Renaissance anatomical illustrations often followed artistic conventions (situating the skeleton in a lifelike pose in a landscape) and played wittily on the tensions between life and death. The contemplation of the skull prefigures Hamlet’s later meditation. Line drawing, Valverde de Hamusco, *Historia de la composicion del cuerpo humano* (Rome: A. Salamanca & A. Lafreri, 1556).
constituent was later shown to be strychnine. In 1817, with Pierre Joseph Pelletier (1788–1842), Magendie performed experiments on emetics and the nature of vomiting, and showed that the emetic properties of ipecacuanha were due to a substance he named emetine.

Together with Joseph Caventou (1795–1877), Pelletier enjoyed a series of spectacular successes in refining the active therapeutic agents in natural drugs: between 1818 and 1821 they obtained strychnine, brucine, veratrine, cinchonine, quinine and caffeine. Nicotine followed in 1828, atropine in 1833. Above all, opium was subjected to analysis. In 1803–4 the French pharmacists C. L. Derosne (1780–1846) and Armand Seguin (1767–1835) isolated from raw opium a crystalline substance whose chemical nature they could not elucidate. The German pharmacist Friedrich Wilhelm Sertürner (1783–1841) showed it was alkaline, and called it morphine.

Through such experiments in alkaloid chemistry, the active principle was being extracted from many vegetable substances long used in pharmacy; and once this was concentrated in chemical form, purity, strength and dosage could at last be regulated. Many new alkaloids were brought to light. Pierre Jean Robiquet (1780–1840) introduced codeine in 1832, Philip Lorenz Geiger (1785–1836) explored aconitine, atropine, colchicine, daturine and hyoscyamine, and in 1860 Albert Niemann (1834–61) isolated cocaine.

These alkaloids set the stage for a pharmacological transformation. The pharmacist and the physician now had potent medicaments which included morphine, codeine, quinine, cocaine, colchicine, ephedrine, atropine, reserpine and digitoxin. The therapeutic potential of the alkaloids was stressed in works such as Magendie’s Formulaire pour la préparation et l’emploi de plusieurs nouveaux médicaments (1821) [Formulary for the Preparation and Use of Several New Drugs]; this pocket book for practising physicians dealt almost entirely with the clinical use of the new alkaloid remedies.

The first chair of pharmacology was established in 1847 at the University of Dorpat (now Tartu, Estonia) and held by Rudolf Buchheim (1820–79), a Leipzig graduate who translated the drugs manual written by the London chemist, Jonathan Pereira (1804–51). Training students in his new pharmacological institute, Buchheim helped launch the science as a laboratory discipline. One of his pupils, Oswald Schmiedeberg (1838–1921), succeeded him at Dorpat and later moved to Strasbourg in 1872, which was then being turned into a German showcase after its seizure in the Franco-Prussian War. Schmiedeberg set up a major centre for experimental pharmacology, studying chloroform and other anaesthetics and narcotics, digitals, and drugs such as nicotine and muscarine with actions related to the autonomic nervous system. Pharmacology had been put on the academic map, and the pharmacologists he trained went elsewhere in Germany and further afield, creating new pharmacology departments.

**Experimental Science in Britain and America**

These laboratory-based research traditions in physiology, histology, cytology, pharmacology and cognate fields found their perfect habitat on the German campus. Anglo-American pastures were arid by contrast. Around 1830 British savants launched a 'Science in Decline' scare campaign, blaming backwardness on lack of public funding, but politicians raised the counter-scare of jobbery, aware that there were no votes in funding science and medicine, and relying on the ritual incantation of Newton, Harvey and other heroes.

The situation for medical researchers was not helped by the rise of anti-vivisection agitation, encouraged by Queen Victoria. This came to a head at the 1874 meeting of the British Medical Association after an experiment by the French psychiatrist Valentin Magnan (1835–1916) on two unanaesthetized dogs led to a cruelty prosecution. Though this failed, a Royal Commission followed. The resulting 1876 Cruelty to Animals Act, a classic British compromise, permitted licensed doctors to undertake vivisection, but only under strict conditions; continuing protests help to explain why the public was not minded to give for medical research.

