Wandering Scientists

Dorothy Hodgkin

I feel greatly honoured to have been asked to give a lecture dedicated to the memory of Maulana Abul Kalam Azad and also happy – honoured because he played such an important part in the history of India and happy because he was such a very sympathetic person, who stood for many ideas I care for. I cannot do better here than quote words Jawaharlal Nehru wrote of him long ago, discussing his qualities as a candidate for the presidency of Congress: "He had breadth of vision, a deep understanding of events and around him every section of Congress would gather and offer cooperation. He represented to me the ideal emblem of united working which I sought, especially at this critical juncture". But Nehru added "extraordinarily sensitive and retiring as he is, it is no easy matter to push him forward in this age of conflict".

Maulana Azad was born in Mecca, where his family stayed for a short period. He was educated at home in Calcutta at first in the manner traditional in learned Moslem families, studying Arabic and Persian, Philosophy, Mathematics and Logic, teaching in his turn when he reached the age of sixteen. As he grew older, he began on his own to study English, modern science and history. So he brought both ancient and modern learning to assist in the creation of India, free and independent.

In his memory today, I should like to speak of some of the changes that have resulted from scientific researches within our life times, his and mine. It has been my great good fortune that my own work has been connected with major discoveries that have widely affected human health and happiness. If I speak today of some of the events that occurred in the study of penicillin, of vitamin B_{12} and insulin seen through my eyes as partly observer, partly participant, I hope we may be able to draw from old experience conclusions helpful for the future of scientific work in India.

The first discovery opening new doors which I observed when I was very young, in fact aged 23, took place in Cambridge in 1933. It arose through a series of chances. There was work in Uppsala in Sweden on the purification and crystallisation of enzymes and particularly of the

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digestive enzyme, pepsin. A young biochemist, John Philpot, went for a year from Oxford to Uppsala and grew the most marvellous large crystals of pepsin (they grew while he was away on a skiing holiday). These were seen by a visitor from the United States, Glen Millikan, who knew J D Bernal (then aged 33) in Cambridge. Bernal had just begun to use the diffraction of X-rays by crystals containing molecules of medical interest as a means of studying their structure – the way the atoms composing them were arranged in space. Protein molecules such as pepsin were then a very large unknown quantity and a challenge. Millikan knew that Bernal longed to work on them, so he asked for a present of some of the crystals and took a tube back to Cambridge in his jacket pocket. Bernal made a very simple discovery – that if the crystals were kept wet they would give very extensive and very beautiful X-ray diffraction patterns, capable of showing how the thousands of atoms composing each molecule were arranged in space. At that moment, forty years ago, we could hardly hope to solve such complicated structures. But I remember still the look of those photographs, the excitement in the air, our dreams of the future.

To test our ways of solving crystal structures we had to turn to simpler and smaller molecules. I was lucky that one I studied seriously was penicillin. Almost everyone knows the story of Fleming's observation, that a chance speck of a mould, *Penicillium notatum*, dropped from the air into a culture plate containing staphylococci, produced a substance which destroyed the bacteria. Fleming's first hopes that he had made an important and useful discovery faded as experiments indicated that the substance was very unstable. He published his observations in 1929 and his paper was seen a few years later by Florey and Chain. Howard Walter Florey (then aged 41) had been recently appointed Professor of Pathology in Oxford; he had come originally from Australia. Ernst Chain (then 29), of Russian origin, born in Berlin, was a refugee from Germany. They planned together, in 1937, a research on the antagonism of microbes, one to another – essentially purely scientific in outlook – and explored the literature from Pasteur onwards for examples of the antagonism they wished to study. "I don't believe the idea of suffering humanity ever came into our minds", Florey was to say, characteristically, later. (In which, perhaps, he was not quite fair to himself. For he also said, in conversation, that he was attracted to penicillin by the fact that it was active against staphylococci and that his little daughter suffered from boils at the time). Out of the list in the literature Florey and Chain chose two of the antibacterial substances recorded for detailed examination, penicillin and pyocyanase, of which pyocyanase had been first observed in 1889.

