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Award of the James Cook Medal to Sir Gustav Nossal on 13 September, 1995, and his Address: Medical Science and Human Goals: a Struggling Pilgrim's Progress

General Meeting No 1053 of the Royal Society of New South Wales was opened by the President, Dr D.F.Branagan, at 6.30 pm on Wednesday 13th September 1995 in the Rooftop Room of the Australian Museum.

The President indicated that this was a special occasion for the Society, and that it was his pleasant duty to introduce the speaker for the evening, and to award to him the Cook Medal.

The Cook Medal was first set up in l947, was funded by Henry Ferdinand Halloran, who had been a Member who had joined the Society in l892 as a 23 year-old. Halloran was a surveyor, engineer and town planner. He did not publish anything in the Society's Journal, but he was a very enthusiastic supporter of research. Halloran funded what were to become the Society's two most prestigious Awards, the James Cook Medal, and the Edgeworth David Medal, the latter the Medal for young scientists.

The James Cook Medal is for outstanding contributions to science and human welfare in and for the Southern Hemisphere. The Society has made some 25 Awards in the 48 years the Award has been established. Only four of the Cook Medal Awards have been external to Australia: but they do include Albert Schweitzer. so I think he must have just got in because he did work close to the equator in Africa, but maybe it was just within the Southern Hemisphere.

We have only had one politician, that was Lord Casey, an engineer, but there have been several other engineers; we've had a chemist or two, agriculturalists, and we've had physicists; in all cases Australians of considerable calibre, but we've particularly had a predominance of medical scientists.

On the Epping Road at Lane Cove, on the way to the Society's office and Maccquarie University, at this time of the year there is a particularly wonderful display of azaleas of the finest quality and in a variety of colours. But there are some that I suppose we could call really purple patches.

And when I look back at the Cook Awards notice that there have been at least two purple patches in the Awards through staff at the Walter and Eliza Hall Institute in Melbourne. They are, of course, first, Sir Frank Macfarlane Burnet, who was awarded the Medal in 1954, and more recently Dr Donald Metcalfe, for cancer research. It's certainly an impressive record, I think, for the Institute, which of course has an unparalleled renown in Australia.

Tonight, Sir Gustav Nossal is the third, and I hope that in ten years time his protégé will be here to follow on the story. I don't think I need to go into Sir Gustav's long and illustrious career: I suppose I can say that he is a Sydney University graduate: he has come from this fair city. He became the Director of the Walter and Eliza Hall Institute in 1965, and Professor of Medical Biology at Melbourne University. He is currently President of the Australian Academy of Science, and he is a Director of the CSIRO and of a number of companies. He is Chairman of the Scientific Advisory Group of Experts on the World Health Organisation on Global Programs on Vaccines. He is a Fellow of the Royal Society, and was awarded the CBE in 1970, KT in 1977; he is a Member of the Prime Minister's Scientific Council.

He has other interests: he has been involved, of course, in the Felton Bequest, in the Gallery in Melbourne. But unlike the original donor of the Cook Award, F.H.Halloran, whose recreation was motoring, Sir Gustav's recreations, he says, are literature and golf. I'm not sure how good at either he is; he says he is promising to get into literature, at least in the scientific sense, in the next few years: and I won' t ask him about his golf handicap!

I think without further ado I should present Sir Gustav with the Medal: on the reverse side the medal reads:

> "Physical Science, Biological Science and Social Science" with a map of the Southern Hemisphere; on the obverse side: "The James Cook Medal for Outstanding Contributions to Science and Human Welfare in the Southern Hemisphere "Awarded to Gustav Joseph Victor Nossal KT, 1994, by the Royal Society of New South Wales"

It is my great pleasure to present this Medal to you.

Medical Science and Human Goals: a Struggling Pilgrim's Progress

Mr President, distinguished Members of the Royal Society of New South Wales, Ladies and Gentlemen: this has been a particularly moving introduction, and a very, very special occasion for me to be back here, in the city that never leaves your heart once you have grown up here, and in particular to be receiving this award under the Presidency of this distinguished person, of my

old University mate, David Branagan: we have been good friends for forty years, and its absolutely wonderful to be receiving this award under his Presidency.

I should immediately state, of course, that it is very wonderful to have the chance of thinking about James Cook: really he was a medical scientist! Long after the controversy about who really did discover Australia is over (and it wasn't Cook), people will remember him as the discoverer of vitamin C, and the prevention of scurvy on those many long boat voyages. And indeed his tremendous enthusiasm for science (he sponsored Banks and many others) makes him truly one of us in science. I think he would be extremely pleased about the giving of this award to scientists and to those interested in science down the years. It is a tremendous honour to receive this medal with its distinguished history: and I can only say it is immensely humbling.

Now having said that, I thought to myself you might all find the title of my talk a little bit self-indulgent: 'Medical Science and Human Goals: a Struggling Pilgrim's Progress. Why did I choose such a sentimental-sounding title? Well, I got to thinking that this medal would probably be the last award which I would receive before my retirement in eight months' time. Its been a long ride in the Walter and Eliza Hall Institute: as a matter of fact, it was thirty years as Director just eleven days ago, on the 1st of September, 1965, when I took over, and now it's coming to an end. I got to thinking about what does it all mean? You know, what has my life been about?

And I came to the realisation quite quickly that society at large has only the dimmest of outlines of what a medical scientist actually does, and of where medical science sits in the great spectrum of national development and world health. So I thought it would be quite good fun, albeit a bit self-indulgent, to sketch the pilgrim's progress, to tell a little about where it all began, to tell you a little bit about what I think is important, and where it may be headed. And I have a subtitle for the Address: the subtitle is called: "From Molecules to Persuasion".

