numbers of children in child sex rings may be common. The lack of information about such abuse is easily understood in the light of the pressures used by perpetrators to ensure that ring activities are kept secret. The known tendency of children to retract statements after disclosure of sexual abuse also makes investigation of sex rings particularly difficult.[12] Parents, public, and professionals must be trained to consider the possibility, and to recognise the warning signs, that a child may be taking part in a sex ring. Children need guidance on how to recognise and avoid inappropriate sexual activities from an early age.[13] They should be encouraged to inform adults immediately of attempted abuse even when this is accompanied by threats or other inducements to maintain secrecy.

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Green College Lecture

Serendipity and insight in immunology

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Immunology, being a branch of biology, is concerned with mechanisms which operate in, and have operated to produce, living creatures as they have evolved on earth. Despite the endeavours of the international astronomers' search for extraterrestial intelligence, seeking messages from other regions of the universe predicated on the assumption that other intelligent beings would use the 21 cm hydrogen or the hydroxyl spectral lines for transmission, the answer to date is silence.[1] There is no guarantee that similar mechanisms function anywhere else than on earth. Consequently, immunological discoveries, unlike those concerning the laws of chemistry and physics, which are reckoned to be valid throughout the universe, cannot be expected to have cosmic significance.

Generalisations in biology are, as far as we know, limited to the past, present, and future behaviour of particular elaborate organisms whose rules we try to discover. Of course, they do not disobey the laws of physics and chemistry, though they probably transcend these as they have hitherto been formulated at the molecular, atomic, or subatomic level. But even the discovery of something as exciting as the genetic code in DNA and all our recent knowledge about how it is translated and regulated concern particular devices which have permitted living organisms to survive and evolve. These devices are so subtle and ingenious that it is difficult to conceive of any others which would perform as well. If self replicating entities capable of independent existence and combining some of the other properties which we associate with life had arisen in quite another way, different devices would presumably have evolved.

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The process of scientific discovery

I state these truisms by way of introduction, because I would not wish to be thought to denigrate the power of insight. Great minds in mathematics and physics, spurred by observations of the natural world, may be able to arrive at verifiably valid generalisations by purely mental processes. They demonstrate thereby that the processes of mental logic conform in some fascinating way with causality as it operates in the physical world. In biology, however, we can begin to obtain understanding only by observation and experiment, which provide facts on which to build hypotheses to pull the facts together and, we hope, predict how a particular system will behave under different conditions.

The process of scientific discovery by experiment was discussed by Peter Medawar in his essay *Induction and Intuition in Scientific Thought*.[2] He emphasised the importance of hypothesis (or, if not so clearly formulated as to be dignified by this term, of hunch) in the design and choice of experiments and rightly added: "A good methodology must, unlike inductivism, provide an adequate theory of the origin and prevalence of error . . . and it must also make room for luck." Luck, of course, will not help unless the researcher recognises it as such, and so implicit in luck is the prepared mind that can take advantage of it.

There is another term for luck which has become established in our vocabulary, presumably because it fills a gap rather than being simply a grander term. This is serendipity. Literally, it means something from Ceylon (Sri Lanka nowadays, Serendip to early Western writers). It was coined by the eccentric minor English writer Horace Walpole, Fourth Earl of Oxford and of Strawberry Hill fame, in a letter written in 1754 to Sir Horace Mann. Walpole

mentions a fairy tale entitled *The Three Princes of Serendip*, probably by the Italian Bocci, in which the princes "were always making discoveries, by accidents and sagacity, of things they were not in quest of." His own example of such a discovery was that "Lord Shaftesbury happening to dine at Lord Chancellor Clarendon's found out the marriage of the Duke of York and Mrs Hyde by the respect with which her mother treated her at table." The importance of serendipitous discovering obviously depends on circumstances. But the concatenation of accident, sagacity—that is, the prepared mind—and discovery of things which were not being sought has been responsible for a substantial amount of innovation in immunology.

With the exception of what Robert Good aptly termed experiments of nature, such as children born without thymuses or with single enzyme genetic defects, there has to be a hypothesis to test, even if it is no more than a hunch. Otherwise, the experiments would not have been designed. There are some, not necessarily cynics, who have argued that the most important function of hypotheses is to make people do experiments.