As they found how to extract penicillin safely, undestroyed, from Fleming's mould and explored its properties, its wide antibacterial action, its harmlessness to animals, almost the whole of the laboratory was drawn into its investigation, and work on their other choice,

pyocyanase, was stopped. By May, 1940, they had enough active material to try a critical test. Of eight mice infected with streptococci, four were given various amounts of penicillin and four were not. All of those given penicillin lived, the others died. Some time about then, I remember meeting Chain in the road outside the Pathology laboratory in a very excited state, looking forward to the day when they would try penicillin on suffering human beings – and might also produce crystals for a structure analysis. The time proved very short. By February, 1941, they had sufficient to test penicillin on a desperately ill patient, suffering from acute septicaemia, close to death in the Radcliffe Infirmary. Miraculously, he began to recover, his temperature fell, his abscesses began to heal. But in six days their supplies of penicillin ran out, he relapsed and died on March 15th. They spent the next few months isolating more penicillin, testing it on a further five patients, most of them children. By August they were able to report in the *Lancet* that, in all these cases, favourable results had been obtained.

The initiation of the research on penicillin had nothing to do with the war, which indeed was a hindrance in the early stages to its prosecution. It was difficulties in persuading British firms in wartime to undertake the large scale extraction of penicillin that led Florey to go to America in 1941 to interest American firms and government research laboratories in its preparation. Later, with Hugh Cairns, he tested penicillin very successfully in the treatment of war-wounded in North Africa. Penicillin research therefore came to be regarded as important to the war and organised under government committees in Britain and America; communications from that time on circulated secretly among the groups involved. Although great improvements in the methods of isolating penicillin resulted from research controlled by the penicillin committee, in retrospect one can see that progress might have been much more rapid if the war and the limitations it imposed had not been in progress. Its one advantage was the imposition of a certain measure of co-operation among the different groups working on penicillin. So some of the first crystalline penicillin obtained in America was flown over for me in Oxford (10 mgr.) and used in the structure analysis. But this analysis by X-ray diffraction was actually carried out in the usual academic way by one D Phil student, Barbara Low (aged 21), some part time help from Charles Bunn and his research assistant, Ann Turner-Jones, then in industrial research at ICI (at first they worked after their official working hours), and myself, partly distracted by university teaching, by child bearing, evacuation problems in the war, even occasional bombing episodes. The delight we had in the atomic arrangement of the atoms in penicillin which we saw in 1945 was hidden from the scientific public by the war organisation.

After the war, there was an enormous expansion in research, spreading freely out from penicillin to other antibiotics, with immense effects on the treatment of a variety of infections

and on public health wherever knowledge existed of modern science. Problems arose in the use of penicillin, partly controlled by the discovery of ways of making new and more stable penicillins – derived at first from work by Margreiter in Austria, partly by the use of new varieties of antibiotic. One very effective one, cephalosporin C, arose from observations of a doctor in Sardinia, Guiseppe Brotzu, who brought, in 1948, to Florey in Oxford a new micro-organism, a species of *Cephalosporium* he had found in sewage outflow in the sea near his home. Many others, too, all over the world, sought to work in Oxford on antibiotics. Florey was sad he had no room for them all.

It was the work we had done on the structure of penicillin that led Dr Lester Smith, of Glaxo Ltd., to bring to Oxford, also in 1948, red crystals he had isolated from liver, of a vitamin, very active in preventing and curing the very serious disease, pernicious anaemia. Behind its isolation was another very instructive trail of linked scientific researches. In 1926 two young doctors, George Minot and William Murphy, tried treating patients suffering from pernicious anaemia with a high protein diet, including liver. (There was a history behind their trial, which I must leave out here). They observed an immediate improvement in the patients' condition and became very rapidly convinced that this improvement was due to some specific substance present in their diet. Impelled by their conviction, biochemists in different universities slowly took up work on the isolation of the active substance. By 1935, a promising stage was reached by Dakin, Ungley and West in Philadelphia – and of these Ungley was a young visiting research fellow from Newcastle, England. The work on the antipernicious factor was somewhat interrupted during the war, but at its end chemists from several large pharmaceutical firms concentrated on the problem and achieved the isolation of the red crystals. There were fascinating links in the developing chains of research; the researchers in America, with Dr Karl Folkers at the Merck Laboratories were helped by the discovery made by Mary Shorb in the Maryland Institute for Poultry Husbandry who found that chicks and bacteria needed a growth factor identical with the anti-pernicious anaemia factor. The factor was found to contain cobalt – and this immediately linked pernicious anaemia in man with pine, an anaemia of sheep, prevalent in cobalt-deficient pastures in Australia. Ungley and West were the doctors in England and America who first tested pure B_{12} on human patients. One of the main series of clinical tests in England which led to the isolation of the vitamin by Dr Lester Smith was made in Newcastle General Hospital.