Gradually English-speaking medical students deserted the hospitals of Paris for the laboratories of Germany. In the 1830s a few would-be chemists were seeking out Liebig in Giessen and some microscopists were enrolling with Müller in Berlin. Within fifty years, however, droves were pursuing biology and medicine in Heidelberg, Vienna, Leipzig, Munich and half a dozen other centres. There were about 15,000 Americans alone by 1914, mostly going for clinical instruction, though some made a bee-line for the laboratories, like the pathologist William Henry Welch (1850–1934), who studied physiology under Ludwig.
Welch's later career was associated with the university that planted the German ideal in the USA: Johns Hopkins in Baltimore. On his return in 1878, after establishing a pathology laboratory at Bellevue Hospital Medical School, New York, he accepted the pathology chair at Johns Hopkins, which he occupied for thirty-four years, building up a research tradition and making a major discovery: the anaerobic bacillus of gas gangrene, Bacillus aerogenes capsulatus. Though the number of American medical schools investing in science remained small, by 1900 there was a ferment of scientific activity at Harvard, Pennsylvania, Ann Arbor (Michigan) as well as at Johns Hopkins, where the medical staff were full-time and so were spared the distractions of private practice. In 1896 Welch helped to start the Journal of Experimental Medicine.

English medical students flocked to Germany too, but in Britain medicine remained heavily clinical, dictated by the demands of bread-and-butter private practice; pure research independent of healing was somewhat suspect and attracted scant state support. Laissez-faire and utilitarian politics combined with Oxbridge's genteel traditions were somewhat suspect and attracted scant state support. Laissez-faire and utilitarian politics combined with Oxbridge's genteel traditions were not conducive to careers in medical research. William Prout had conducted his animal chemical researches privately; and the talented neurophysiologist Marshall Hall (1790–1857) never obtained an academic post, doing all his experiments at home and funding them with patients' guineas. From the 1830s, however, the founding of University College and King's College London began to change things. William Sharpey (1802–80), an Edinburgh graduate who had studied in Paris, was appointed in 1836 to the University College chair in anatomy and physiology, a post he held for thirty-eight years. The father of British academic physiology, he trained fine students, including Joseph Lister (1827–1912) and Michael Foster (1836–1907).

By the 1870s English physiology was beginning to thrive—indeed, as Ludwig's generation died off in the 1890s, leadership passed to Britain, thanks largely to Foster, who set physiology on its feet as an autonomous discipline. Moving in 1870 to Trinity College, Cambridge, he bred a research school that included Sherrington, Dale and Adrian, and these in turn promoted the discipline in the universities and medical schools. Foster's studies of the heartbeat (was it muscular or neurological in nature?) were expanded by these protégés into wider explorations of the physiology of the autonomic nervous system and the chemical transmission of nerve impulses. He also helped to set up the British Physiological Society (1876), founded the Journal of Physiology (1878) and organized the physiologists' first international congress (1889).

Meanwhile at University College London, John Burdon Sanderson (1828–1905) taught physiology, and when he moved to Oxford as the first Waynflete professor of physiology, his place was taken by Edward Schäfer (later Sharpes-Schäfer) (1850–1935), who played a pioneering role in the investigation of hormones.

FRANCE: CLAUDE BERNARD

And what of France? French medicine was so closely identified with the hospital that it was slow to assimilate the new German initiatives; the newly nationalized universities remained engines for instruction, examining and accreditation rather than research. In the German-speaking world, the jigsaw of diverse small principalities (political unification did not occur until 1871) nurtured local pride, the upshot being a score of prestigious university departments and institutes, pursuing distinctive research programmes, stimulating competition and creating a lively job market. In France, by contrast, Paris stood alone; extreme centralization, the product of the Revolution, produced uniformity, and the ensconced hospital tradition discouraged new initiatives.

Nevertheless, Laennec, Louis and Broussais had worthy successors. Pierre-François Rayer (1793–1867), who became dean of the Paris Medical School and physician successively to King Louis Phillippe and Napoleon III, researched the gouty kidney; and Jean Cruveilhier (1791–1874) presented the first description of multiple sclerosis in his Anatomie pathologique du corps humain (1829–42) [Pathological Anatomy of the Human Body]. Pick of the bunch was Gabriel Andral (1797–1876), who succeeded Broussais at the Charité. An eclectic ('by necessity', he wryly commented), he aimed to reconcile the pathology of Laennec, the statistics of Louis and Broussais' physiology, while rejecting the idée fixe of inflammation as the root of all disease. The attempts he made in his Traité d'anatomie pathologique (1829) [Treatise of Pathological Anatomy] to integrate physiology and pathology proved fruitful (see below).