Having lived through an important part of the growth of immunology, I am aware from personal experience or from acquaintance with the people concerned how little the original purpose of some important experiments had to do with the discoveries which emerged from them. This is rarely obvious from the published accounts. The somewhat standardised structure of papers prescribed by the editors of most scientific journals and the shortage of space do not encourage writers to introduce their findings by explaining that they were looking for something quite different. By the time a paper is published the findings have usually been married with current ideas and made to look as though they were the logical outcome of an original hypothesis. This was the theme of Medawar's essay *"Is the scientific paper a fraud?"* Sometimes, however, the authors have revealed, though not usually in the seminal papers themselves, how far chance played a part.

I give one example, from among many possible, of how accidents and sagacity led to the discovery of things which the investigators were not looking for. This does not detract from the sagacity—that is, the prepared and sharp minds—of those who recognised their importance or, more importantly, followed them up. It concerns work with which I was associated, thus acknowledging my own debt to Dame Fortune, so that I can without embarrassment reveal the debt of other colleagues.

The genetic control of immune responses

One of the major advances in understanding what controls stimulation of lymphocytes by foreign antigens has been the recognition that the major histocompatibility complex antigens of the lymphocytes themselves are concerned. The initial evidence for this came from experiments which had quite another purpose. A lymphocyte stimulated by an antigen can secrete up to several thousand molecules of specific antibody per second. We know nowadays that this is the result of switching on specific genes and that interaction with the antigen is only one way of triggering this. But at one time it seemed important to know whether any molecules of antigen were actually present in the cell making antibody and in some undefined way directing its synthesis. I discussed with Michael Sela, then head of immunochemistry at the Weizmann Institute, how one might be able to detect a single molecule. We decided that if a large synthetic polypeptide which he had made and which evoked good specific antibodies in rabbits was synthesised from amino acids in which all the hydrogen atoms were tritium (hydrogen-3), it would be radioactive enough for us to be able to detect a single molecule in a histological section by its capacity to produce silver grains when overlaid with photographic emulsion. Since cells forming antibody could also be detected in the same section by immunofluorescence it should be possible to detect whether there were any molecules of antigen in them. The polypeptide in question was p (Tyr, Glu)—p D-L Ala--pLys, (T,G)-A-L, which is shaped like a bottle brush with the antigenic sites being similar and at the end of the bristles.

While Israel Schechter in Israel was synthesising the radioactive material, starting with 100 Ci of tritium in a hut in the desert, I set out to make sure that it would be possible to detect antibody forming cells in mice. For this purpose rabbit antibody against the (T,G)-A-L would be needed. Sela supplied a sample of non-radioactive (T,G)-A-L, which was injected into rabbits at Mill Hill; no antibody resulted. He sent another sample and some antiserum which he had prepared so as to be certain that when antibody was present I could detect it. Once again our rabbits failed to respond. These rabbits were from a breed called Sandylop, with nice large ears, which we usually used for raising antibodies. Two other breeds of rabbit were also available, and in desperation I tried immunising some of these. They responded just as Sela had led me to suppose that they would, and it was a warning that breed could influence the capacity to respond.

The actual experiments in mice were to be done mainly by a visiting worker from the USA, Hugh McDevitt. The first thing to do was to make sure that mice would make antibodies against (T,G)-A-L, and so he tested all the inbred strains available. Some responded well and others hardly at all. We arranged to do the experiments with mice which responded well. When Schechter arrived with the precious tritium labelled (T,G)-A-L we found that it had become insoluble and useless as a result of radiation damage. All was not lost, however, because meanwhile an alternative radioactive label, iodine-125, had become available. This label was much more radioactive atom for atom, and enough atoms of ^{125}I could be introduced into (T,G)-A-L to make it highly radioactive without, we hoped, altering it appreciably. The experiments went ahead as planned and indicated that a cell making antibody did not contain more than 15 molecules of antigen, which was the lowest we could detect.[3] Meanwhile, Nossal and colleagues, using a different antigen labelled with ^{125}I, had shown that fewer than three molecules needed be present. This seemed a good enough answer, though by the time these experiments were done few immunologists would have expected any other.