To give you a sort of glimpse of what I would like you to take away, I actually believe that medical science is a seamless web, and to improve the health of humanity, including our own citizenry, we will need everything: from molecular science, the understanding of DNA, and the biochemistry and genetics of the cell; and the physiology of bodily systems, which has been my main line of activity; through the more applied sciences of pathology and clinical medicine; and right through to the very applied population sciences of epidemiology and public health. You need all these in order that the discoveries speed their way to as large a proportion of the citizenry as possible in the shortest possible tine-frame.

So roughly speaking, I want to divide the talk into three not quite equal thirds: I will talk a little bit about the science that I've done. That's going to be a touch hard, but I promise you it won't take more than fifteen minutes. There's got to be a bit of science in a talk like this, or it would be trivialising the occasion!

Then I wanted to talk for a while about what this great science of immunology means for the world, in terms of the total population, not that one-third of a percent of it which lives in Australia, or indeed that approximately one-sixth of it which lives in the fully-industrialised world.

And then lastly, I want to talk briefly about the work that still has to be done, when the medical scientist and the medical professional have finished, before the society at large can benefit from anything that happened.

Early Motivating Influences

I want to set the scene by describing in just a very few minutes how I even got to thinking about medical science. I had started medical school in 1948, and there may be a few people in the room who might remember that at that time we only had five years of secondary education in New South Wales. So I was a little young starting, all of sixteen years old when I entered medical school: just imagine that, making a decision about what you are going to do for the rest of your life at the age of sixteen! Amazing to think back on.

And we had in 1948 probably the height of that big wave of repatriated soldiers, who were the ex-service men and women, who swelled the year to a very large size. Now, I remind you, there was no quota in those days: anyone who passed the Leaving Certificate examination, or to be quite precise, who matriculated, which meant you had to get five subjects (four subjects would pass you, five subjects gave you matriculation), anyone could get into medical school. And so we were six hundred in first year.

We had a rather profane medical student song which had as its refrain '50% must fail, 50% must fail'. And it was actually literally true, because in fact in second year we started anatomy: that was the main subject, and the main way of learning anatomy was carving-up the human body. And there were a maximum of thirty-two students to a body. So you can work out the sums: with a few slippages from second year, and second year repeats, they could only pass three hundred of us, because there were only ten tables! Eight people to a quarter body, trying to carve it up, when I think back, was really quite ridiculous.

So 50% indeed did fail, and when I woke up and recognised that I was really now a uni student, I was already in the third year! By then I was eighteen, and sort of getting out of childhood and into adulthood. And a group of us from what you might call perhaps the brighter kids in the class, said 'listen, this is no good, we're not learning anything: if we're going to learn anything, we're going to have to teach ourselves'. Which is probably not a bad adage to take through life, if you think back; you know, the best learning may be that which you do for yourself.

So we started in this little group to give each other seminars: that is to say, one person might read up, for example, how blood cells are formed; another person might read up about the Krebs cycle and intermediary metabolism in cells and biochemical features; and a third person might read up the latest thing about Jack Eccles' work on the nervous system. And we would read into these topics, and then give it in very digestible form to the six, eight or ten kids that formed this particular study group, the end result being that we did pretty well in the exams if one of those topics perchance turned up! Of course, if it didn't, it was just for our own interest and so forth. This process of digging into the medica1 literature gave me a real feeling for research.

Two other things things contributed to my choice of science. First, I had an elder brother who had done science, not med., and had become a biochemist. He was quite a few years older than myself, and of course you tend to hero-worship your elder brother. He had moved to Adelaide, but he always used to bring back friends for the ANZAAS Meetings. In those days in the 'forties, ANZAAS was a big thing: it was THE national science meeting. And these people would come and stay in our family home. My head, as a thirteen or fourteen-year-old kid, would be buzzing with the wondrous researches that these people were doing. And that helped too.

So in the event, I took a year off to study viruses at Sydney Uni, under a chap called Pat de Burgh, a Senior Lecturer in Bacteriology. He was a virologist, a very clever man, and during that year (he only had two students doing this Bachelor of Medical Science course) he took us down to Melbourne and we spent three days at the Walter and Eliza Hall Institute, one day at the

Fairfield Infectious Diseases Hospital, and one day at the Baker Institute: three of the great centres of medical research in Australia. And I guess I got hooked during that week. I found that so fascinating that, at the ripe old age of twenty-one, by now, I said 'gosh, I've got to give this thing a try'.

But life had stored up one funny little surprise for me: you see, I thought this business of the viruses and the biochemistry would be my life. Now, why viruses? Because they were the smallest form of life. And why biochemistry? Well, it was a little before DNA broke, but I really thought biochemistry would turn out to be the king of the sciences, of the life sciences, because it was the most basic. That did indeed turn out to be true, except now they call that branch of biochemistry 'molecular biology', which word had not been coined in 1952.

So here was I, seeking to discover all the secrets of the life process by becoming a biochemical virologist. What could be better than to sit at the feet of the world's greatest virologist, Mac Burnet?

In 1957, I tiptoed into his lab, having graduated in medicine, done my residency at Prince Alfred Hospital for a couple of years; all my friends thought I was mad to go and do this research business. Why, with another two years you could have become a Member of the College of Physicians, and you could have become a cardiologist, and put your shingle up on Macquarie Street, and it would have been fantastic: they all thought I was absolutely crazy to go into this research business.

But I tiptoed into Burnet's lab, only to find out that he had switched his interests from the virus, the cause of many diseases, to the immune system, the immune defence system which fought the virus diseases.

To be frank, I had absolutely no interest in immunology, none whatsoever! But the die was cast, I had set my life to moving down to Melbourne, with my wife and tiny little baby daughter. Hence I was perforce an immunologist!

So, you know, things happen in strange ways: my brother being a biochemist, Pat de Burgh being a biochemical virologist, my meeting Burnet at such a young age, and hearing him talking about the polio virus and the polio vaccine. Fantastic stuff for a twenty-one year-old. And here I am, the virologist perforce turned immunologist.

