Papers and Originals

Thomas Linacre at the Portal to Scientific Medicine*

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To join the illustrious band of lecturers who have been privileged to pay homage to Thomas Linacre over four centuries of medical upheaval is indeed an honour for which I must offer the Master and Fellows of St. John's College, Cambridge, my sincere thanks tinctured with commiseration for their unworthy choice. Clearly it is too late now to undo the harm, and I must endeavour to save their collective faces by trying to persuade you that our beneficent Hygeia tolerates all sorts of practitioners, just as she finds room in her all-embracing bosom for the sick and neglected, whatever their station in life may be.

But there is another reason why I should take courage in presuming to address you on this occasion. It is a very special and almost poignant occasion to those who seek " the seats and causes of diseases," the recent founding of a College of Pathologists in the land of Linacre. As the first president of this fraternity which already shows promise of embracing adherents to the discipline of pathology from many parts of the Commonwealth, and indeed the whole world, I recall with admiration and good will that prototype of learned institutions the Royal College of Physicians of London, and its founder and first president, Thomas Linacre. My theme is the need for cultivating a sympathetic understanding between the practising doctor and the laboratory investigator. In Thomas Linacre I see an ideal launching-point for this crusade, so let me begin with some remarks on

Thomas Linacre the Physician

Little is known of how Thomas Linacre became interested in the practice of medicine. We can indeed surmise that the long-established tradition of a priesthood, whose duties included the care of the body as well as the soul, was the precursor of a body of practitioners, many of whom rejoiced in some sort of knowledge of the classical writings, that held itself aloof from the apothecaries, barber surgeons, and tooth drawers. We find no record of regular fees paid to the physicians of the Courts of Henry VI, VII, and VIII. Royal attendants came and went according to the temper of the monarch, as when Henry VI dismissed three physicians and two surgeons who attended to his diet and recommended remedies for his mental condition, and replaced them by the Dean of Salisbury.

Whatever may have been his earliest dabblings, I think it most likely that Linacre seriously turned his attention to medical affairs in the course of his journey to Italy somewhere about 1486. You will recall that Linacre was part of the embassy headed by his mentor and possibly distant relation, William de Selling, dispatched to the Court of Pope Innocent VIII by King Henry VII of England. Such a journey alone must have been a revelation about the way men lived, when the cities of France and Italy vied with each other in magnificence and squalor, where everywhere hovered the menace of bubonic plague, the sweating sickness, and cholera. Memory of the great waves of death that pillaged the life of nearly every portion of the human world, coloured by the murderous civil wars, the decline of faith as the true essence of religion was submerged in the unprecedented cynicism of the pre-Reformation, drove thinking men to the isolation of the monastery or the seclusion of the scholar's study. The cry of an earlier epoch, " God and his saints slept," found its echo in an age of papal conclaves admitted by the orthodox historian of the Papacy, Ludwig von Pastor, as among the most deplorable in the annals of church history, from which emerged vacillating, pusillanimous pontiffs who were often at the mercy of unscrupulous and rapacious brigands masquerading as members of the Sacred College of Cardinals. Scarcely a little court in Europe escaped from the miasma that threatened to overwhelm Europe in anarchy and civil war. And yet the first cool, refreshing breezes of the Classical Renaissance were fanning the smouldering embers of the old world into conflagrations that would purge religion and learning of so much of its dross and rekindle man's imagination and lead it into the highest spheres of intellectual curiosity.

Sufficient information does exist for Thomas Linacre's sojourn in Italy to be traced in detail, though there remain many uncertainties about the duration of his stay and the extent of his studies in the great centres of learning. At Padua, the kindly fostermother of so many scholars of our race, he took his doctor's degree with great distinction on 30 August 1496 (Mitchell, 1935), which was later confirmed at Oxford after his return by an act of incorporation, and it is thought that he was shortly afterwards incorporated by Cambridge. Linacre's friendship with the Medici ruler of Florence, Lorenzo Il Magnifico, who was a constant sufferer from gout, probably brought him the acquaintance of Lorenzo's doctor, Petrus Bonus Avogarius. We possess at least one of the latter's epistles to Lorenzo, written from Ferrara on 11 February 1488 in reply to a request for a remedy for the latest attacks of his patient's malady. Here are some extracts, translated by Janet Ross (1910):

" To begin with, ante omnium Your Magnificence must be purged before the beginning of the Spring . . . if pains are felt the part is to be rubbed with the ointment made according to the recipe I have given to Messer Aldovrandini, which he will send to Your Magnificence. The pains will then cease, but should they return, and even if they do not return, some medicine must be taken to carry off the offending matter. . . . In order to prevent the return of these pains you must get a stone called saphire, and have it set in gold, so that it should touch the skin. This must be worn on the third finger of the left hand. If this is done the pains in the joints, or gouty pains, will cease, because that stone has occult virtues, and the specific one of preventing evil humours going to the joints."