VARIATIONS AMONG STRAINS OF MICE

The purpose of recounting this is in the follow up. McDevitt recognised that the strain variation in the response of mice to (T,G)-A-L was important. He tested crosses and back crosses between responder and non-responder strains and concluded that the capacity to respond was determined largely by a single gene. To find out whether this was something of general importance he consulted Michael Sela, who suggested using a similar polypeptide, (H,G)-A-L, in which the tyrosine was replaced by histidine. When this was tested they again found responsive and unresponsive strains, but the strains were different. So they tried a third polypeptide, which included phenylalanine instead of tyrosine, and the strains responding were again different. Shortly before, Donald Schreffler at Bar Harbor had worked out how to distinguish the H2 major histocompatibility antigen complex of all the strains, and when these were compared with their responses to the various antigens which McDevitt and Sela had observed it became clear that responsiveness must be controlled by a gene or genes lying within the H2 complex.[4] These became known as immune response genes. They are now recognised as part of the class II major histocompatibility locus and as all important in the immune response.

Luck, converted to serendipity by McDevitt and Sela, played a part at four points. Firstly, the antigenic determinants—namely, the three amino acids at the end of the bristles—were all alike on each of the polypeptides and so only a narrow antibody response was evoked, unlike that to an ordinary protein with many determinants. Secondly, the initial screening of the mouse strains was for a quite different purpose. Thirdly, the second polypeptide chosen behaved differently from the first; if, for example, a large atom such as iodine has been introduced on the tyrosines of (T,G)-A-L the antibody response against it would have shown no strain variation. Fourthly, the scrutiny of responses and H2 specificities immediately suggested the association between the two. Of course, the discovery would have been made sooner or later by someone. At about the

same time Benacerraf found that two different strains of guinea pigs showed pronounced differences in their ability to respond to a antigen made from a quite different simple polypeptide, but the histocompatibility antigens of guinea pigs had not been studied. McDevitt and Benacerraf joined forces to put this whole novel aspect of immunology on the map.[5]

Importance of insight

Other discoveries in which serendipity played a large part include[6]: the role of the thymus in immune responses; cooperation between lymphocytes derived from the thymus and those derived from bone marrow in antibody responses; complement lesions in cell membranes seen under the electron microscope; the ability of some plant lectins such as phytohaemagglutinin to act as polyclonal mitogens; the discovery of hepatitis B virus; the ability of anti-lymphocyte antibodies to suppress cell mediated immunity; "radioactive suicide" of antigen specific B cell clones by highly radioactive antigens; the role of follicular dendritic cells in germinal centres in generating B memory cells; the H2 system in mice; the role of granulocytes in type III allergic reactions; and even the discovery of monoclonal antibodies produced by hybridomas. The list could be much longer.

Of course, most discoveries have not depended on chance. Rather, they have depended on careful testing of hypotheses intended to fit together and interpret existing knowledge or the development of new techniques which make it possible easily to observe things which were otherwise too difficult or impossible. Two such techniques which come to mind are the invention of immunoelectrophoresis by Grabar and Williams, which enabled antigens in complex mixtures to be recognised and even identified, and Albert Coons's invention of fluorescent antibodies, which allowed individual cells containing antigens or antibodies to be identified. The experimental results have provided the clues needed either to extend or to modify the hypothesis. In immunology things usually become more rather than less complicated. Nevertheless, however much care goes into choosing a system to study which ought to be amenable, most workers would, I think, be prepared to admit that luck is important.

When I look back on the conceptual advances in immunology which have taken place during my working life, including those made by serendipity, they all required insight. Some came from logically conceived and skilfully executed experimental work—for example, R R Porter's elucidation of the structure of immunoglobulin molecules and J L Gowans's demonstration that lymphocytes are the cells responsible for specific immunity. Others, however, arose from radically re-examining current ideas and were primarily feats of reasoning. The mental effort entailed, however, was likely to be worthwhile and the arguments likely to be accepted seriously by others only if there were at least some hints that currently accepted hypotheses were deficient and in need of modification and if the new hypotheses were susceptible to experimental verification. Here are four examples.