The structure found for vitamin B_{12} by X-ray and other methods proved to be of great fundamental interest; the molecule was complicated and had many novel features which presented a challenge to synthetic organic chemists. Its synthesis was achieved by 75 organic chemists at Harvard and 56 at Zurich from about 30 different countries working with R B

Woodward and Albert Eschenmoser. The last link in the synthesis was actually made at Zurich in the spring of 1972 and the news was telephoned by Eschenmoser to Woodward, who reported it immediately in Delhi to an international meeting of chemists gathered here. I was able to check the effect of the announcement when I met, last week, colleagues from Calcutta who were present at the symposium.

The way the vitamin works is still being studied; it is necessary to control reactions of vital importance to our metabolism. We do not synthesise it ourselves, but obtain it from protein sources from animals to micro-organisms. In countries like India, where many are vegetarian, there is a higher than average risk of anaemia. Now, in any country where treatment can be obtained, patients suffering from this disease have as long an expectation of life as average or better.

Diabetes is a much more common disease than pernicious anaemia; its distribution varies in different countries; usually between 1 and 2% are sufferers in greater or lesser degree. The effect of the disease, when it is acute, the melting away of the tissues of the body leading rapidly to death, were described two thousand years ago and more. Today, no-one need die from diabetes who can obtain medical care and injections of insulin.

There were a number of observations leading to the conclusion that diabetes was due to the lack of a hormone, insulin, ordinarily present in the pancreas and a number of research workers, particularly Paulescu in Rumania, obtained extracts from the pancreas showing some activity in animal experiments. But 1921 and Banting's work marked a critical change in outlook for all sufferers from diabetes.

Fred Banting was a young doctor (29) who, not being very successful in medical practice ("the patients stayed away in droves") helped with teaching medical students. Reading for this purpose about diabetes, he got an idea of how possibly to obtain an extract of the pancreatic hormone, insulin. It was an idea so urgent that it led him to give up his practice, sell his house and his cat to provide for his living, and to persuade Macleod, the Professor of Physiology at Toronto, to let him work in the university. Macleod arranged for him to have space in some sheds, apparatus and dogs, and a young student to help him in vacation, Charles Best, 22, half way through his medical course. Together in the course of six months, Banting and Best were able to make an insulin preparation sufficiently pure to be used clinically on diabetic patients. As with penicillin, they tried their experiments first on a boy who seemed near to death. He recovered, and other remarkable recoveries followed; patients began to gather in Toronto from near and far. Rapidly, other scientists were brought in to improve the extraction and purification of insulin and large scale industrial production followed.

Insulin proved to be a protein molecule, considerably larger than B_{12}. It was the first protein molecule of which the chemical structure was found, by Sanger and his colleagues at Cambridge, and the first to be chemically synthesised almost simultaneously in 1963-65 by groups in Aachen, in Pittsburgh and in Peking and Shanghai. I first heard the possibility of the synthesis discussed in Peking in 1959 when I visited Peking University. There was a group of young chemists gathered round after a lecture I gave on Vitamin B_{12}. They said "We hope you do not think we are too ambitious; we are planning to synthesise insulin". Naturally, I could only encourage them – but their project was really very adventurous. They had to make many of the reagents and chemicals for the synthesis themselves which would in the western world be bought from industry. Soon I was in touch with the insulin synthesis being carried out in the west, in Aachen and Pittsburgh. And I went back in 1965 to Shanghai to see how the Chinese synthesis of insulin was developing and to compare notes on the progress of all three investigations. Essentially the procedures followed were very similar. And news passed between the three very separate insulin groups as each new stage was reached, so that each seemed to know exactly what was happening to the other. The synthesis is, however, difficult and lengthy; it does not yet provide a new source of the protein for treatment of diabetic patients, though that too may come some day as methods are improved.

Neither chemical sequence nor synthesis tells us the actual way in which the atoms in insulin are arranged in space – which we need to know if we are ever to understand its biological action. To obtain this knowledge, we had to use Bernal's experiment with which I started this lecture, pass X-rays through wet insulin crystals, and then interpret the results. (I was, indeed, fascinated to see in 1971 that the Chinese research workers, remembering Bernal's observation, keep a small sample of their synthetic crystals, wet, covered on a slide, under a microscope, for everyone to see who passes through the Shanghai Industrial Exhibition.) So, I return to my beginning, and our hopes when we first saw X-ray diffraction effects from pepsin crystals. Over the forty years that have passed since then techniques of measurement and calculation have enormously improved and ways have been found, largely by Max Perutz, and John Kendrew, to interpret the X-ray diffraction effect from protein crystals. Max Perutz himself came actually from Vienna in 1935 to Bernal in Cambridge, hoping to work on the protein, haemoglobin, for his D Phil degree. John Kendrew was drawn in through talking with Bernal in a jungle in Ceylon in the middle of the war of the problems on which they would like to work once the war was over. Bernal suggested the structure of proteins and so led Kendrew to join Perutz in Cambridge after the war. Through their work the atomic arrangement in the proteins, haemoglobin and myoglobin, became gradually visible between 1955 and 1960.