A mixture of superstition and simple treatment, obviously ; Lorenzo died in 1492, most likely from renal failure, though his mind seems to have been clear to the end.

Linacre's stay in Oxford was largely taken up with teaching and translating Greek, but he found some time for the practice

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of medicine. Certainly at least one of his distinguished pupils consulted him in his latter years when his reputation as a busy, discreet court physician with a large fashionable London practice had been established. Erasmus suffered for a number of years from the stone to which he makes reference in several of his letters. Thus in 1511, when he was 45 years old, he writes to his friend Ammonius:

"On the day of the conception of the Virgin, I was delivered of some rocks after much distress. May be you will add this stone to the corner-stone of my devotion."

Two years later we have the following letter to the Archbishop of Canterbury, William Warham:

"Your Erasmus has been through a dangerous tussle with the Stone, the worst he has had yet and to make things worse he has fallen into the hands of doctors and apothecaries, of butchers and harpies! The pain has settled in the flanks and I am still in labour. When and what I shall bring forth is anyone's guess. Perhaps this attack is due to the beer which I have had to put up with for want of wine."

And the Archbishop replied:

"If we begin a letter by wishing 'Health' to those that are well, how more appropriate is it to wish you who are ill the same, even though the omens suggest that you are already purged of your stones, now that we have celebrated the Feast of the Purification. What business have you with stones? You are not mixed up with any great building enterprise. Since stones are not your concern get rid of the encumbrance as quickly as you can, spending what money is required to have them carried away along with thirty angels I have paid to the account of . . . Goldsmith of London. Use this golden physic for your cure. I would gladly buy it for you at a higher price."

The two letters we possess from Erasmus to Linacre, one written in Paris in 1506, the other at St. Omer on 5 June (1516), are equally illuminating. Here is the medical portion of the latter.

"A sudden attack of mild fever has led me to give up a sea voyage, especially as our doctor, Ghisbert, advises against it. Would you be good enough to send a note of the medicine you prescribed for me when I was last in London, as my boy has left your prescription at the apothecary's, and I shall be very glad to have it again. More[1] will tell you the rest of my news. Farewell."

The former he sent off to Linacre after a long and unpleasant Channel crossing, starting from London, instead of Dover.

"We have reached Paris, in other respects without damage, but I caught a troublesome cold during our four days at sea, which even now gives me a severe pain in the front of my head. The glands under the ears are swollen on both sides, my temples throb, there is singing in both ears. And all the time I have no Linacre at my side to exert his skill in relieving me."

Poor Erasmus no doubt caught a severe cold in the head during the journey, developed sinus trouble and perhaps catarrh of the ducts to the ears from the nasal cavities, with enlarged glands in his upper neck. How well we sympathize with Erasmus in his longing for his own doctor, who brings relief not so much by his remedies but through his calm, unruffled bedside manner! Times indeed have not changed with the common cold and its complications. I cannot help but feel that Linacre may indeed have been one of those "beloved physicians" who quietly stand behind the pomp of history. At any rate that tough Welshman, King Henry VII, and his even tougher son, Henry VIII, couldn't do without him, although they insisted that a pet astrologer be called in for many of the medical consultations. And we can never forget that it was largely Linacre's influence that induced King Henry VIII to give permission for the incorporation as one body and perpetual community a college of all men of the same faculty of medicine in London and within the distance of seven miles thereof. This was the beginning of our glorious Royal College of Physicians, whose history has for over four centuries embodied all that is admirable in medical practice and discovery in its annals.

[1] Sir Thomas More, Lord Chancellor to Henry VIII, scholar and martyr.

Linacre the Scientist

But what about Linacre, the propounder of the science of medicine, in contrast with the court physician, the successful society practitioner? History has been too much for him, just as it has been for those old Italian cities that lie decaying in the sun-drenched lowlands of Lombardy and Tuscany. There can be no escape from the opinion that his greatest claim to fame lies in his exposition of the Hippocratic principle, transmitted through Galen and the canons of Avicenna, Rhazes, Averroes, and a host of almost forgotten Arabian scholars, together with the part he played in founding the Royal College of Physicians through his influence with King Henry VIII. Of his contributions to classical learning and its spread in Renaissance England others must speak for me, and I am content to leave the assessment to posterity. But I am puzzled, nay baffled, by the tenacity with which this man of acute sensitivity and intellect, living much of his life with desperately sick people, clung to the stale, outmoded theories of the physicians of the past, and remained content—so it would appear—with fitting his own observations on the living into the ancient framework. This, I admit, is a strong criticism and would not please some of my starry-eyed predecessors in the lecture chair I have the felicity of occupying to-day. Nevertheless, I am prepared to defend my attack by recalling for you another aspect of medical history that has not been given its proper place in the pious eulogies of the past. I refer, of course, to the acid test of all hypotheses about disease, their translation into the cold facts of anatomy, and especially of morbid anatomy. From this faltering step forward has come the vast science of pathology which not only controls the conscience of the practising doctor but preserves medicine from stagnation and complacency by its courageous refusal to be overawed by the past, the present, and, indeed, the future, by its ceaseless efforts to straighten out a wealth of observation into working rules and laws, and above all by the enthusiasm for the truth it inspires in its devoted acolytes.

