CHANCE, DESIGN AND DISCOVERY*

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Were I about to preach a sermon, which I am not, I might take as my text some part of the ninth chapter of the first book of Samuel, and though I know that being all good Welsh Calvinists you will immediately appreciate the allusion, yet in case there be one here who is not so informed, I would recall that it is told there how Saul, the son of Kish, went out to seek his father's asses, which were lost, and found a kingdom—the kingdom of the Israelites. I should use such a text because this story was remembered by the colleagues of the German chemist Wöhler when in 1828 he set out to make ammonium cyanate by treating potassium cyanate with ammonium sulphate, expecting by double decomposition to get potassium sulphate and ammonium cyanate and to separate them by crystallization. Under the conditions of his experiment, however, he found to his astonishment that a fairy godmother had given him urea, which has the same chemical composition as ammonium cyanate but a different arrangement of the atoms. This discovery wholly upset the then firmly-fixed notion that animal products could not be made in the laboratory, but only by some mysterious 'vital force.' Wöhler wrote to Berzelius: 'I must tell you that I can prepare urea without requiring a kidney or an animal, a man or a dog.' This event was the beginning of synthetic organic chemistry.

Why have I commenced this address to you, the young men of 1952, eager to enter upon your great heritage of the wonders of modern discovery, and to discharge your therapeutic thunderbolts at the suffering bodies of your patients, with this piece of past history? I will tell you. It is not so much that I am *laudator temporis acti* but that the present is the child of the past and the parent of the future, and if we are to look into the future we should learn something of the present and the past. And so for a brief moment this afternoon I want, with you, to look at the story of present

achievement, and to consider how this was won and how we may use the knowledge we gain for what lies ahead of us.

When you get old and tend to sit in your chair dreaming,

'Gone the fires of youth, the follies, furies, curses, passionate tears,

Gone like fires and floods and earthquakes of the planet's dawning years'

and you look up the valley which lies behind, you sooner or later become aware that you are seeing things as it were through the other end of the telescope; and that instead of the distance being made big for you you see a view in which things are dwarfed and shrunken to much smaller dimensions, and a lot of them seem hardly worth talking about.

In this mood of philosophical equanimity let us look back on medical progress and see what it all amounts to and how it has come about, and this involves something of medical history. Now when you are young and eager and everything is to get, you are apt to be impatient of medical history. So often this seems a matter of musty old cracked-back, calf-bound volumes with yellow pages, written perhaps in quaint stilted English or—worse still—in 'dog Latin.' But do not be put off by this idea; it is nothing of the sort but is a fascinating study of exploration and slow advance into the unknown lands of knowledge that lie along the edge of our Continent of Things Certain. It is a study of trial and error, of false paths, of whole generations under the sway of wrong ideas leading to wrong treatment and God knows what in the way of casualties—and the old tale yet goes on. A friend of mine said to me the other day, 'In the 18th century hundreds of people lost their lives through blood being taken out of them needlessly; today people are being killed through blood being put into them needlessly,' and I—who only that morning had seen the body of a young man, dead as the result of an incompatible blood transfusion, given after an operation of

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convenience, could only agree with him sadly. But I was talking of medical history and I would ask you not to disdain any of it and to remember that all is knowledge and that you are members of a learned profession. In the urgency of accumulating that vast mass of facts—right and wrong, relevant to your lives as well as irrelevant—which is required of you, it will not be easy to cultivate and to maintain that interest in general learning which used to be associated with the word 'Doctor.' But I counsel you to do it; it is worth struggling for; if only that it will give you resources within yourselves which you can turn to at any time and under any circumstances, and which will abide with you as a continuing solace:

'When all the world is old, lad, and all the trees are brown,

And all the sport is stale, lad, and all the wheels run down.'

