pressure. The increase in cardiac work was then said to give rise to metabolites which, furthered by the

TABLE 2. Scheme of Starling's views on the circulatory changes associated with exercise expounded in his Linacre Lecture in 1915 (published in 1918), and as modified in his lecture at the Royal Army Medical College delivered in 1919 (published in 1920); see text



arterial pressure rise, then increased myocardial 'tone', and 'the heart gradually returns to its normal volume even though it is doing increased work' (see Table 2). In this lecture Starling was concentrating attention on intrinsic mechanisms of the heart governing cardiac adaptations. He merely mentions that the heart is subject to the control of the central nervous system by means of its inhibitor and augmentor nerves, and that

it may send messages to the nervous system which will affect the blood vessels in other parts of the body.

In his later lecture at the Royal Army Medical College, Starling adopts the synthetic approach. First of all he describes, as in his Linacre Lecture, the reactions to exercise, of a heart depending only on its self-governing mechanisms. He then considers the effects of a reflex control of the heart superimposed on these mechanisms. These come into play when, as a result of the steady increase in diastolic inflow due to increasing muscular activity, the heart just fills the pericardium. At this stage the pressure on the venous side of the heart increases and gives rise to the Bainbridge reflex. The heart quickens and the venous pressure falls. With increasing inflow this reflex acceleration progresses until the heart is beating at maximum stroke volume and at maximum rate. He then superimposes upon this background the effect of adrenaline release into the circulation in causing a further acceleration of the heart, an augmentation in the energy available at each beat, and a diminution in both systolic and diastolic volumes.

Finally, Starling points out that these reflex mechanisms can take place in an animal deprived of its cerebral cortex, and that 'On top of these, we must imagine the cortex... taking charge of, initiating and controlling the reflex mechanisms', and that 'The part played by the higher centres... involves changes in the heart, respiration and circulation, anticipatory of, and of a similar character to those which will be excited by the muscular activity itself' (Table 2). These are the views which he re-states in the 4th edition of his *Principles of Human Physiology* published in 1926, 1 year before his death. Perhaps the most telling and graphic passage in the RAMC lecture relates to the significance which Starling placed upon the work from his own laboratory. He wrote: 'The extraordinary powers with which the heart muscle is endowed represent but the central fortress of the system, and under normal conditions are protected, and, to a large extent, prevented from coming into play by the activities of the defending positions and outposts provided by the central nervous system and its servants. It is only when these other defences fail that the heart is called upon to display those reactions which are at once brought to light in our study of the isolated organ'.

When it is remembered that Starling delivered this lecture nearly 50 years ago, it was a remarkable imaginative forecast of many of the present-day conceptions of the integrating mechanisms brought into play by exercise.

In this lecture I have only covered a very limited field of Bayliss and Starling's research activities. I end with the thought that in the course of time, here in this latter-day scientific home of these two great masters, all aspects of their scientific achievements and ideas upon which so much has

been built, will be analysed and criticized, as surely they themselves would have wished. But this is not all, for we must also reflect that their lives were enriched by an almost life-long friendship, by a close family association, and by the affectionate regard of all those who had the good fortune to work for them. What greater destiny can man desire?