Lattice hypothesis

The first example is J R Marrack's lattice hypothesis to explain the combination of antigens and antibodies so as to form precipitates, in which the proportions of the two could vary. When he first became interested in proteins they were regarded vaguely as colloids which were not susceptible to study by the normal methods of chemistry. He became convinced, however, from examining the binding of calcium by serum proteins that colloids were subject to definable and verifiable physical and chemical forces acting between distinct protein entities.[7] He chose antibodies because he knew that they could precipitate with antigens, even though many workers doubted even their existence as separate entities. In 1930 he showed that interaction between diphtheria antitoxin and toxin could be studied quantitatively, and in 1934 he proposed that the specific affinity of antibodies for antigen was determined by the shape of the molecules and the spatial distribution and strength of polar forces. He even concluded that each antibody molecule must have two combining sites whereas antigen molecules had several. Although he had no knowledge of the structure of antibody molecules, let alone having seen electron microscopic pictures of them, the ways in which he suggested that they could join together to form lattices would have been quite familiar to polymer chemists, but at that time polymer chemistry was in its infancy.[8] At the First International Congress of Immunology in 1971 Marrack was one of five persons who received its distinguished service award "for revolutionary ideas that have become commonplace in his lifetime."

Self tolerance

A similar citation could be applied to the proposal of Burnet and Fenner in 1949[9] that if animals could recognise all foreign antigens they must theoretically be able to recognise "self" antigens and that there must be some means whereby this was prevented; in other words, specific immunological tolerance must exist. Because twin cattle sharing a common placenta appeared to tolerate each other's red cells in their circulation they suggested that tolerance was a feature of fetal life and immaturity of the immune system. The mechanisms proposed by Burnet to explain how this could happen were somewhat implausible, and, although the concept of tolerance certainly jolted accepted ideas, its importance was not really accepted until 1956, when Medawar and his colleagues showed that newborn mice of one strain could be made tolerant of cells of another.[10] Even now we do not fully understand how self tolerance is brought about; nor do we understand why it sometimes fails and autoimmunity results.

Clonal selection

For many years it was generally accepted that when antigens evoked an immune response they did so by directing the synthesis in cells of new antibody proteins which somehow contained a pattern complementary to that of the antigen. This idea did not fit in with what was known about protein biosynthesis; nor could it account for the well known fact that when animals were reimmunised with the same antigen a much longer lasting and more rapid response resulted. The suggestion for an entirely new approach came from Niels Jerne in 1955.[11] He had studied antiviral antibodies and antitoxins using sensitive assay methods and had found that traces of antibody were present in the blood of animals which had never had any known contact with the antigens. To explain this he proposed that the body contained cells which normally make a wide range of different immunoglobulins, giving rise to the background level of natural antibodies, and that when antigens were introduced they combined with pre-existing antibody and the complex somehow stimulated the cells to replicate more of the same kind. This idea of regulation by natural selection could not be supported on biochemical grounds, but it set the stage for the clonal selection hypothesis proposed in 1957 by Talmage and Burnet and fully developed by Burnet in 1959.[12] This postulated that after a randomisation of pattern among differentiating lymphoid cells in embryonic life, each lymphoid cell carried genetically determined molecules expressed either as receptors for antigenic determinant or as specific antibody which it could secrete. Interaction of antigen with the appropriate cell could stimulate it to proliferate and to secrete its antibody, so that the immune response reflected the population dynamics of the totality of lymphoid cells. This explained immunological memory and, if self reactive cells had been silenced, tolerance. It was difficult to explain how the number of genes for all possible antibody specificities, which intelligent guesses put at 10^8 or more, could be present in the genome, but the hypothesis made such good sense and was confirmed by so many subsequent experiments that it was very rapidly accepted.

Only much later, when it became possible to examine single clones of lymphocytes and to apply the techniques of molecular biology to them, have we been able to explain how the population of

lymphocytes can apparently express more genes than their total DNA could code for. To go into this would go beyond the scope of this article, but in essence it turns out that the gene for each antibody molecule is a composite made by the random joining together of several pre-existing genes, each of which exists in up to 100 separate versions. This mechanism by itself would suffice to provide an enormous diversity, but an even greater diversity is added by somatic mutations which occur when the lymphocytes proliferate. Some obscure studies of the genetics of immunoglobulins[13] had suggested that only some device of this sort could explain what happens, but until it was actually shown by the molecular biologists to occur I think that no one would have believed it possible.