A more immediate and maybe more practical advantage in knowing something of how present information has been acquired, is that it is an easy method of learning and remembering. I made that discovery when I began to teach, and it helped me, for I have a bad memory. If you take the isolated statement that 'Vitamin B₁₂ is the haemopoietic factor requisite for the maturation of the cells of the erythroblastic series, from the megaloblastic to the normoblastic phase,' you have a mere jargonal assertion of fact that you may or may not remember in times of trouble in the examination hall or the *viva voce*, and you have nothing to tag it on to. But if you call to mind the former procession of patients, such as they were in my time, inevitably becoming yellow and dying of pernicious anaemia—a sequence which had continued uninfluenced by either mighty tomes or a hundred forms of treatment, or by convincing theories propounded with the weight of authority by the famous German professor, Ehrlich, and the well-known London physician, William Hunter—a macabre procession that had gone on without interruption since ever the disease began; and if you then turn another page and come to the seemingly distant and unconnected academic observations of Whipple, made about 1920, that dogs rendered anaemic by bleeding got their blood back most quickly if they were fed on liver; if you then look back into one of those musty books of the year of the Franco-Prussian War, and find that the Englishman Fenwick discovered that the stomach was diseased in pernicious anaemia, you begin to get a slant on the malady which escaped both Ehrlich and Hunter. And if you then remember the experiments of Castle on men, and how he found that meat partially digested in the healthy human stomach and then taken out and given to patients

with pernicious anaemia arrested the progress of the disease and restored the lost blood, you see the whole jigsaw puzzle of isolated pieces fit suddenly together, and you have a complete and satisfying picture of pernicious anaemia: a disease of the stomach (Fenwick), which is unable to manufacture a substance formed by the digestion of protein (Castle), which is stored in the liver and is required for the normal building of red blood cells (Whipple).

This story is a well-known one. So well known that I have hesitated to repeat its details before an informed audience. But I have done so because it illustrates very well many of the facts which bear upon discovery and progress. Ehrlich and Hunter were the victims of wrong hypotheses. Bound by these, like Prometheus upon his rock, there they stayed. Fenwick's discovery was made, forgotten and rejected: its significance was not recognized and the time was not, perhaps, quite ripe, nor the technique at hand for its development. Whipple was not trying to discover a cure for pernicious anaemia, he was working on blood regeneration in general and he made an incidental observation, which gave a clue to Minot and Murphy, who utilized it in the treatment of this disease; and finally the crucial experiments of Castle had to wait until technical advances made the ready analysis of intragastric digestion possible. Misconception, failure to use an observation, chance, technical achievement—all are there in this relatively simple story.

If I were asked what single factor had contributed most to medical discovery, I should reply 'chance.' But I should hasten to qualify this by saying that the gifts which that Fairy Godmother brings only come to those who are industrious in using them and whose minds are ready to receive them. You cannot find diamonds by walking in the pebbles of a South African river with your eyes shut, though you do it all your life. This association of chance with an ability to recognize the gift, if and when it comes, has impressed all who have been interested in the history of discovery and has, perhaps, been best put into words in the celebrated saying of Pasteur, that 'In the field of observation chance favours only the prepared mind.' And I would go yet further and add that the boundaries of any discovery are set by the limits of the technical resources of the time. Technical methods are the necessary handmaidens of the research worker, but in saying this I would state immediately that elaborate technical methods are most certainly not necessary to the discovery of new facts, any more than they are necessary to the evolution of new ideas; indeed, they may by their very elaboration become a bar to progress. By all means let us employ instruments of precision

if we have them, but let us not throw up our hands in despair if they are out of our reach. 'The machine,' said Chesterton's Father Brown, 'cannot lie. Neither can it tell the whole truth.'