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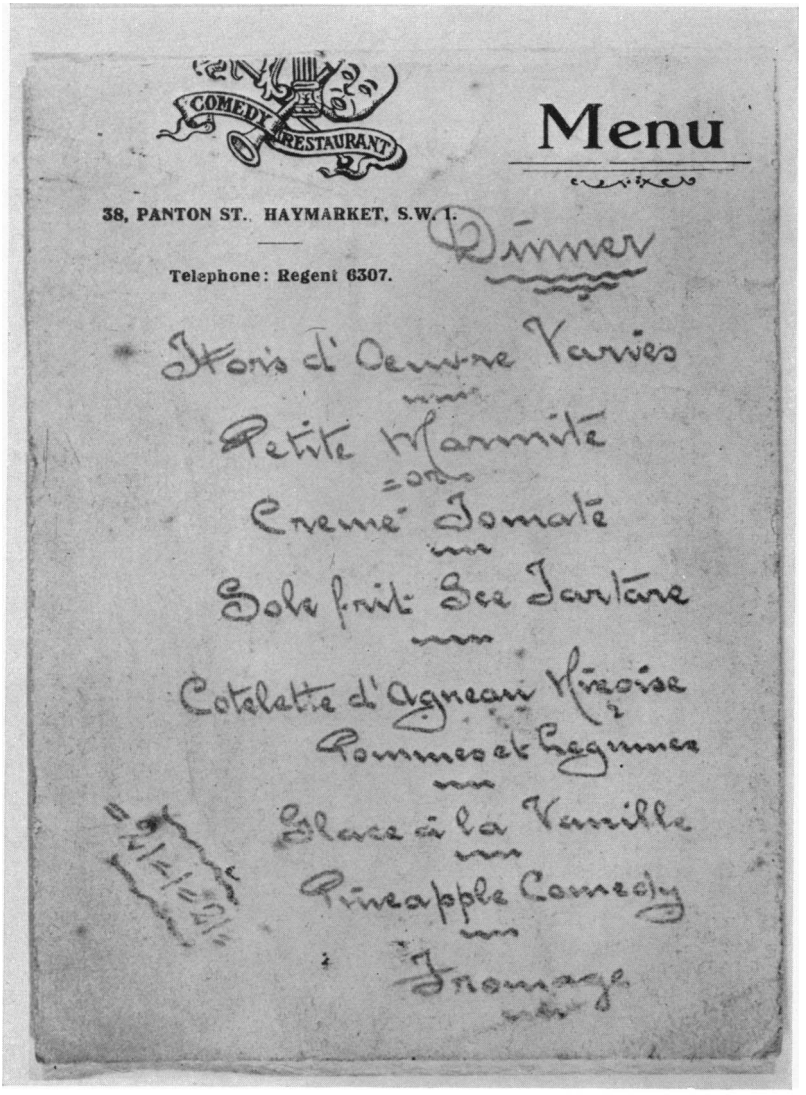
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Telephone: Regent 6307.
Dinner
Hors d'Oeuvre Varies
Petite Marmite
ou
Creme Domate
Sole frite Sce Tartare
Cotelette d'Agneau Maroise
Pommes et Legumes
Glace a la Vanille
Pineapple Comedy
Fromage