The network hypothesis

A further example of new insight derived from turning accepted ideas upside down is the network theory put forward by Niels Jerne in 1974.[14] He examined the consequences of considering that every antibody must be unique because the combining site for one antigen must be different from the combining site for any other. Thus perhaps antibody molecules would be treated as "not self" and could evoke an immune response even in the animal which made them. If so, when an antigen stimulates the occasional lymphocytes which can recognise it, and these proliferate and secrete antibodies, these in turn may stimulate other lymphocytes which can recognise the unique combining sites to make anti-antibodies. These in turn may evoke anti-anti-antibodies and so on. Hence, the whole immune system will form an interacting network, and the introduction of any antigenic stimulus will disturb the whole equilibrium. This bold hypothesis was not based purely on speculation. Evidence originally produced by the late Jacques Oudin suggested that antibodies could indeed stimulate anti-antibodies,[15] but no one had carried this observation to its logical conclusion. Jerne's hypothesis at the time seemed brilliant, but not helpful for those who were trying to find ways of controlling immune responses. Some of his colleagues, however, devised a means of testing its predictions, and they could be verified in rather special cases to begin with but enough to make immunologists realise that they must be prepared to consider in quite a new way how immune responses can be switched off or kept going. There are many people nowadays hoping to use anti-antibodies for purposes ranging from making novel vaccines to controlling some kinds of autoimmune disease.

Following wherever the trail leads

I began to think about serendipity and insight when I was a member of some grant giving bodies, which did their best to allocate sensibly the funds which were available. Applicants were supposed to outline in some detail what they proposed to do, and why, and what they hoped or expected to discover. This was entirely reasonable, but it struck me how difficult it would be to fulfil the grant honestly and yet to allow for luck or the chance observation which, if followed up, might uncover something really new. I myself had never had to write a grant application—in fact, I wrote my first one when I was over the age of 65—and it was no easier than if I had been much younger, despite all my experience in reviewing the grants of others. For most of my working life I had been on the staff of the Medical Research Council, with a bread and butter job in biological standards for the first 10 years or so, but otherwise not only free to decide what line to follow but provided with the facilities to do so. Quite often this meant following one's nose, but a nose, naturally enough, susceptible to scents which came from other immunologists on the international scene. In fact, before the Medical Research Council set up a peer review system for its own establishments there was a sort of unseen continuing peer review going on by virtue of a wish to be concerned with some aspect of research which would interest and could be discussed with colleagues both at home and overseas. But there was no requirement to write grant applications, and I realise how lucky I was.

In so far as I want to convey a message it is that finance of research should always contain a substantial proportion of funds to provide scientists who have proved themselves competent and to have inquiring minds with the security and facilities which will allow them to go in some agreed general direction but be free to follow wherever the trail may lead. I am sure that this is understood by the Medical Research Council and by other bodies such as the Royal Society and the Wellcome Trust. But to put it into practice, while at the same time funding ad hoc projects and allowing young research workers to try their wings, requires enough funds to do both. I am not sure that the government also understands this.

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What are the possible side effects of local anaesthetics used by chiropodists and what emergency first aid measures should they take in such cases. Also, is it advisable for them to be issued with adrenaline?

When used in small volumes and in low concentrations there are no side effects of local anaesthetics. Provided that chiropodists stick to the guidelines under which they have been trained they should experience no difficulty in using local anaesthetics in their every day practice. If used in larger volumes then some knowledge of the general pharmacology of the drug and of its toxic dose should be attained—for instance, the maximum recommended dose for lignocaine hydrochloride by injection is 200 mg (20 ml of 1% lignocaine hydrochloride without adrenaline). Should this dose be exceeded or should the injection inadvertently be given intravenously then the main effects are excitation of the central nervous system and will include nausea, convulsion, and, less commonly, depression of the cardiovascular system. The emergency first aid to deal with such occurrences would have been taught to the chiropodists during their training—for example, maintenance of a basic airway, breathing, circulation, and the general care of the patient.

The second part of the question may be viewed in two ways. Adrenaline should not be used in conjunction with lignocaine or any other local anaesthetic drug in the periphery where there is a chance of causing intense vasoconstriction and thus tissue and eventual limb damage. To use adrenaline as a resuscitative drug would require more extensive training of chiropodists in advanced life support methods. The possibility of them needing to use adrenaline is small; hypersensitivity reactions occur mainly with ester type local anaesthetics (amethocaine, benzocaine, cocaine, and procaine) and these are best avoided. In summary, I believe it is safe for chiropodists to use simple amide type anaesthetics such as lignocaine in low doses, at low concentrations, and without added adrenaline. Every chiropodist who is trained in injection in local anaesthetic techniques should also be trained in the basic pharmacology of the drugs, the problems of such administration, and the emergency first aid required should such an injection go wrong.—D A ZIDEMAN, consultant and honorary senior lecturer, London.