Even with the experiences of Perutz and Kendrew to guide us, it took many years and some twenty research workers spread over the years to solve the crystal structure of insulin. At the moment when, finally, in 1969 we saw through our calculations a picture, understandable though blurred, of the atoms in insulin, four of these research workers were still working with me in Oxford – Eleanor and Guy Dodson from New Zealand, Tom Blundell from Oxford and Vijayan from Bangalore. (It was Guy who said to me earlier, when Vijayan asked to work with us – "We should get him, his name means Victory".)

The first map gave us suddenly a great wealth of information, though not all that we needed, either in extent or certainty. We looked forward to many years of exploration and consolidation. Only two years later, to our surprise, came unexpected news (I first got an inkling of it in 1971 on a journey to Hanoi). A map showing details of the structure of insulin had also been calculated, by measurements independent of ours, in Peking. I went myself to see it, in 1972, to compare sheet by sheet our evidence with that obtained by enthusiastic young workers in the Institute of Physics. I had sent ahead news that I would bring our maps on tracing paper, with the structure drawn at a scale of 1cm. to 1 Å, and they drew their maps to the same scale to aid comparison of our results. Sheet by sheet, we could see the same atoms, though drawn by very different hands, and so gain confidence in all our conclusions.

The analysis carried out in Peking had begun only a few years earlier, at the beginning of the Cultural Revolution. It was the product, clearly, of great scientific skill and hard work. And it was linked to ours by only thin threads of wanderings which helped to initiate it, wandering west by Tang Yeuh Chih and Liang Tung Tchai, and east by J D Bernal, John Kendrew and myself.

There are larger problems still ahead of us, and on the way to solution by the methods Bernal initiated, the problem of the structure of the antibodies, for example, many times the size of insulin, which provide our body's own defence in the battle against disease. But I must now turn to more general conclusions from my stories.

Human nature is, of course, full of horrible depths, jealousies, greed, anxieties over proper recognition of individual merit. All through the war, in the penicillin research, we nurtured suspicions, probably often unjustified that reports from America came to us more slowly than necessary, priorities being protected. Justifiably, we were dismayed to find that indeed some stages in penicillin preparation had been patented there, although the original isolation had been left unprotected by Florey and Chain. Many scientists still feel strongly over the honours awarded for the isolation of insulin. Should not Charlie Best, though only 22, have shared the

honour, as he did share some of the money, of the Nobel Prize? Or perhaps Paulescu, who made many similar experiments to those made by Banting? Yet there are also good streaks in us scientists. Wherever I went in the U.S.A. just after the war, I found it delightful to talk over the research on penicillin with those who took part in it; everyone was so glad to have contributed something, however small. All our old enemies became our old friends. The same sense recurred in the research on B_{12} and on insulin. All those who have taken part share in some measure in the happiness of success.

The lines of research I have described have certain characteristics in common. Often the initiating observation or discovery was made more than once; bacterial antagonism was observed many times over and even studied extensively and purposefully before Florey and Chain pursued penicillin. Pancreatic extracts active against diabetes in dogs were obtained by others before Banting; even the effects of liver on pernicious anaemia were observed before Minot and Murphy. No doubt a number of causes contributed to final success; technical advances for one. But there does also seem to have been in each case one or more individual's overwhelming conviction of the possibility of success. As success grew more likely, very many were drawn, and gladly, into the cooperative efforts necessary for full achievement.

In all these researches, the initiators were young, or youngish, and their collaborators often very young. Not that the old never have good ideas or are very useful (Fleming was old). Only it is difficult to work quite so hard when one is old – I speak from experience. And one's mind is full of cares, less open to new and bright ideas. It is also less easy suddenly to give up everything else and set out on a new life.

The parts played by pure and applied research are inextricably mixed up in these investigations. It was observations on the degeneration of pancreatic tissue that spurred Banting to action – but insulin and the cure of diabetes that he sought. The isolation of B_{12} in George Minot's day was extremely difficult – twenty years of development in scientific techniques were necessary to secure it. Many of the researches outlined (and particularly my own) have been concerned with finding the structure of the active molecules. They are often not of immediate practical use, though ultimately they may be helpful.