—But let us go back to chance, meaning the gift it brings to those who can use it, and ask ourselves what it has contributed to the progress of discovery, and put it into the scales against the processes of logic and the discoveries which result from planned investigation. To take the second matter first. I doubt if the logical sequence of ideas leading to great results can in the field of medicine claim any achievement as monumental as the work of Pasteur. Every medical student should read Vallery-Radot's 'Life of Pasteur.' There is an English translation, but read it if you can in the original French and—even if your French is not quite equal to the task—read it in the original French! The son of a tanner, he graduated as a chemist and early made the discovery that optically inert tartaric acid was a mixture of dextro- and laevo-rotatory forms and that the crystals of these two, which he separated by hand, were optical isomers; thus he resolved a problem which had puzzled the most renowned chemists of the day, including Gay-Lussac and Berzelius. What is, perhaps, not so widely known, though it is there to be read in his writings, is that in investigating the properties and preparation of tartrates he found that a certain organism could utilize in its metabolism only the dextro-rotatory form of tartaric acid and was incapable of using the laevo-rotatory and—extraordinary fact—the organism he named was one to become world-famous 85 years later, *penicillium glaucum*.

Biology had entered his world and for the rest of his life he was to work at it; being led from fermentation to putrefaction, from putrefaction to the action of micro-organisms in the body and the study of infective disease, and so on to the protection of animals from microbial infection and, finally, to his crowning work upon the virus disease, hydrophobia. The details of this long odyssey are for all to read and I have barely recapitulated the chapter headings, but though the process was logical, and to us today may seem more so than perhaps it was did we know the intimate secrets of laboratory life, yet it is stated by Duclaux and repeated by others that chance put her finger in the pie at one critical period in this masterly progression. The whole basis of Pasteur's work on immunization lay in the isolation of the causal organism, the production of a strain of attenuated virulence for the animal, and the setting up of active immunity by means of sub-clinical infection with this attenuated strain. An undesigned event showed him the way. He had been experimenting on the cholera of fowls and the organism

which causes this. On going away for a short holiday he found on his return that most of his cultures were dead or inactive, and in attempting to revivify them he inoculated them into fresh fowls, but he found that these failed to contract the disease and were none the worse for the inoculation. Later, he obtained some fresh virulent organisms and found that whilst these killed ordinary fowls in the ordinary way they did not kill the fowls he had inoculated with his old cultures; to his surprise these animals survived. They had been immunized by inoculation with dead and attenuated cultures, and the phenomenon of active immunization by such means, which was to occupy the rest of his life so fruitfully, was laid bare. Nothing in this detracts at all from Pasteur's glory, which is imperishable, for he had the mind to appreciate the value of the unforeseen fact and the general principle to which it pointed, together with the remorseless energy to follow the clue thus found, to the prevention of chicken cholera, of anthrax and to the crowning work of his life—the prevention of hydrophobia in those bitten by a mad dog. He achieved this, be it noted, when he was well over 60 years of age.

Paul Ehrlich, the German chemist and biologist, whose name I have mentioned to you already, may also be looked upon as one whose steady and unremitting pursuit of an idea brought discovery and triumph in the end—and there is much in this. Perhaps the idea is heightened in a way by the fact that his most famous discovery was named '606,' this being the 606th of a series of preparations tried in the search for a drug potent against the spirochaete of syphilis and, at the same time, relatively harmless to the human body. If anything at all suggests a logical sequence this does. Ehrlich was impressed from the beginning by the specific nature of some aniline dyes in staining organisms and conceived that if a micro-organism could be stained specifically in the tissues it should be possible to manufacture a substance of antiseptic properties which, in a like manner, would link itself specifically to the organism and kill it whilst showing no affinity for the body tissues. He laboured long with dyestuffs on these lines, and about 1904, in trypan-red, he had some success and reached the conclusion that phenol derivatives and the introduction of a halogen group into the benzene ring gave the most promising results. But the goal still eluded him, and then he switched to arsenical compounds which were not dyes and had, in a desultory manner, been used for years in the treatment of syphilis and the allied condition of trypanosomal diseases. I often wondered what profound chain of reasoning caused this step. Only a few weeks ago in searching for something else I found out. It appears