I see no signs in contemporary evidence that Linacre thought of disease in this fashion. And yet in Italy dedicated men had overcome not inconsiderable obstacles in attempting to trace the seats and mechanisms of the symptoms they knew so well, by dissecting the dead subject or scrutinizing the parts of the body they wrenched from their victims in an attempt to cure the sufferer. A Florentine in the early fourteenth century, Mondino dei Luzzi, wrote the first textbook of anatomy based upon dissections of the human body. The American historian of pathology, Esmond Long, tells us that public as well as official permission for the intimate investigation of the body was freely given, especially when crime was suspected, while fourteenth- and fifteenth-century French and Italian surgeons have handed down an impressive record of anatomy, physiology, and pathology that was circulated among men of learning. There seems little doubt that the opposition of the Church has been grossly overestimated; indeed, by the late fifteenth century we meet with curious instances where high church dignitaries assisted artists as well as doctors to perform dissections. Listen to this quotation from Vasari in his life of Michelangelo. "The prior of Santo Spirito permitted the artist to use a room in which he dissected many dead bodies. To show his gratitude for this opportunity to study anatomy, Michelangelo carved a crucifix in wood and gave it to the prior" (Vasari, 1960: Betty Burroughs edition). Only recently has the rediscovery of this crucifix in the Church of Santo Spirito been made known to us in enthralling fashion.

But what is not generally appreciated is that necropsies were performed with the consent and, I suspect, at the request of private individuals with enlightened opinions upon the nature of disease and the possibility of its transmission. Lynn Thorndik (1928), the distinguished American historian of science and magic, recounts one such instance among the personal papers of a Florentine doctor, Bernard Tornius (1452–97), family

physician to a judge of good family, high social standing, and considerable property. The necropsy record of a 12-year-old son begins with a tactful word of sympathy to the bereaved parent, concisely reviews the results of examinations, briefly enumerates the prosector's five findings on the nature of the disease, explains clearly the diagnosis, and suggests prophylactic treatment for the remaining children, with the highly intelligent warning that such treatment may have to be changed according to time and circumstances by the attending physicians. There is sufficient description of the abdominal organs to make a modern diagnosis of septic thrombosis of the large abdominal veins with pyaemia and multiple abscess formation in the liver due, I suspect, to an appendical abscess. The terminal symptoms of heart failure, with irregularity of the pulse, bouts of fever, suppression of urine, and, at last, failure of respiration are clearly stated, but the explanation advanced for the condition is an incomprehensible farrago of Galen and Avicenna, and quite worthless.

Even more remarkable is a little book by Antonio Benivieni (1443–1502) that has been translated and annotated with sympathy by Charles Singer and Esmond Long. Benivieni came of an ancient and noble Florentine family, was a true Renaissance product, a successful physician and professional anatomist, and a shrewd man of property. He was probably on the staff of the hospital of Santa Maria Nuova and other large hospitals in Florence when Leonardo da Vinci was dissecting the human body and exploring the causes of sudden death. Benivieni was family doctor to many famous families such as the Medici, the Pazzi, and the Guicciardini, a friend of Savonarola, and may have attended the family of Lorenzo Il Magnifico (1449–92) when Thomas Linacre was a welcome guest of the latter and gained the friendship of his sons Pietro and Giovanni, afterwards Pope Leo X. Without doubt Benivieni made post-mortem examinations without restrictions of any kind. At any rate in his *De abditis nonnulis ac mirandis morborum et sanationum causis,* published in 1507, five years after his death, he gives a vivid account of practice in Florence as carried out by an unusual, inquiring mind. As we know the tiny book to-day, it consists of 11 surgical and medical cases to which are appended about 15 necropsy reports, most of which were apparently prepared by Benivieni. Among them are descriptions of gallstones, parasites, stones in the bladder, hernias, wounds, gangrene of the extremities, diseases of bone and joints, a few tumours, and the lesions of syphilis which swept through Europe about this time.