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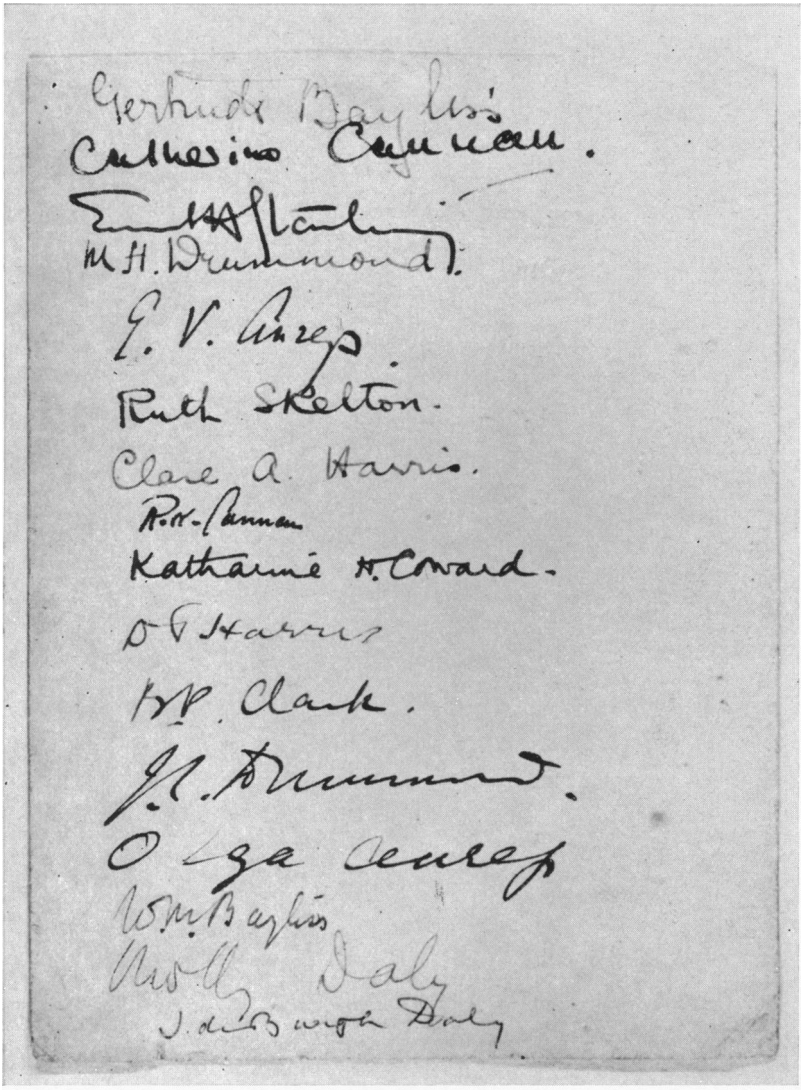
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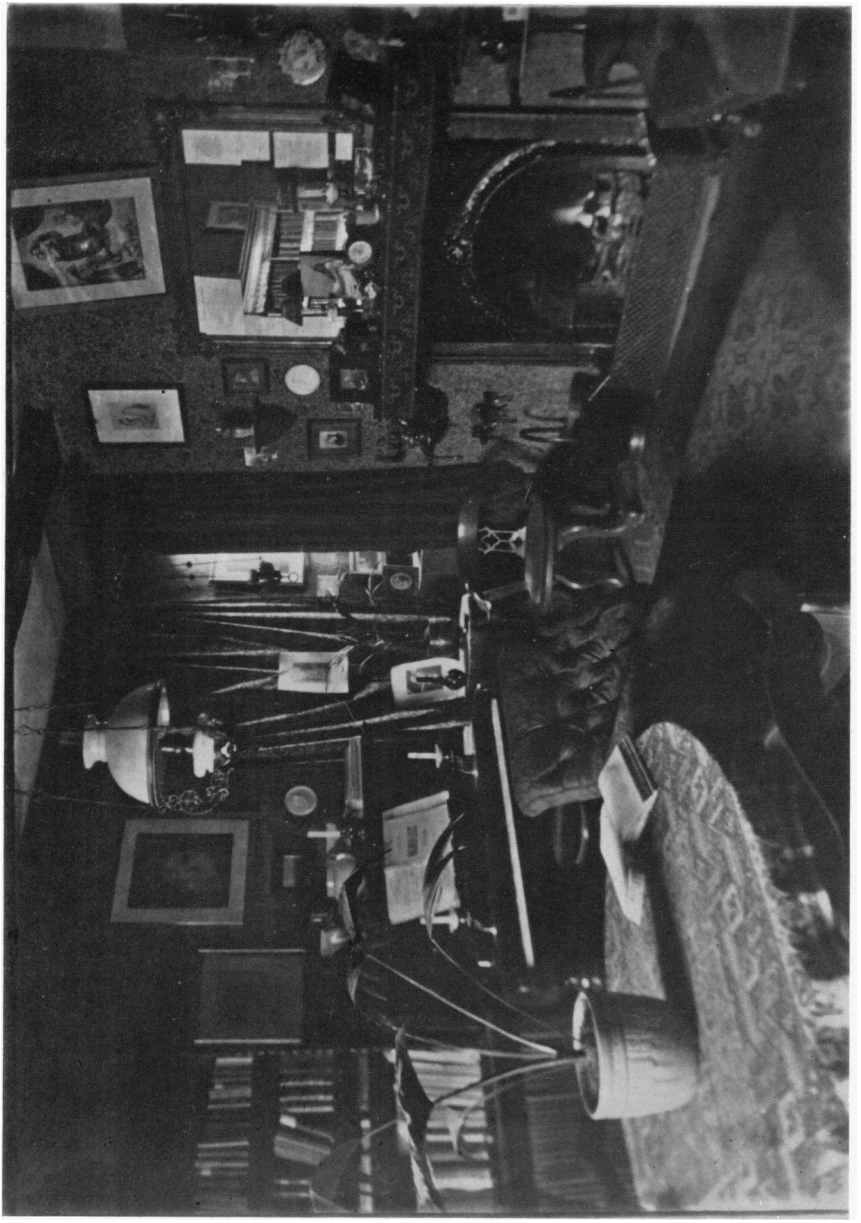
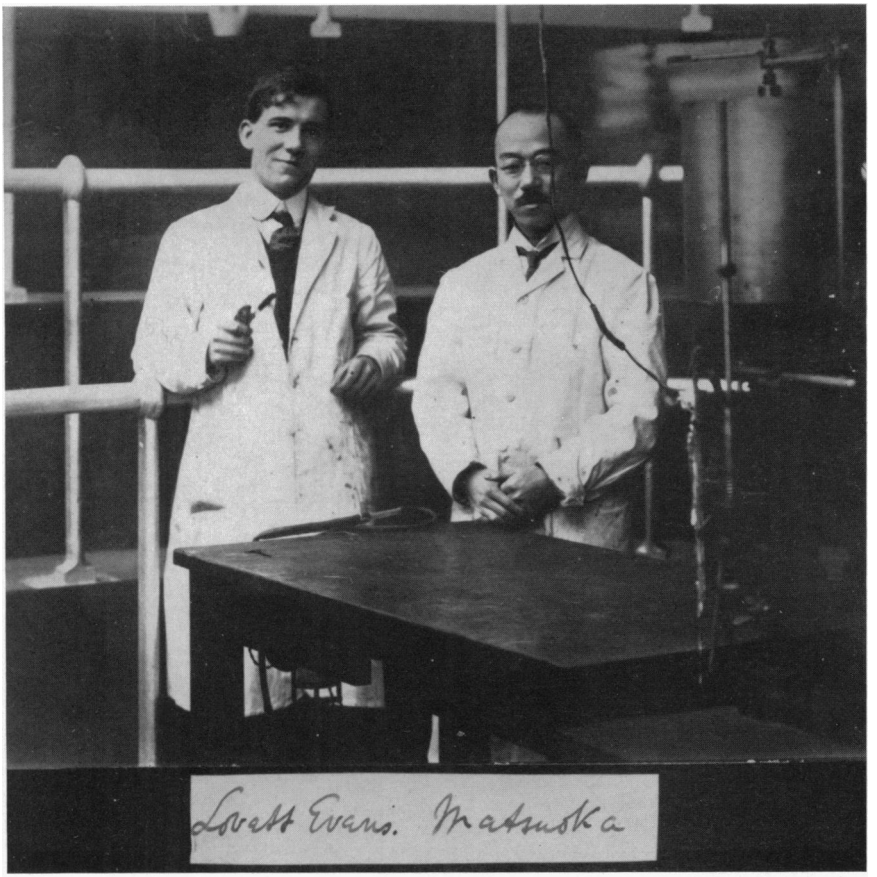
E. V. Cowell.
Ruth Skelton.
Clare A. Harris.
Katharine H. Coward.
O G Harris
W.P. Clark.
J. M. Drummond.
Olga Cowell
Wm Bayliss
Daly
J. McWilliam Daly

b




Lovett Evans. Matsuoka

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EXPLANATION OF PLATES

PLATE 1

Menu and signatures of those present at the dinner celebrating Starling's return to the laboratory, 21 January 1921.

PLATE 2

Bayliss's room at Wadham College, Oxford; *ca.* 1886.

PLATE 3

C. Lovatt Evans with Y. Matsuoka (*ca.* 1913). Lovatt Evans was Sharpey Scholar, 1910–1915, Jodrell Professor, 1926–1949 and first Bayliss–Starling Memorial Lecturer, 1963.