that a man with the good Welsh name of Wolferstan Thomas had been experimenting at Runcorn on the action of atoxyl in curing trypanosomal infections in animals and Ehrlich heard of this. He went to Runcorn, saw Thomas and on his return to Germany he took up the investigation of atoxyl, which is a benzene ring compound containing arsenic and a pretty dangerous drug (it causes optic atrophy and blindness), and from this beginning he ultimately evolved salvarsan, the first great milestone in the history of chemotherapy. But the trail which Ehrlich blazed has been continued by others who have found rewards as great or greater than did their master, for it followed directly upon his work on the dyestuffs that his pupil Browning, an old teacher of mine in Glasgow, developed the flavine group of dyes as wound antiseptics; these did valuable service in the later years of the first world war. Nearly 20 more years passed and then Domagk (1935), who had behind him the great German chemical industry, showed the extraordinary action of the azo-dye sulphonamidochrysoidin, or prontosil, on streptococcal infections in mice. But even so there was an element of the unsuspected in this. Domagk knew that this dye prontosil—a red dye—was inactive in the test tube, and the Frenchman Tréfouël was able to show that the efficacy of the prontosil was mainly due to its being broken down in the animal body into para-amino-benzene sulphonamide which is a comparatively simple compound and not a dyestuff at all, and one which had already been known to chemists for 27 years, but had lain *perdu* and had never been tried as a therapeutic agent. It might be said, fairly, that a false trail led to the discovery of its action. However this may be, the hunt was up. The organic chemists and the chemical manufacturers rushed in and in the twinkling of an eye produced innumerable variations of the substance of many different advantages and ranges of activity. To one of these (M. and B. 693) I certainly owe my life. But although they did not know it then the fairy, Chance, had already spiked their guns for them in 1928 by dropping a spore of *penicillium notatum* on a culture plate of a London bacteriologist—of which more anon—and chemotherapy, strictly speaking, became overshadowed by antibiotic therapy, after a considerable latent period and through the energy and vision of Florey.

Now let us look a little at the more direct activities of this Dame Chance. In one way or another she has had a finger in every medical discovery and the more you come to know about this the more you find it holds. There are few names we revere more than Jenner's, and yet it was a village girl who told Jenner that she was immune to smallpox because she had had cowpox,

and as he was 49 when he started inoculation with cowpox lymph, and had been in medical practice as apprentice and doctor already for 36 years, it is evident that he pondered the matter long. The legend of immunity to the greater disease from the lesser was well established in the West Country, but in Jenner's mind—the friend and correspondent of that insatiable man John Hunter, who explicitly urged him to try the experiment—the seed fell upon the prepared soil.

In the year that I was born (1889) von Meering and Minkowski in Strasburg disputed whether a dog could live without the great digestive gland the pancreas, and like good scientists they tried the experiment. To their utter surprise—and the fact was first spotted by the laboratory attendant—the dogs which lived after the operation became diabetic and remained so during their short survival. Von Meering and Minkowski went on (the major partner was Minkowski) to show that ligation of the pancreatic duct by itself, and the exclusion from the intestine of the pancreatic secretion, had no such effect and thus, it may be said, the science of endocrinology was born.

I do not want to weary you with the continued recitation of these ancient instances, but I cannot leave this theme without recalling the beginnings of another great branch of medical science—knowledge of the vitamins. An appreciation of the necessity for certain ill-understood accessory foods is as old as the hills and it begins with scurvy, that curse of seamen, navies and maritime explorers, since ever men began to voyage upon the deep waters. L. J. Harris in a most readable little book upon the vitamins has written:

'The scurvy flew through the schooner's crew as they sailed on an Arctic sea,
They were far from land and their food was canned

So they got no vitamin "C".'

The long story of scurvy is a mixture of accurate observation, obscuration, misconception, acute insight, and pompous self-sufficiency and ignorance, and the history of scurvy and its prevention in the Royal Navy and amongst Arctic explorers alone would make up a lecture in itself. You should read it in Drummond's book 'The Englishman's Food.' Poor Drummond who last summer was so foully murdered in France. But it is not of scurvy and vitamin C that I wish to talk, but of the events which led to the discovery of the beri-beri vitamin: for this was really the beginning of the modern phase of knowledge; and here I must pay tribute to Dutch scientists for the part they played.