In certain cases attempts are made to associate symptoms with diseased organs, so that Benivieni has been called the " father of pathological anatomy " by French writers of a much later epoch. This, of course, is a gross exaggeration, for there is no semblance of order or classification or the perception of principles in the compilation, and much of it still lies under the tyranny of Galen and the Arabian writers and, indeed, is often credulous. How could it be otherwise, since the structural basis of the human body was still far from known and its workings had hardly been explored. It needed the genius of a Vesalius and a Harvey to provide a lodestar for the vigorous enthusiastic science of medicine that owes its true rebirth to Jean Fernel (1554), who taught that " much disease has a special and localized seat in this or that organ," and above all to the Italian Giambattista Morgagni, whose *Seats and Causes of Diseases* truly ushered in the modern period of pathology.

Placed side by side with his contemporaries Linacre, I confess, affords a sorry sight. Were there no doctors in England daring enough to break away from Galen and the Arabian group ? Did Linacre the scholar, the popular court physician, merely represent a façade of charm and bluff that is not unknown in our own times in even the most exalted circles ? I think the answer is not so easy as all that. A distinguished Linacre lecturer, Sir George Newman (1926), made the point that Linacre aided the advance of medicine by making available the actual texts of the best ancient authorities as a foundation upon which clinical observation and experimental investigation could begin a medical renaissance. With a revival of the Hippocratic tradition of careful observation of clinical detail and case-reporting, there followed the great clinical advances of the following centuries. But I must remind you that this resulted only when the frameworks of anatomy and physiology were built up on a secure foundation of accurate observations and placed in their proper position against the clinical screen.

Medicine Enters the Scientific Age

Medicine passed into a truly scientific age when observation on the living and the dead was transformed by Harvey's proof of a dynamic circulation of the blood and the functional discoveries that quickly flowed from this fertilizing idea. Now began the long series of researches that welded function and structure of organs into a whole and enticed men to seek for the very origins of disease. With the publication of *De sedibus, et causis morborum* (1761) by Giambattista Morgagni, anatomist and first great pathologist, a practising physician of Padua, the friend of emperors and popes, the humble servant of the distressed, a fertile theory of disease burst upon the world, the aims of which are still far from being exhausted. The introduction of the microscope and its speedy technical development soon confronted observers of living tissue with cells, and a new phase of medicine began with the suggestion that cells are units of life of all kinds, and cellular injury lies at the basis of disease and death.

In Rudolf Virchow (1825–1902) we hail a new Morgagni who, with the prescience of genius, turned to the fertile sciences of chemistry and physics for help in finding out why precisely these cells go wrong and how perverted structure and function are translated into sickness. When minute components of cells, the organelles, were located and at last characterized as organs in their own right, the way was paved for the fundamental discoveries of genetics, cellular physiology, and reproduction. Bacteria, and with them the recognition of bacterial infection and immunity, followed by the discovery of viruses and their special relation to disease, were fitted into cellular theory as the outcome of long years of patient observation and experimentation by such masters as Louis Pasteur (1822–95), Robert Koch (1843–1910) and their pupils.

And now we have entered an equally fertile domain of discovery with the advent of astonishing improvements in techniques and technical apparatus, whereby we can grow isolated cells under new environments and subject them to injury of all kinds, lay bare the submicroscopic phase, and approach very closely the molecular domain of the cellular components and measure the finest adjustments consequent upon the most subtle upsets in cellular function, as, for instance, when muscle cells contract or the nerve impulse runs its course from nerve cell to nerve-ending. How long it will take to translate these laboratory discoveries into the symptoms and signs of human disease is impossible to say, and beyond my imagination. Nevertheless, I shall attempt to show you how progress is being made in this admirable programme by reference to a field of research from which I expect great things in the times ahead.

Pathology in the Living Tissue

A great deal more will be done in the future by following, step by step, with the naked eye, helped by various optical devices, the way in which a disease process starts and pursues its course. Such an undertaking really augments, and carries to a further stage of accuracy, the observation of clinical signs as they come and go in a sick patient. Indeed, from time to time similar devices have actually been used with human beings in a fashion free from such criticisms as subjecting the patient to unnecessary handling or mental distress. On the contrary,

his interest may be aroused and the investigation may even become a useful part of the treatment through the enthusiasm of the investigator and the feeling that something concrete is being done about the illness. I have little doubt that a great new branch of medicine could be built up in this way. We have already watched something closely allied to it in the form of clinical science that was so keenly pursued in his latter years by Thomas Lewis and his pupils. I have heard this somewhat scornfully dismissed as "physiology in action." Lewis would have nothing to do with that kind of facile cataloguing, if I understand him correctly. For him each clinical sign was a challenge that must be met, with its own set of tools, by a special way of attack that intuition and experience suggested and, if necessary, its own inventions. I have long thought that pathology, which has claimed the honourable title of the "science of disease" for many centuries, must turn its attention to similar ways of thinking and exploration.