Beyond the hospital system, France created few niches for researchers, as is revealed by the chequered career of François Magendie who, though a brilliant experimentalist, long languished in clinical posts. But the fact that lavish facilities are not everything is shown by the
career of his great protégé, Claude Bernard (1813–78). Though he never enjoyed the establishment of a Liebig or a Virchow and, lacking such an institutional base, did not create a research school in the Ludvigian manner, Bernard proved second to none as an experimentalist and thinker.

The youthful Burgundian’s ambition was to shine as a dramatist, and one of his plays, *Rose du Rhône*, was performed in Lyon when he was just twenty. But a shrewd critic persuaded him that his métier lay elsewhere, and so he turned to medicine, moving to Paris to become in 1841 Magendie’s assistant at the Collège de France. There was no looking back: in a dazzling career he gained chairs at the Sorbonne and the Museum of Natural History, the presidency of the French Academy and a seat in the Senate. Bernard’s brilliance lay in his superb experimental techniques, based, as with Magendie, on bold animal experimentation. (His wife turned anti-vivisectionist; they separated in 1870, but not before he had spent her dowry to finance his research.)

Bernard’s experiments covered many aspects of physiology: the oxygenation of blood; blood temperature and its changes; the opium alkaloids and the sympathetic nerves; the vasodilator nerves and their role in regulating blood-flow; and the action of poisons like carbon monoxide (which he found killed by displacing oxygen from haemoglobin) and curare, the South American alkaloid which killed by muscular paralysis.

Curare studies led Bernard to conclude that certain drugs acted at strictly localized and well-defined sites, discounting old convictions that drugs had some general bodily influence. Curare worked only where a nerve met the muscle on which it acted, causing paralysis by preventing the nerve impulse from making the muscle contract. Similar specific action points became recognized for other drugs; such drug ‘receptors’ later assumed huge importance in pharmacological research.

His key investigations overturned an old tenet: that whereas plants could synthesize complex substances, in animals fats, sugars and proteins could be broken down (as Liebig’s animal chemistry attempted to show) but not built up. Experiments Bernard conducted in 1855 showed that if an animal were fed on a sugar diet, glucose could be recovered from the portal vein leading from the gut to the liver, and from the hepatic veins carrying blood from the liver to the circulation. Sugar had evidently passed through the liver. Feeding it on a sugarless diet, he found, as expected, no sugar in the portal vein; but the blood in the hepatic veins surprisingly contained high glucose concentrations, and sugar could be extracted from liver tissue itself. Evidently the liver was producing sugar independently. In other words, the body could make its own chemicals in normal functioning – for the sugar here produced was not pathological, as in diabetes. The process was called by Bernard ‘internal secretion’, the first use of a term later fundamental to endocrinology.

Further experiments confirmed that the sugar was not formed in the blood, but was a result of some sugar-forming substance in the liver; in 1857 he discovered this and called it glycogen (a kind of ‘animal starch’), showing it was stored for later use by the organism as glucose and broken down when needed. Extending these carbohydrate metabolism researches, he found sugar in amniotic and cerebro-spinal fluid, and explored the breakdown of sugar by the tissues. In similar studies he examined the function of pancreatic juice. Juice from a living animal had first been collected in the seventeenth century by Regnier de Graaf who, finding it acid, had held that its function was to separate out the nutritious parts of the food. Bernard’s teacher Magendie had also obtained pancreatic juice from a living animal but, while suspecting that the pancreas was a salivary gland, was baffled as to its physiological function.

Once again, Bernard performed a series of ingenious experiments. He found there was no secretion in a fasting dog but that, once it had eaten, the descent of the acid chyle into the duodenum stimulated the flow of pancreatic juice which transformed starch into sugar (maltose). In other words, digestion in the stomach was only a preliminary to the further digestive action of the juices released from the pancreas.