Discoveries in Cellular Immunology

The big problem in immunity was the number of things you can become immune to. The vast diversity of antibodies, each capable of recognising portions of different bugs. And, you know, that had been known for a long time. But then along come Watson and Crick, and they tell us that DNA is the master molecule, and they tell us information is carried in DNA, and it can't be carried into the cell by a foreign invading germ, by the proteins of a virus or a bacterium.

So three people: Niels Jerne in California, David Talmage in Denver, and Mac Burnet in Melbourne, came up with this theory, for which Mac Burnet received enormous credit. The theory said that the antibody molecule is not shaped or patterned as a template against the vaccine molecule, the antigen. Rather, it is pre-formed in the body existing as a receptor on the surface of the cell. All that the antigen then has to do is to come and stimulate the right cell, and then through mutation afterwards, a really good antibody would be formed, exactly congruous to the antigen.

I said to myself, gosh, this is a bit crazy. We'd,all been brought up to think that this direct template notion, which had been around for about twenty years, and had been backed by the great Linus Pauling (one of the few people to win two Nobel Prizes), must be correct.

Burnet challenged me to think again, and I said 'I think we can disprove this very quickly: I am considering immunising a mouse or a rat with three different vaccines (three different antigens, to use the technical term), get the antibody-forming cells from the lymph node or from the spleen of these animals, and very quickly show that each cell will produce all three antibodies'. Now if that's true, Burnet's clonal selection theory is dead. It was a Popperian situation: I could perhaps disprove the new hypothesis.

Well, of course, there weren't any methods for studying antibody formation by single cells, and I had to invent those, and fundamentally, we came to a pretty simple conclusion, and this will appeal to many of those of you who are physicists or chemists, and understand the law of mass action.

If only one cell is producing antibody in tissue culture, and you were to put it into, say, one mil in a test-tube, of course the antibody formed would be extremely dilute, and you would never detect it. But if in point of fact you could confine the environment into which the cell puts out its antibody to a tiny little droplet, of perhaps a ten millionth of a millilitre in volume, then the antibody titre, as we call it, the antibody concentration reached at the end of a four hour or twenty-four incubation period, would be exactly the same as if we'd put 100 million cells into 10 ml, because it's a question of concentration. So we could get a high concentration of these antibodies into these tiny, tiny little droplets, which we stopped from evaporation by surrounding them with minera1 oil.

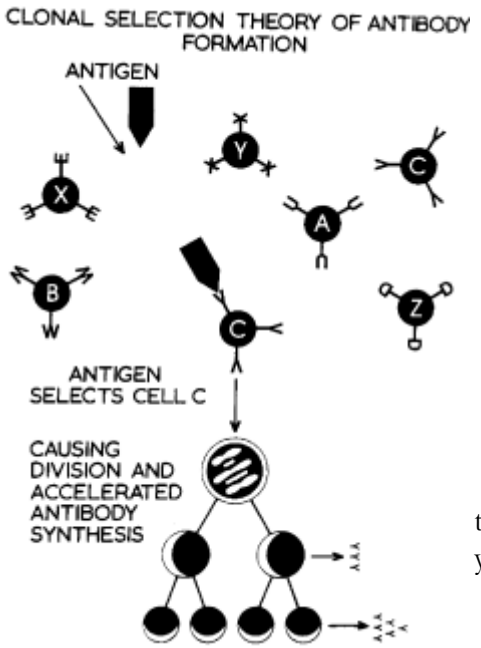

Fig.1 [Click on image for larger version] The revolutionary aspect of the clonal selection theory of the antibody formation was that it saw the antigen only as selecting a cell with a corresponding receptor, not as carrying new information into the cell

And then we used as a titration method, an antibody detection method, a very tiny number of motile bacteria, instilled into that droplet by micromanipulation, which, if any antibody were present, would immediately stop swimming and begin to clump; if no antibody were present, then they would swim happily for half an hour, after which you would terminate the experiment.

The resulting thing was, that one cell always formed only one antibody. The first little step had been taken towards suggesting that this clonal selection theory (see Fig.l) could indeed be true. Just a little side-light to history: we worked on antibody formation by single-cells for about five or six years, but we weren' t clever enough to recognise how brilliant it would be if we could immortalise those antibody-forming cells by fusing them to a cancer cell.

And that is exactly what Nilstein and Kohler did, for which they won a Nobel Prize, and for which you now have monoclonal antibodies that are widely used in diagnosis, in therapy, and in industrial applications. One of the greatest tools of modern biology is monoclonal antibodies.

We laid the groundwork for that work: we did the pure science, but we didn't do the applied science. Hence the seamless web, the need to continue this matrix of scholarship all over the world.

I should go on to say that the very fact of this highly diverse repertoire of antibody genes and antibody-forming cells, means that every single cell makes antibodies that are a little bit different. And hence the monoclonal antibody has a razor-like precision of recognition: that's what determines its special properties.

The next thing we did was to say 'well we've got to disprove this direct template hypothesis more clearly'. What we did was to make the antigen very highly radioactive with an extremely high specific activity of radioactive iodine, which was a convenient isotope for registering on photographic film. And we injected this very hot antigen in limitingly small amounts into rats (see Fig.2). Then we performed what we call an autoradiograph: it was really taking an X-ray on a single cell, basically.