Something already has been done in a naive sort of fashion, and it is a strange irony of its history that the pathway was clearly marked out in the early days of its existence but allowed to fall into disuse and decay through the triumphs of the vigorous young science of cellular pathology. Thus "living pathology," as it may be called for convenience, will study the course of disease in living human subjects as manifested in tissues easily accessible to the investigator, as well as in laboratory animals best suited for the production of a faithful replica of that disease. It will watch the responses of cells, blood-vessels, and lymphatics as they come in contact with the agent that causes the disease, seeking for disturbances in distant tissues of allied or remote relationship, recording the conditions that favour or suppress the cause of the upset, probing into measures that may be expected to bring about early cure and restoration of injured components. Many of the methods used in such basic studies are ready for use, others will have to be invented or adapted from other experimental branches of medicine, and, above all, the fundamental sciences of physics and chemistry. There must be no limits to the territory that is raided in the search for an attack that is apt, flexible, and provocative. But since all such aspirations are likely to be dismissed, on an occasion such as this, as pious hopes or inflated imaginings of a world-weary veteran, let me tell you about one such incursion into "living pathology" made by my former pupil, Professor R. M. L. Mehrotra, of Lucknow.

Urinary Bladder Infection

Infection of the urinary bladder is a well-known complaint among the two sexes, especially as men grow older and are faced with the menace of prostatic enlargement. This happened with Linacre and Erasmus. Women develop it most frequently during the child-bearing period, and pregnancy and the puerperium are often unpleasantly complicated by bladder inflammation which can be traced to infection with the common bacterial inhabitants of the large bowel. In other instances, renal infection decides the onset of this cystitis. Many ingenious researches have probed the mechanisms that underlie the condition, and human observation has established an important direct relation between obstruction to the excretion of urine from the kidneys and bladder and liability to infection. The link between the two is still obscure and is largely a matter of hypothesis. It is precisely at this point that Mehrotra's beautiful investigation brings much light into the picture. I do not intend to weary you with details of his technique, which I can best illustrate by showing you two diagrams of his simple apparatus and some photographs of what he saw when he perfected his methods.

The bladder of the anaesthetized rat can be made available for study under almost normal conditions by carefully opening the lower abdominal cavity with aseptic precautions, isolating it from the surrounding coils of intestine with moist cotton-wool, and inserting in close contact with any part of its very thin wall a transillumination device (Fig. 1). This consists of a long quartz rod, rectangular in section, with one end bevelled at 45 degrees and polished so that this portion can lie against the bladder wall. The other end of the quartz rod, which itself is a very poor conductor of heat, is placed close to a tiny mercury-vapour lamp (250 watts) which was developed for use in submarines during the second world war. The patch of brightly illuminated bladder wall can then be insinuated under a microscope and the blood-vessels, muscle bundles, and even the connective-tissue cells can be seen by the observer at various magnifications according to the optical system of the lens he employs. Two other devices are necessary for the experiment to be successful—a method for keeping the wall of the bladder moistened with salt solution at the body temperature of the animal, and the insertion of a tiny catheter into the cavity of the bladder through the urethra, which is connected to an apparatus for varying the pressure within the bladder cavity and its wall (Fig. 2). Such a muscular organ as the bladder is constantly changing its muscular tone, which may dampen down any pressure artificially induced. This factor can be

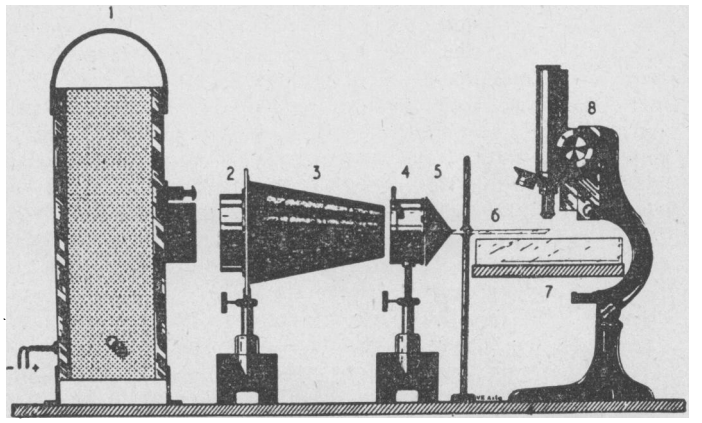

FIG. 1.—Apparatus for transilluminating the urinary bladder of living rats (side view). 1. Mercury vapour lamp enclosed within an asbestos case. 2. Compound lens. 3. Shade for light. 4. Abbé condenser. 5. Shade for light. 6. Quartz rod. 7. Wooden table for animals. 8. Microscope.