The *Introduction à l’étude de la médecine expérimentale* (1865) [Introduction to the Study of Experimental Medicine] spelt out Bernard’s philosophy in a grand vindication of the experimental method for biomedicine. Hospital medicine, he insisted, had two limitations. Being an observational science it was essentially passive, akin to natural history; and the sickbed involved too many imponderables to permit precise scientific understanding. Scientific progress demanded active experimentation in strictly controlled environments. Moreover, the pathological lesion which the clinicians had fetishized was not the ideal entrée to disease, since it was its end-point. In short, pathology was blind without physiology; pathological processes could best be studied in experimental animals in regulated laboratory surroundings.

Taken together, physiology, pathology and pharmacology formed the triumvirate of experimental medicine, allowing exploration of the
relations between normal and pathological functions, in particular at the biochemical level. Rather as with charity among the Christian virtues, of the three sciences physiology was the foremost, because diseases, Bernard taught, were not ontological but the result of excessive or defective physiological functions; conversely, as his curare experiments had shown, drugs or poisons acted only by altering such normal or abnormal functions.

Science should proceed by testing hypotheses through experimentation. Although (he conceded) the life sciences were not strictly reducible to physics and chemistry in the manner suggested by the German materialists, science would stand or fall by one golden rule: determinism. If physiological events were in some ways less certain than physical ones, that was a consequence of the multiplicity of variables encountered in complex living organisms.

Bernard was no reductionist or materialist; animals and humans were not puppets or Cartesian automata, and this was because higher organisms created their own internal environment (milieu intérieur), their living cell communities. Complex physiological mechanisms adjusted the sugar, oxygen and salt concentrations of the blood and tissue fluids. Body temperature was equilibrated in response to external fluctuations through temperature regulation (e.g., sweating), alterations in blood pressure and oxygen supply (e.g., panting), and changes in the water and chemicals (electrolytes) in the bloodstream. It was thanks to these sustaining mechanisms – later termed 'homeostasis' by the Harvard physiologist Walter Cannon (1871–1945) – that higher organisms achieved a measure of autonomy within the determinism imposed by natural law. ‘The stability of the internal environment’, Bernard declared, ‘is the prime requirement for free, independent existence.’ Physiology’s key role for future medical investigation was thus established, and hospital medicine somewhat sidelined. ‘An author has defined sickness as “a function that leads to death”, as opposed to a normal function that sustains life’, he observed.

I do not need to say that this definition of sickness seems to me pure fantasy. All functions have as their object the sustaining of life and tend constantly to restore the physiological condition when it is disturbed. The tendency persists in all morbid conditions, and it is this that already constituted for Hippocrates the healing power of nature.

Like Virchow, Bernard thus elevated the physiological model of disease above the anatomo-pathological. ‘Medicine is the science of sickness; physiology is the science of life; thus physiology must be the scientific basis of medicine.’

CLINICAL PRACTICE AND CLINICAL SCIENCE

The pathological gaze penetrating the diseased body and the eye of microscopy formed part of wider attempts to apply the methods of science to the whole medical enterprise, including the regular business of clinical medicine. Alongside failures in the body’s structure or architecture, defects in its functioning would also be studied.

For a long time practical medicine got by almost without technology. ‘We had few instruments of precision,’ recalled Robert Morris (1857–1945), looking back on the beginning of his medical career in New York in the 1880s:

There was the stethoscope which, then as now, gave inside information in accordance with the sort of ear that was behind it. The clinical thermometer required three minutes for registering temperature, and people in general were more or less unfamiliar with its meaning. An old Irish lady in one of our Bellevue Hospital wards would not allow a thermometer to be put in her mouth on the ground that the doctor had put it in that of a patient in the next bed who had died less than an hour afterward. . . .

Before the year 1870, in this country there were no laboratories excepting those of anatomy, because the expense of laboratories seemed too great for the teachers who divided fees that were received from students.

But the desire was expressed for more precise recording of physiological processes and pathological events, and this was to materialize in new visualizing and measuring devices like Ludwig’s kymograph. The piecemeal observations typical of earlier investigations were transformed into systematic bodies of knowledge; take for instance what became the specialty of haematology.

In the seventeenth century the microscope had first afforded glimpses into the composition of blood. Swammerdam and Malpighi noted ‘small globules’ which were red blood cells, and Leeuwenhoek found that most mammals had circular red globules, while those of