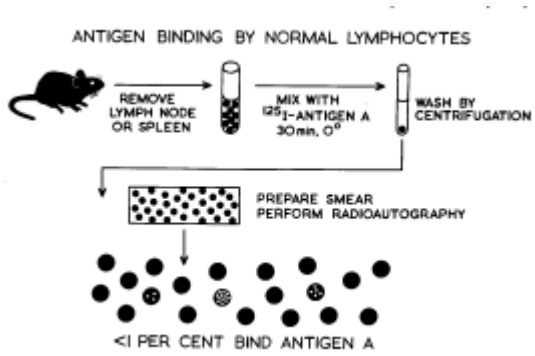

Fig. 2: [Click on image for larger version] This experiment shows that normal B lymphocytes are very heterogenous in their capacity to bind a given antigen, antigen A. The great majority of cells do not bind at all. Some bind it just a little bit. Only a very occasional cell, perhaps 1 in 10,000 or 1 in 100,000 binds with high affinity. If this cell can be separated, culture experiments show that it will form antibody to antigen A.

Wherever the isotope goes, you get a little dark silver grain in the photographic emulsion that you've applied to the cell. An antigen-containing cell would be black with dots on it. A cell without antigen would have no developed silver grains on it. We went through hundreds of single cells and finally proved that these cells had no antigen in them. In point of fact, we could have detected easily four molecules of antigen in the cell, and we found absolutely none. So the direct template hypothes is was untenable as there is no antigen in the antibody-forming cell to act as a template.

That actually rated a fairly sizable story in the New York Times, about half a page, and it is an interesting reflection on U.S. science journalism that so much publicity can be given to a totally basic-science discovery.

We went on (and you won't believe it, we took a total of eighteen years from the first experiment to the last) to provide a formal proof of the clonal selection theory.

We did this by actually fractionating normal lymphocytes, normal white cells on antigen layers, recovering a tiny fraction (ne cell in ten thousand or one cell in 100 thousand) capable of binding that antigen. We could then culture, in single-cell microcultures, the antigen-specific cells, and we could prove that the only antigen against which those could form antibodies was the antigen that had been used in the fractionation procedure: it couldn't form antibody to anything else.

So here if you want, in a totally un-immunised animal, we found the needle in the haystack, we found that one cell that would make that one antibody, ready with preformed receptors.

A very important thing happened when Jacques Miller joined me, another Sydney University graduate, who had been working in London for quite a few years; Miller was an expect on the thymus, which is the big lymphoid organ in the chest; and I had been working a lot on bone marrow.

Miller, Warner, Szenberg, Mitchell and others worked out that the white cells in the blood, which we call lymphocytes, the cells of your immune system, belong to two great families: those thymus-derived, now called T-lymphocytes; and those bone-marrow-derived, called the B-lymphocytes. The thymus makes T-lymphocytes, bone-marrow makes B-lymphocytes. They leave these organs and reach the lymph-nodes and spleen and the circulating blood, and this is your defence army.

The two types of cells do two entirely different jobs: the B-lymphocytes make antibody: they are the cells that go wrong when you have agammaglobulinemia, which you treat with injections of gamma globulin, The T-lymphocytes, on the other hand, don' make antibodies, but they do mediate a strong inflammatory response.

Think of the B-cell as a policeman with a gun that can shoot an enemy at a long distance: a B-cell-making antibody in the lymph-node could kill a small-pox virus entering via the big toe, because the antibody moves in the blood-stream.

The thymus-cell, the T-cell, is more like a wrestler, who wrestles a foe in close combat by direct cell contact. It turns out that the T-cells are particularly important in viral infections, because they are capable of killing virus-infected cells, and therefore of cutting short an infection, and stopping the spread from cell to cell. T-cells also fight infections by promoting inflammation and strengthening the action of scavenger cells. One kind of T-cell is the target in AIDS.

We found out two more things: we found out that the T-cells and B-cells had to collaborate in order for a good immune response to go forward; and we found out ways of distinguishing and separating the different kinds of lymphocytes.

Now are you beginning to get the drift of my story? Here was research that was genuinely the purest of the pure. Our purpose was solely to find out how the immune system worked: how cells make antibodies; how the genetic code works in terms of antibody formation; what the thymus contributes to immunity; what the bone marrow did; how the cells interacted with one another: pure science, with no applied intent.

Along comes something like the AIDS virus, but because of this prior work, and of course, a lot of other work from around the world which I haven't had a chance to mention, it is possible to understand the AIDS virus, define its target, and grow it in the test-tube. Had that prior basic knowledge not existed you would never have been able to grow the AIDS virus, and nobody would have been able to develop immuno-therapeutic AZT or DDI or any of the other drugs,

nor would you have had a chance to create experimental vaccines. Unfortunately we do not yet have an AIDS vaccine about which we can be confident.

So, basic science, applied science, the seamless web.

Now, the last thing that I want to say in terms of my own scientific work, is that to the immunity, there is a mirror image. You make antibody to lots of things: you make antibody to viruses and bacteria, you also make antibody and a strong T-cell attack to someone's kidney graft, if I choose to place a kidney graft in your body in order to cure your chronic renal failure. We have to use drugs to keep that immune response at bay. But you don't make antibody to yourself.

Now there's a deep puzzle here. Why should another person with the greatest of vigour reject my kidney, no matter how carefully stitched into his body, and why should that person so readily allow his own kidney to live without rejection? There's got to be some principle behind that.

We've also now worked on this subject of immunological tolerance (see Fig.3) for, well, in my case, thirty-eight years; and we've got a long way towards determining the secret of how it works. When I say 'we', I must immediately add that it was really the global peer-group.

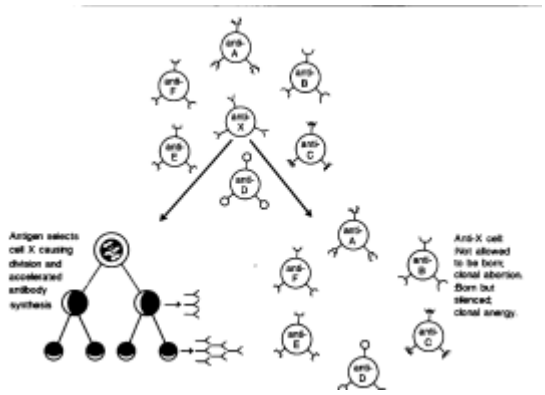

Fig.3 [Click on image for larger version] Immunological tolerance (right-hand side of the diagram) is more or less the mirror image of clonal selection (left-hand side). If the antigen encounters the lymphocyte population while the latter is still immature, as would be the case with a self-antigen, the cell is either deleted or rendered anergic.