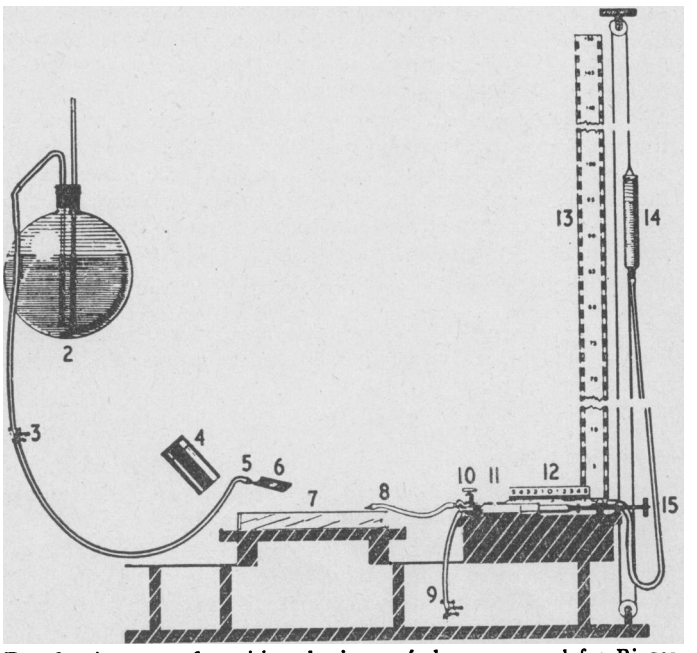

FIG. 2.—Apparatus for raising the intravesical pressure and for Ringer drip. 1. Thermometer. 2. Vacuum flask containing Ringer's solution. 3. Clamp for adjusting the Ringer flow. 4. Receptacle for ether anaesthesia. 5. Hypodermic needle for delivery of Ringer drip. 6. Coverslip holder. 7. Wooden table and Perspex tray for animal. 8. Adapter for urethral catheter. 9. Clamp. 10. Three-way stopcock. 11. Glass syringe. 12. Capillary pipette and scale. 13. Vertical scale calibrated in cm. 14. Water reservoir. 15. Adjustment screw for the syringe.

adjusted by enclosing the bladder in a small plastic box, which restricts it to a certain size, so that circulatory changes in the wall can be studied after unrestricted pressure rises with or without variable tone. Thus a close imitation of conditions as they exist in human bladder obstruction can be established at will.

With this set-up Mehrotra has produced all of the structural features of bladder distension and its effects on the blood-vessels of the wall. He has shown how the blood-flow slows down and stops, the blood-vessels tear and bleed, and he has brought forward good evidence that bacteria deliberately introduced into the general circulation of such animals—an imitation of blood-poisoning—come to rest in the compressed vessels and pass out into the adjacent tissue, there to produce acute inflammation. More surprising still is Mehrotra's demonstration that beyond a certain pressure increase in the bladder similar changes are found in the renal pelvis. Most likely this is due to the pressure also rising in the upper urinary passages, with slowing of the blood-flow through their walls and the localization of any bacteria present in the blood at these regions, with pyelitis and infection of the kidneys. Other experiments performed by Mehrotra have shown that the retention of infected fluid within the bladder cavity will in time induce cystitis and pyelitis, so that the clinical impression associating raised pressure with infection as the cause of cystitis and pyelitis is indeed confirmed. Pressure-rise alone is not enough, though it may damage the bladder wall quite severely if prolonged. Increased pressure is a menace to the health of the urinary passages ; it is fired into more serious action when pathogenic bacteria are circulating in the blood or are excreted in the urine.

Chemical Effects of Pressure

But this is merely the beginning of the story and I should have liked to tell you at length about the fantastic series of events that pressure induces in the chemistry of the bladder-wall cells, whereby a set of chemical compounds—chemical mediators of inflammation as they have been aptly labelled—is set free. A time-table for these chemical events can be made out from which may be predicted what is happening at almost every interval of time. I think that a brief summary of this may interest you, even though many of the details are still far from complete. The time-honoured term "inflammation" gathers together a number of events that are fired off in all living tissues when they are injured. No matter what may be the nature of the injury these events turn up in much the same sort of order ; they overlap one with the other, sometimes are more vividly sketched in the inflammatory picture than at others, or they may even be submerged in other events. Recent investigations now allow us to fit these events into two broad categories:

1. *A fluid-phase reaction* in which the tiny blood-vessels of the injured tissue become more leaky, and are greatly distended with blood which flows at first more rapidly then sluggishly throught the cavities of the vessels.