But, you may say, all these discoveries I have described have led to happiness for certain individuals only, who might have died, but who lived. For others, these discoveries may have made life even more difficult and particularly in India, more people living than ever before and food still often scarce. I find myself thinking you can only solve problems if you really work on them, intensively, with everyone working together. Gandhi once said "Anything that millions

can do together becomes charged with a unique power." There has already been experience in different parts of the world in the techniques by which poverty can be diminished; it is necessary first to raise the standard of living for the poorest; and this requires the cooperation of everyone, work from all for everyone's needs. In my own wanderings I have seen this transformation of life happening in different degrees in many countries and particularly most recently in China and in Vietnam. In 1960, I discussed with one of the Chinese scientists from Shanghai in a bus in London during the Royal Society tercentenary celebrations his own part in the process. For a time he had left the laboratory and worked in a village. Since he was there only for a few months, he could only help to initiate changes in village life and say to the people, "Now you can do everything yourselves". A fortnight ago I was talking to two peasants of my own age in a village near Vinh in Vietnam of how exactly they themselves had set about changing their own lives. First five villages came together and from village meetings each chose one representative. Together they planned two cooperatives; one agricultural for the avoidance of famine and drought, and one for handicrafts. Their first organisation in 1930 was suppressed but after many struggles and the war it exists again today. All in the village are literate – greatly helped in this direction by the existence of an ancient Vietnamese epic poem they mostly knew and could follow when learning to read.

Many events of this kind have occurred in different parts of India. Yesterday, I found myself reading Maulana Azad's own plans for education in India and his ideas that all educated people should spend at least two years of their lives in teaching (as he had done, when young). In 1949, he wrote of some of the first reforms he introduced: "From the very first day of the programme, villages in Delhi have responded with an enthusiasm which is beyond all expectation". But India is very large and the processes of change have met with many obstacles, particularly from wars. There still is great poverty; population still increases, and though scientific ways exist for limiting population, they too seem only to become effective as living improves.

We should, however, take heart; the processes of change can go much faster than you might expect. Bernal used to like to quote a paper by Semyonov likening the rise of the standard of living he had observed in remote regions of the U.S.S.R. to a chemical auto-catalytic reaction, each change speeds up the next stage of development. In the context of my stories, I remember George Minot was a diabetic who might not have lived to work on anaemias in 1926 had Banting and Best not isolated insulin in 1921.

I have lost a little my early thread of wandering scientists who may make possible the unexpected leap forward. Most of the wanderings I have been describing are very ordinary

academic wanderings in the pursuit of knowledge. Very often they involve, the young journeying abroad for further scientific training. Occasionally, I must confess, the wanderers settled abroad for the rest of their lives and were lost, at least in part, to their own countries. Such was Florey, who came from Australia as a D. Phil student to Oxford and stayed there most of his life, becoming President of the Royal Society in London. Though he cared about scientific work in Australia and helped in its development, his working presence was missed there. On the other hand, many of the wanderers did return home and brought their researches to unexpected places, as Ungley brought vitamin B_{12} to Newcastle. The full potential of these wanderings for scientific growth can only be reached in a world at peace. But they may also help to bring such a world into being. Very often now they carry us across boundaries separating deeply divided countries. It is easy to talk happily and constructively about proteins here in India, and in Russia and in China; in America and also in Vietnam. It seems unthinkable as we talk that there should be deep conflicts between the peoples of these countries. Peace, again, is something for which we must work positively, for the healing of the wounds of war and renewing of brotherhood across frontiers new and old.

Particularly individuals may, of course, be very important. Maulana Azad, who we remember today, chose his name liberty when he was young and in his life was a symbol of fraternity, co-operation between all communities in India. The first episode I read about him was very characteristic. Mahatma Gandhi broke his last fast, on the 18th January 1948 at 12.45, by receiving a glass of orange juice (8 oz. with glucose 1 oz.) at the hand of Maulana Azad. More than two hundred thousand citizens of Delhi had signed a peace pledge in response to Gandhi's desire to restore complete communal harmony.

It may not even be desirable now to restore in terms of national sovereignties the Unity of India for which Maulana Azad so greatly hoped. But peace over all the continent, freedom to meet and work together for the divided peoples can restore the community he lived for.

"A nice lot of excitement here about the Nobel Prize award – I wish you could all share it."

Dorothy Crowfoot Hodgkin

in a letter to one of her coworkers, K Venkatesan.