Tolerance, the capacity to tolerate yourself, is the opposite of clonal selection. It is in fact a negative action of antigen when it acts on the white cells under certain circumstances. And it comes in two flavours: either an actual physical killing of the anti-self cells, or a non-lethal regulatory signal, which I termed 'clonal anergy' in 1980. To my great pleasure, that word has stuck, and we now recognise these two forms of tolerance, anergy and deletion. Right at the moment, my main work is actually in tidying up the exact difference between those two.

Vaccination and Other Practical Goals: Association with NHO

I want to move on to the next stage, because that's all a little bit technical.

Round about the middle to late seventies, I became very impressed with the selfishness of what we were doing. I thought to myself 'O.K., here I am running the Hall Institute, here we are doing all of this basic science, here we are having fantastic fun, we're actually becoming world-famous

(I shouldn't say it, but it's true), doing this basic science, which has given us a lot of pleasure. But to the extent that we're working on diseases: on multiple sclerosis, on leukemia and other cancers, what in fact were we doing to be true to the Pasteurian heritage? What were we doing about vaccines, what were we doing about tropical diseases, what were we thinking about the third world, what were we doing about poor countries?' The answer was nothing.

So I did two things; I started a large program under Dr Graham Mitchell at the Institute, which I won't talk about today, which is searching for a malarial vaccine, and which has now reached the stage of early clinical trials: we then hope to go into larger field trials, either late this year, or, more probably, early next year. So the malaria vaccine work has been slowly rumbling along as an effort that we started in direct response to this pain in my breast that we hadn't been true to the Pasteurian heritage.

And the second thing I achieved was, through invitation, to become tied up with the World Health Organisation. And I'm now the Chairman of what they call the Global Program on Vaccines and Immunisation. And this program has three components:

First is the delivery component, called EPI, the Expanded Program on Immunisation, the naked aim of which is to get the common childhood vaccines, which all our kids get, to every single one of the one-hundred and thirty million children that are born into the world each year. That's an amazing goal, isn't it'? A suberb challenge to meet this aim. Now that of course means that we have to have, for all the world, vaccine supplies and vaccine quality control.

The second goal therefore is to work out politically how to transfer the technology to some of the larger third world countries, such as China and Indonesia, enabling them to make at least some of their own vaccines, and somehow to make sure that we haven't got two classes of vaccines, one with good quality control, and one that may be inferior.

The third and very important goal is Vaccine Research and Development, or VRD: more vaccines, particularly for diseases where we don't have vaccines yet. This third component in its turn has three components:

First, to promote the development of new vaccines of importance to the world, and prepare for their introduction into the Expanded Program on Immunisation; secondly, to simplify vaccination procedures; and thirdly to develop cheap simple new diagnostic tools.

In regard to the second item under VRD, vaccination procedures, my colleagues in WHO have a slide that looks a bit like St. Sebastian: its got arrows sticking all through, except that the arrows aren't arrows: they're syringes with needles. We can't have children looking like pincushions. Our own children have already received a lot of vaccination shots by the time they're eighteen months: they get their DPT at 2 months, 4 months, 6 months. Polio is fortunately given as drops. Then they have measles, mumps and rubella. Now there's the excellent meningitis vaccine. Imagine if we had twelve more other good vaccines, we could get into a consumer revolt, even in the developed countries, let alone in an African village, where you might have to walk five miles to get to the little station where this vaccine is given.

So simplified vaccination procedures are very much required.

As you come close to the total eradication of diseases (and that is very close for polio, could be a reality for measles, and is a reality, of course, as you all know, for small-pox), before you can

cease vaccination, thereby saving huge amounts of money, you have to be damned sure that it's completely gone. For that you have to have excellent surveillance mechanisms.

And thinking of remote African and Indian villages, that means cheap and simple new diagnostic tools, the third item listed in the Vaccine Research and Development agenda.

The Expanded Program on Immunisation

Now a few words on the Expanded Program on Immunisation. There are seven vaccines that are supposed to be going to all the children of the world: diphtheria, pertussis, tetanus, polio, measles, BCG for tuberculosis, and hepatitis B.

We in Australia do not use the tuberculosis vaccine for two reasons; there isn't much TB left, thank God (but it could come back); and also the BCG is not as good as it should be (there is a requirement for more research development of a more satisfactory TB vaccine). Vaccine for hepatitis and from 1995, according to the World Health Assembly should be going to all countries with a high carrier rate. Vaccine for yellow fever is also required in some countries. The program has made great progress in poliomyelitis.

In the Peoples Republic of China, where the birth cohort is 23 million children each year, they had one case of polio in 1994, one certified case: remarkable progress. And we have set our cap at global polio eradication by the year 2000. A very tough task! A very difficult goal to achieve: it will, as with smallpox, be Africa that will be the hardest nut to crack.

We have some countries both in Africa and in the Balkans where civil strife could frustrate the procedure, but we are making really excellent progress. And you imagine the world without polio, you imagine the world where no-one has to get the polio drops any more, and it's been estimated that the net present value of polio eradication is thirteen billion US dollars. The costs, we believe, to get this point will be a hundred million a year extra to what we've got each year between now and 2000.

Immunisation coverage over this period has gone from 5% of the developing world to 80%: but unfortunately I have to tell you it appears to have have stalled then, and the last 20% are going to be very difficu1t to get.