2. *A cellular response* whereby the white blood corpuscles leave these vessels in increasing number to congregate at the sites of injury.

Methods of precision have been worked out for analysing the fluid-phase reactions from which most of our exact knowledge of inflammation has been obtained. Cellular responses are proving more difficult to exploit, although some progress has been made. Our time-table must therefore be confined to fluid-phase events, and here is the form it now takes, though ideas are apt to change overnight so vigorous is the pursuit of this fascinating subject.

Within a *few minutes* of injury, histamine is set free from damaged cells and initiates, but does not sustain, the vascular sequelae. The latest and most plausible explanation of this histamine release comes from the Finnish investigator Urnäs (1961), who thinks that a ferment (believed to be a phospholipase), which normally exists on the covering membrane of certain cells (mast cells—and probably of all cells) in an inert form, becomes activated by injurious agents. The activated ferment then destroys part or whole of the cellular membrane and quite likely some of the cytoplasm, as a result of which histamine is released (Fig. 3).

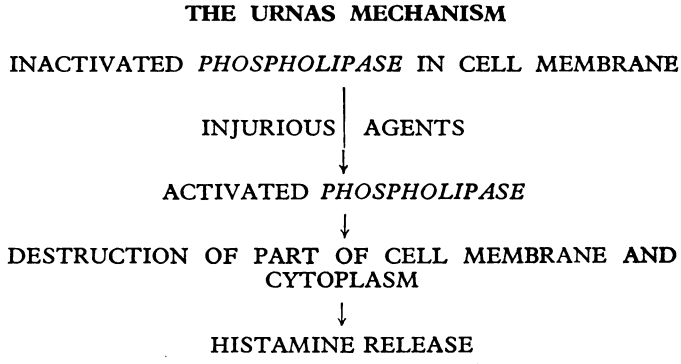

FIG. 3

In some animals, at any rate, serotonin, or 5-hydroxytryptamine, is liberated in parallel with histamine. This happens most often when the brain or intestines are damaged. The tiny blood platelets that circulate in the blood along with the red corpuscles and white blood cells are also rich sources of serotonin. From this release come similar fluid-phase reactions as result from histamine, though they seem to last longer than the latter. But in either case the chemical responses seldom cover more than an hour after the damage is initiated, yet the natural responses may go on for many hours or days. Obviously some other explanation must be sought for such sustained responses.

Since the pioneering researches of the American pathologist Menkin we have recognized polypeptides as the chief candidates for this prolonged reaction. Much of Menkin's work has been modified, corrected, and broadened out by Professor W. G. Spector and Derek Willoughby (1963) and now fits in rather well with the fundamental pharmacological discoveries about the blood polypeptides known as plasma kinins made by G. P. Lewis and his school. Ferment action can convert some of the special proteins that occupy the fluid portion of our blood (globulins) into active peptide, bradykinin. At least two such ferments have been studied: plasmin or blood fibrinolysin, which does its work rather slowly ; and kallikrein, which is very potent in forming kinins from serum. These and the plasma kinins they form have the power of inducing prolonged fluid-phase responses under certain conditions, but their role in inflammation has yet to be established. They are candidates for the part rather than chosen actors.

Another factor still under consideration is the permeability-increasing globulins of Miles and his colleagues, lactic acid and certain agents associated with the formation of fibrin from the blood. It is all too apparent that progress is slow in this most difficult of fields ; nevertheless I am convinced that sooner or later the obscurities will fall into line with the discovery of a fairly simple chemical mediator and vague ideas of physical disturbance and infection will be translated into precise chemical reactions freed from the mysterious and the empirical. In this way will be erected a new science of experimental pathology, part of a truly scientific medicine.

Conclusion

You will forgive me, I feel sure, if I conclude this lecture in honour of the memory of Thomas Linacre by qualifying my seeming attack on his reputation as a physician in several ways. No one can look at the career of Linacre without experiencing

admiration for a man whose natural inclination was towards the scholar's life, yet who was drawn into the practice of medicine and the mitigation of suffering by his pity for and desire to help poor suffering England. Maybe destiny decided that his unique relation to the sovereign as personal medical attendant and instructor of the royal children, along with an unusual gift for diplomacy and the tactful handling of proud men and their dependants, fitted him for a special role in the progress of medical affairs. At any rate, through such patronage and access to the throne, Linacre and his little band of devoted medical colleagues initiated a revolution in the organization of the profession and sounded a call for higher standards in training and ethics that has constituted the grandeur of the Royal College of Physicians throughout its long history. The fact that he advocated the out-of-date scholastic approach to medicine by his devotion to Galen and the ancient writers, and that he ignored the signals of a new science which had already appeared above the horizon, has its warning for those of us who engage our lives in the detection and prevention of the ravages of disease. We, too, are faced by the tremendous upsurge of science in general and of scientific medicine in particular. The challenge is, I believe, a much more serious one in medicine than in other disciplines, for it is all too easy for the doctor to take refuge in the time-honoured beliefs of the past and rest content with delegating, often with scarcely concealed contempt and patronage, the duty of investigation to a little band of dedicated workers. No one who has come through an illness, least of all myself, will decry the God-given qualities that warm the personality of the born clinician and make him an ever-present help in times of trouble. But these gifts are still menaced by pretence and humbug which is not confined to the ignorant and indolent but threatens the seats of the mighty and successful.