In 1886 the Dutch Government, which has always had a fine record of enlightened medical work in its East Indian dependencies, sent two

scientists, Pikelharing and Winkler, to the East Indies to investigate beri-beri, including also a young army doctor, Eijkman. They believed for a time that they had discovered an organism as the cause of the disease and the two senior men returned to Holland with it, leaving Eijkman behind to dot the i's and cross the t's. For two years he laboured at this and then chance took a hand. Eijkman was working with chickens and funds being short he had to feed them upon what was left from the ward kitchens and, to his surprise, he found that they developed a disease which was the same as the beri-beri they were so concerned with. The staple native diet was rice and Eijkman and his assistant Grijns began to look into the matter and found that only polished rice gave hens beri-beri and that this disappeared when they were given unpolished rice, or could equally well be cured by feeding them upon the stuff removed in polishing. Thus was the substance vitamin B discovered in 1901, though some years were to elapse before it received this name.

It is to Pikelharing, Eijkman's chief, that the credit must go of realizing that here was an entirely new principle in the causation of disease: that this could result from the lack of something in the food in quantities so small that its calorific value was negligible. Up to this time dietetics had been a matter of calories; professors decided how much food was required to provide the calories necessary for subsistence in prisons and the ungrateful convicts failed to thrive—and so on. True von Bunge at Basle in 1890 had posed the question: 'Does milk contain, in addition to protein, fat and carbohydrate other organic substances which are also indispensable to the maintenance of life?' But like Pontius Pilate he did not wait for an answer. Pikelharing took up the work Lunin and his chief von Bunge had left at an inconclusive stage, and as a result he was able to write in 1905: 'It is impossible to keep an animal alive by feeding it on protein, fat, carbohydrates, the necessary salts and water . . . something more must be present,' and 'There is an unknown substance in milk which even in small quantities is of paramount importance to nutrition' and also 'Undoubtedly this substance not only occurs in milk but in all sorts of foodstuffs.' Hopkins in this country obtained similar results in very beautiful quantitative experiments in 1912, and showed that the explanation given by the critics of the new views (which were now beginning to be discussed in a number of quarters); that the animals became bored by the monotony of their diet and by merely failing to eat fell into a decline, was untrue. And so the vitamin story began and went on, and the end of it is not yet. The good fairy had other gifts to bestow in the same field,

and one of these was thrown to the Norwegians Holst and Frölich in 1907, when they tried to produce beri-beri in guinea-pigs by diet. True enough they produced a disease, but it turned out to be scurvy—and in this way they discovered an essential tool which previously had been lacking: an animal, other than man, upon which the efficacy of anti-scorbutic substances could be tried, and thus gave an immense impetus to the investigation of vitamin C. I may add that Szent-Györgyi first isolated pure vitamin C from the adrenal when studying the nature of reducing substances in its cortex. He called this substance hexuronic acid and found it also in lemon and other vegetable juices, but did not realize that he had obtained crystalline vitamin C until much later. He, too, was looking for an ass and found a kingdom.

And where has all this brought us to? If I might put it in as few words as possible I would say, 'Progress from known data may be planned; for discovery we are indebted to chance.' One might liken the matter to the difference between the biological processes of continuous variation and mutation. Once given the new idea, the new fact, the mutation in our routine of perceptions, then we can apply our minds to its perfection: we can polish it up and show its different facets, as is done by a host of busy little people once a discovery—such as that of the antibiotics—is made. But we do not as a rule have the wit to go out and look for the new fact. It was the fairy Chance who dropped the spores of *penicillium notatum* on Fleming's culture plate in the dusty bacteriological laboratory at St. Mary's Hospital—and it was the same fairy who arranged that the organisms growing around should be of a species sensitive to penicillin; if they had been *B. coli* and not staphylococci we might still be without penicillin. The whole story and all the similar stories, of which there are many, fill me with humility and also with a sense of contempt for the powers of the human intellect we are so conceited about. The history of discovery is the most salutary corrective to the view that you can purchase it by the lavish outpouring of money and the creation of vast research institutes. It is true, and all that I have told you goes to show it, that discovery only visits those who are working in the fields over which she hovers, and who have both the prepared vision ready to recognize her gifts when they are bestowed and the mind and industry to put them to use; nor would I be so foolish as to decry the value of intensive work upon any new fact. But the great gifts come from on high; they can be neither bought nor commanded. They are not the perquisite of principalities or powers but of ordinary men who have used such gifts as God has given them.