The plan was for 95% reduction of measles deaths by this year: there has been a very significant reduction of these deaths, probably not quite to the 95% of the 2 to 3 million deaths per year that is "normal". All told, vaccines prevent 3 million deaths per year, but 2 million vaccine-preventable deaths remain. Sixty percent of the deaths which the present vaccines could stop are being stopped, forty percent of them are still eluding us. Now what's the total picture?

There are 12 million deaths of children in the world each year: 9 million of these are due to infectious communicable diseases. Only one quarter of the pie is accessible with present vaccines. We have three quarters of the deaths from diseases for which no suitable vaccine has yet been made. What are these diseases?

The biggest killers are two-fold: the diarrhoeal diseases, both bacterial and viral; and acute pneumonia of infants, which is particularly a problem in our own part of the world, where, in Papua-New Guinea, for example, pneumonia beats malaria as the number one killer. Malaria is a further enormous problem: there are somewhere be tween one and two mil lion deaths per year from malaria each year.

If you pool both childhood and adult deaths, there ace nearly three million deaths per year from tuberculosis, I think that in itself shows that the BCG is not doing a good job. We have to do a lot better. And consider the number of deaths from measles: 2 to 3 million per year. One reason is that the current measles vaccine is not active in very young children, and the second is that measles and bacterial complications from measles are much more serious in a third world setting.

Measles is immuno-suppressive, and the immune response is not good for about a year after the attack, or not as good as it should be. That means that if you're under-nourished, and if you are in a situation of constantly being exposed to infectious micro-organisms every single day, your resistance will crumble, and so this overall measles death incidence is about 2 to 3 percent; it's still not high, but when everybody gets a disease, you can calculate what the toll is.

Now, the existing measles vaccine is much less efficient, when antibodies of maternal origin persist at the time of immunisation. I've told you everyone gets measles, right? They've either been immunised or they've had the disease, so Mum has antibodies. Those antibodies cross the placenta, enter the foetal blood stream, protect the child against measles over the first four months of life.

But then, gradually, the maternal immunity wanes; and the vaccine doesn't take too well before 9 months, even in developed countries. So we have a blind period and many unprotected infants. We have to devise a measles vaccine which works in the presence of low levels of anti-measles antibodies derived from the mother.

Now, another important development would be a single-dose tetanus vaccine. But why'? Well, I've told you that this EPI program is new, and I've told you that, previous to its existence about 10 years ago, vaccine coverage was 5% in the developing countries. This means that young mothers- to-be aren't protected against tetanus. Right?

So, they have their babies, in a little African village, where there have been domestic animals, where the hygienic conditions are not good. As you all know, tetanus spores (a) live for a long time, (b) are carried in animal faeces, or human faeces for that matter, and they can remain in the ground for a long time. End result: neo-natal tetanus: when the little baby is born, it gets tetanus, it dies of lock-jaw, with the horrible frothing at the mouth, that we now only read about in text-books; that you maybe have heard as horror stories from some older uncle or grandmother.

Now we've got to stop that: and we've got to catch these pregnant women, but we may not be able to get them to come back for three in jections. And actually, they certainly need three, they may perhaps in fact even need four, depending on where in the world, and how good the vaccines are, and so forth.

So we need a one-shot vaccine which gives a lasting effect to simplify the vaccination schedule. And that is, as I say, overall, quite apart from tetanus, a very big goal in our research program. Applied research: not very glamourous, not nearly as Nobel-Prize-winning as monoclonal antibodies. But this applied research is enormously important.

And so we come to vaccine combinations: we come to new ideas about immunising via mucosal surfaces. We come to oral vaccines: easier and cheaper; no needles, no need for sterilisation of syringes; no AIDS transmission, no hepatitus-B transmission, if your autoclaving equipment breaks down. Of course disposable needles and syringes are the ideal, but sometimes difticult to achieve in a third world setting. A very new idea is nucleic acid vaccines, which we won't be able to go into tonight. Oral vaccines are certainly one simplification of vaccine delivery.

From Molecules to the Persuasion Game

So much for the responsibilities that I think we carry for the third world. But I want to end up on a surprising note, a note which you might find a little bit unusual.

I've actually come to the view, over the last seven or eight years, that the medical science, and even the public health application, such as these public health vaccine programs, are only two-thirds of the story: the final third of the story relates to human behaviour.

Now, let me surprise you: you believe that smoking rates have gone down: they have: 30% of the population still smokes, and that's 45 years after Richard Doll first showed that smoking causes lung cancer, and 30-plus years after it was shown that smoking was responsible for much of heart disease. We're only just now starting to see the down-turn of lung cancer rates in men, in Australia, and we have not yet seen the end of the rise of lung cancer deaths in women: it's still rising.

That's what I mean by persuasion. You can't just be a scientist: you've a1so got to be a marketer: you've got to get your ideas across to both the profession and the public at large.

I wanted to talk for a moment about STD's. I think Australia has done a wonderful job in STD's; but the pressure has got to be kept up.

We cannot be complacent, we have to keep investing, we have to keep spending money to keep AIDS out of the heterosexual community, and to continue to reduce its impact on the gay community, and on the intravenous-drug-using community. It's got to be a persuasion game, it's got to be a case of smart marketing.

Let me tell you a story about vaccines. There's a new vaccine, which your kids and grandkids are getting. It's called HiB. It's the vaccine against the worse of the two forms of bacterial meningitis: a wonderful vaccine. Efficacy rate in the high 90's, side reactions virtually unknown.

And we're doing a good job in introducing it: but the most brilliant job has been done in the United Kingdom, where they blitzed the population with an expensive media campaign, a little akin to our road accident campaign in Victoria, which you may have heard about: the horrendously graphic ads which showed the effects of drink driving and the effects of speed, and which in their way have made Victoria the leader in the world in reduction of traffic deaths.