We who spend much of our lives in training the oncoming member of our profession must be especially alert to challenge and combat the shoddy and the sham, the facile explanations, the dead-hand of plausible empiricism. Like Linacre, we are standing at the portal of a dazzling, unbounded world of medical science, entry to which calls for courage, imagination, and the highest qualities that bless the human spirit. May we not be found wanting when the opportunity of playing our part comes our way.

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REFERENCES

Mehrotra, R. M. L. (1953). *J. Path. Bact.*, **66**, 79.
Mitchell, R. J. (1935). *Eng. Hist. Rev.*, October, p. 696.
Spector, W. G., and Willoughby, D. A. (1963). *Bact. Rev.*, **27**, 117.
Thorndike, L. (1928). *Ann. med. Hist.*, **10**, 270.
Vasari, G. (1960). In *Lives of the Artists*, edited by Betty Burroughs, p. 260. Allen and Unwin, London.

Intrauterine Transfusion for Haemolytic Disease of the Newborn

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Despite advances in the treatment of haemolytic disease of the newborn, the only remedy against stillbirth has been premature delivery, which is ineffective before 32–34 weeks' gestation and in which prematurity is a considerable additional hazard. Liley (1963b) has reported successful intraperitoneal transfusion of the foetus *in utero* and has shown that Bevis's (1953, 1956) method of spectrophotometric examination of the amniotic fluid is a useful guide to the selection of patients who are likely to have stillborn or severely affected foetuses (Liley, 1961, 1963a). Since then McCrostie (1964) has reported another successful case.

In this hospital we deliver each year nearly 200 mothers who have rhesus iso-immunization, and despite selective premature delivery, exchange transfusion, and attempted resuscitation of hydropic foetuses, we have a stillbirth rate of about 8% and a neonatal death rate of about 6%. These new techniques offer the prospect of more exact selection of affected infants, a reduction in the degree of prematurity, and the possibility of preventing hydrops foetalis. We have now performed intrauterine transfusion on six occasions and feel that our experience might be of some value to others attempting this form of treatment.

Case 1

Gravida-5 aged 26. Estimated date of delivery 13 January 1964. Blood group A rr ; husband's group O R_1R_1. First pregnancy, 1958: miscarried at 10 weeks. Second pregnancy, 1958: a healthy 6-lb. (2,720-g.) infant at 39 weeks ; no antibodies found. Third pregnancy, 1960: spontaneous delivery at 33 weeks of an infant weighing 2 lb. 11 oz. (1,220 g.) who was not affected with haemolytic disease, and who survived and is normal. Fourth pregnancy, 1961: spontaneous rupture of membranes at 31 weeks ; anti-D antibodies of titre 1:8,000 discovered ; patients transferred to Lewisham and delivered spontaneously of hydropic infant who died 80 minutes later.

Present Pregnancy, 1963.—Anti-D titre 1;8,000 in albumin ; at 31 weeks spectrophotometric examination showed a very high peak at 450 mμ (optical density 0.85), indicating very severe haemolytic disease. The patient and her husband had heard that intrauterine blood transfusion could increase the chance of the baby's survival and requested that we attempt it. She was a slim woman and the fotal parts were easily felt.

The technique advised by Liley was followed exactly. On 14 November 1963, at 32 weeks, 20 ml. of 76% Urografin was injected into the uterine cavity and an antero-posterior and a lateral *x*-ray film were taken. Five hours later a further lateral *x*-ray film did not show any Urografin in the foetal gut. The foetus was clearly hydropic (Fig. 1) and we presume that this prevented it from swallowing. Under local anaesthesia an 8-cm. Tuohy needle was introduced into the uterine cavity, the stylet was removed, and a syringe with saline was attached. As the needle advanced inside the uterine cavity, saline was injected. It was hoped that when the needle met with the foetal abdomen there would be resistance to the injected fluid, which would indicate the position of the needle, and that when the needle entered the foetal abdomen ascitic fluid would be aspirated. After several unsuccessful attempts this technique was abandoned. The needle was advanced under the direct feel of the hand, and this showed that the texture of the tissue through which the needle goes could be distinctly felt. When the

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