A moment ago I used the word humility. I used it and I would commend it to you in a special sense, meaning an absence of the conceit that goes with ignorance. If you want to see an illustration of this sort of conceit, portrayed by a master hand, go and look at the picture of 'Ignorance' by Dalziel in the 'Pilgrim's Progress.' It is worth looking at again, if only to see a fine woodcut by a master of that craft and to send you back to a great piece of literature.

Too much confidence in our scientific attainments, considerable though they may be, expose us to dangers against which we must be eternally vigilant. One is the uncritical acceptance of authority and authoritative pronouncements, and this you have to be especially on your guard against now that medicine has come under the administration of the State and the importance of the individual withers. There will be a temptation to impose methods of diagnosis and treatment from above, it makes for easy administration. But, believe me, the gentlemen in Whitehall do not always know best, though they have the advantage of consultation with the best authorities extant. The history of medicine shows only too clearly, and sometimes with tragic emphasis, how the accepted dogma of today is the error of tomorrow.

The other danger which comes from confident self-satisfaction is the dislike for new ideas. How disturbing they are! Do you remember the play 'Milestones'? It has been said with much truth that the attitude of men to new and surprising discoveries is that they say, firstly, 'It is untrue,' next 'It is of no importance' and finally, when the truth is so absolute that it cannot be doubted, 'We always knew it,' and this fault of distaste for new ideas is not limited to the lower levels in the scientific hierarchy; the highest are fallible. The Royal Society refused to allow Jenner to present his findings and wrote 'He ought not to risk his reputation by presenting to the learned body anything which appeared so much at variance with established knowledge, and withal so incredible.' Note that phrase 'established knowledge.' Time and again established knowledge has proved to be established ignorance. Crystallized, petrified, and

built into the stony structure of static minds. Beware of authority. Do not be overshadowed or browbeaten by pompous elders. Cultivate scepticism, scorn dogma. 'Prove all things: hold fast to that which is good.'

How fallible is dogma! In that fascinating book 'The Sea Around Us,' you can read how in 1938, off the coast of South Africa, some fishermen caught in their trawl a fish which the most learned biologists, zoologists, paleontologists, geologists and archeologists had pronounced to have become extinct 60 million years ago, with the last of the dinosaurs and when the chalk hills of England were beginning to be formed. Think of it! Sixty million years. A long time. Suppose Jones had said in his zoology viva that *Latimeria* might be found swimming off the Cape! Short shift for Jones in 1937—but honours for him in 1939!

Now to you who have listened to me so patiently it may sound as if this is a story of cynicism tinged with disillusionment—but it is not so. Father Mendel planting his peas, parson Stephen Hales tying down his young mare and finding the blood pressure by inserting a tube into her femoral artery, Leeuwenhoek grinding his lenses and looking at his 'little animals,' Shaw Dunn trying to poison the kidney and poisoning the islets of Langerhans, Wöhler trying to make ammonium cyanate and making urea; they were all urged on by an itch of curiosity and each in his own way became a begetter of modern medical science. To the seeker his reward. There is no crock of gold where the rainbow ends, but there is and always has been much to be found. Much that may delight and gratify and, if it is not a material, will always be a spiritual reward. And so I would counsel you in your progress through this life, and in the practice of the high art for which you are equipping yourselves, to remain seekers and to cultivate in the garden of your souls that plant of curiosity that will yield satisfying fruit. And at the end of it all, when the light is failing and the shadows lengthening on the grass, even if the fairy has not dropped a glittering prize in your path, you will find that you have been the better doctors and will have acquired merit and peace.