So we've got to be marketers, and we've got to get into the persuasion game, and we've got to take public health and preventive medicine very seriously. Right at the moment, you and I are spending eight and a half percent of this country' s Gross Domestic Product on health. But of that, 97 to 98% is spent on the sick now, here today's sick. I wouldn't deny the genuine demands of those sick today.

But we very rarely think about public health, preventive medicine, positive health promotion, health education; the simple things: avoidance of smoking, avoidance of substance abuse, eating a healthy diet, getting a very diversified diet, having your blood pressure checked regularly, having a mammogram, having a Pap smear, and possibly, as the next major step, the introduction of fibre-optic sigmoidoscopy for the early diagnosis of colon cancer.

These unglamourous things, actually very straight-forward, on which we spend the two or three percentile, can have a major impact on mortality and morbidity, and are in many ways a much more appropriate expenditure of the health dollar.

But you see, its tough, because when grandma's sick, let alone when a child is sick, you'll pull out all the stops. There is nothing that you won't do to urge the politicians to build that extra liver transplantation unit or two, somehow make sure the district hospital doesn't close, or somehow doing something for the one already sick.

The more cerebral activity of preventing the 30 years of pathology which leads to coronary artery disease, through a healthier diet and exercise, and keeping people of a reasonable weight, that doesn't grab the public imagination nearly as much.

That's why I need to talk about it with you, that's why I'm absolutely delighted that our friend from the 'Australian' is taking avi6 notes, because this is really important. We've got to redress the current imbalance between acute crisis medicine which uses high-tech intervention, for people who have been harbouring pathology in the body for thirty years, and the future, which depends on research, the search for better cures, and on education for preventive medicine and public health. Thank you very much.

(Applause) President: Thank you, Sir Gustav.

Questions from the Audience

President: Sir Gustav has indicated to me he is certainly prepared to answer questions and take on discussion: I'm sure there will be many who would like to take advantage of this.

Dr F.L.Sutherland: If you are reducing infant mortality, by the vaccination progam, does that not create a bigger population problem to the world?

Sir Gustav: It's a very important question, fortunately it does have an answer: in the 25 years or so since I have been interested in world health, I've talked to literally dozens, if not scores of people from the developing world, and people interested in the development process.

They are absolutely unanimous on one thing: that is that you can sell birth control only in the context of maternal and child health. If you can guarantee a woman she will have a healthy child, and if you persuade the woman that spacing the births will add to that child's health, you have a chance.

If you attempt to control the human population by high death rates (really, in a sense, what you're saying: doing something that doesn't reduce the death rate, but maintains a high death rate), the sheer answer is that people over- compensate, and more particularly do they over-compensate since the green revolution has produced plentiful foodstuffs in most of these countries (even India is now a net expocter of food: if you remember thirty years ago how many famines there were in India).

So as countries leave true poverty, and begin to enter newly industrialised status, the pattern has always been exactly the same: reduce the infant mortality rate, and your birth-rate will come down at an increased rate. Increase the death rate, be it by famine or pestilence, and human beings over-compensate, because, don't forget, there is no social security in these countries. The only guarantee for your old age, which probably hits you in the '50's is your living male children.

So wouldn't you too guarantee that you'd have a little bit of redundancy left, so that you don't starve when you're old if you can't work any more'? And that is absolutely clear-cut.

It's a hard one to explain, I mean, it's a bit counter-intuitive: you say, O.K., population size is a mixture of birth-rates and death-rates: there's two ways of controlling this: increase the death-rate, or decrease the birth-rate: the fact of the matter is, increasing the death-rate doesn't do it.

Lady questioner: Is there any work on a birth control vaccine'?

Sir Gustav: Yes, a lot of work. The answer is: there is right here and now a birth- contro1 vaccine: it is a vaccine directed against the hormone human chorionic gonadotrophin, which is produced by the ovary in the first few days of pregnancy (it is produced actually as the ovum travels down the Fallopian tube): it's absolutely essential for implantation of the fertilized egg in the womb.

And that works: it doesn't work perfectly: it's been primarily trialled in India, and it's reversible. It don't seem to have any side-effects, but the problem with it at the moment is that it only works in women who get an antibody titre over 50 nanograms per millilitre, and only 70% or so of the women at the moment do that.

So you cannot say to them "go away and have unprotected sex": you've got go and say to them "come back to my tent and have an antibody test": and that just won't work in a field situation: antibody tests for everybody are just far too expensive. So there is need for a stronger vaccine.

There's also a male vaccine which is being developed in India. It is not permanently sterilising, but it attacks the outer coating of the sperm, and makes the semen essentially sperm-free; and it works in cattle.

Now, whether you going to get that accepted in the human setting (knowing what the male of the species is like) I don' t know.

But it is working in a veterinary setting, and it's being strongly promoted by some of the more liberal elements in India to reduce their terrible problem of the sacred cows, wandering around and eating all the food, and not being able to be of use for anything. And there are many people who say a male vaccine will be required, and I think this is an alternative.

I actually believe that for women (and men, but the burden seems to fall chiefly on women) to have the total control over their own fertility will demand a variety of techniques, suitable to different ethnicities, to different physiologies, to di fferent religious beliefs, and to different cultural patterns. And we have seen very clearly with the pill that slavish adherence to one method only isn't going to do the trick, at least not for a 1ife-time. Certainly birth control vaccines will have a glace in the future.

Dr G.C.Lowenthal: What about the effect of HIV/AIDS? Presumably the effect of it will be found in time to reduce populations? Is there a development in the resistance of the virus to drugs?

Sir Gustav: Yes, this is a very topical subject today, there's no question. Had I been giving this lecture five years ago I would have said to you that there are really no good anti-viral treatments, that most of what we have is far too toxic.

Now, since then we've had two, I would call them, wonder-drugs: we've had AZT in the HIV situation, and we've had interferon, which has had its biggest success in hepatitis-B and -C. Both of them have drawbacks, and with the AZT, it is exactly as you've said, the very rapid development of resistance.

Although, I would say to you, that my colleagues, such as Penny and Cooper, and others at Saint Vincents, who are so fantastic in HIV, tell me that the in-vitro resistance doesn't always mean that the drug has stopped working in vivo. There might be some little discordance, and there are people who believe that AZT should be given for longer than the 9 or 12 months, until the disease has developed. But this is a very special virus with quite extraordinary mutation rates, and I think that the fact that AZT works for at least 9 months or so, has given a whole filip to the field of smart antiviral drugs. There are more coming down the track.

Interferon is a different kind of substance. That's not a drug: it's a natural substance of the body. If you want, its the body's own defence against viral infections, apart from the immune system, and it can be mass-produced by recombinant DNA technology, that is a genetic engineering technology, and its been what we call in the trade a 'sleeper'.

Sales of interferon were very disappointing shortly after its introduction, but more uses are being found as doctors learn how to use the drug better (its expensive, of course). The main areas in which it has had greatest success are certain forms of cancer and overwhelming viral infections. There is progress. We do not yet have the 'penicillin for viruses', something as completely non-toxic and also very broad in its effectiveness as the antibiotics, but the progress is now quite good.

Further question from Dr Lowenthal: The other side of that is what you might call the reaction to the innoculation or vaccination: I mean, a vaccination takes hold of an agent of the body, and no doubt the system reacts to it, and to some extent it may need another vaccination to cure the first vaccination.

Sir Gustav: Well, look, you're also right there, Dr Lowenthal. There is no medical intervention, even taking an aspirin, one aspirin, which is entirely risk-free. So any medical intervention has a risk-benefit aspect. Take anaesthetics: you know, I receive from the Medical Board each year the report on anaesthetics deaths in Australia. And its not a very small number: it's not like three, you know: there are always numbers of 20, 40 or so anaesthetic deaths per year: the accidents which shouldn't happen but do.

I can tell you that with vaccines slight reactions are very common: by slight reactions I mean the reddening of the injection sites, a sore lump in the groin, a fever. Or even, with the measles, mumps, rubella vaccine, a little bit of a rash, just a few little marks of colour; these are what you might call in the trivial class. The fever may not happen, we're often told now to give the kids some Panadol, because that'll avoid a bit of trouble the next day.

Now you're not reallY referring to these. There are, occasionally, more serious reactions, and the worst of the reactions has been with the whooping cough component of DPT. In roughly one case in two thousand, the whooping-cough vaccine will cause febrile convulsions. This is not dangerous, but is extremely distressing, as any of you who have had kids or grandkids who have had convulsions will agree.

However, the serious complication of an encephalitis, leading to permanent brain damage, has been intensively investigated in every English-speaking country in the world, most prominently

in the United States. A blue ribbon panel has recently published the incidence of serious CNS complications as somewhere between one in 200,000 and zero. In other words, it is so rare, that even this profound investigation could not deny the possibility that the few cases which appeared in the year in the United States were totally due to chance. So the serious complications are vanishingly rare.

There is now an acellular pertussis vaccine which has no whole bacteria in it: it just has material from the bacteria, much purer, totally non-reactogenic, and it works wonderfully. Your grand-kids will be getting this vaccine within a year or two; whether the African villagers will be, is a very different question. That's where I have to be persuasive and optimistic, as the vaccine is much more expensive. But the technical problem is now solved.

With polio, incidence of reversion to virulence of the Sabin vaccine is estimated at somewhere between one in half a million & one in two million. Not negligible, if you happen to be the one in two million; and in the United States there is now a very lively debate as polio transmission has ceased, to ask the question whether the old Salk vaccine, which is killed, and therefore entirely safe, should come back: they're talking about two shots of Salk vaccine followed by two doses of oral Sabin vaccine.

Once again that's a question of cost. The injection is much more expensive, it has to have much more virus in it than the oral (which multiplies itself in the gastro-intestinal tract) . So aren't these nice questions? We can afford the luxury of debating it for the one case in two million. I think the African villagers cannot afford the luxury of that debate: they will have to stay with the Sabin vaccine for now.

Dr E.C.Potter: There's a lady living in France, who, if she lives for six weeks or so, will become the oldest person who has ever lived . She was born in 1875: do you think there is something to learn from studying the extreme aging?

Sir Gustav; Oh, look, I think that is a totally fascinating question: I happen genuinely not to be an expert on the question, but it is not only worthy of study, but it is being studied extremely intensively. However, not quite so much in people, but more in mice & cats. For the very simple reason, that a rat and a mouse live for three years, and therefore you can work towards four & a half year-old rats, but you can't do a lot of work for 120 year old women.

There are some fascinating things that are already clear: let me hit you with the clearest, which was surprising: that malnutrition can lead to huge prolongation of life. Huge! So if you feed mice & rats a low-protein diet, and have the mice rats go through their lives looking like a Belsen concentration camp victim, they'll live longer.

The fact is that puberty is delayed, menarche is delayed, and the menopause is delayed, everything is delayed; but so, of course, is mental development. So, I mean, this is a trivial example, because it's a life totally lacking in quality: it's not realistic. But it does show that the life-span, as such, is not absolutely fixed, and there are profound things yet to be learned about ageing.

However, I would put it to you, that the real centre-point of the ageing dilemma is encoded by that very brief statement that I've already made: a fly lives for a few days, a mouse lives three years, a dog lives fourteen, a human lives eighty: then there's standard deviations on either side. Now, no mouse has ever lived to eighty, no dog has ever lived to forty: dogs might get to twenty-two or something, so there seems to be some program, some program entity which we

don't understand at all, that's got to do with the nature of species and speciation, that determines how long that particular biological species will live. What that program may be is is the subject of very intense investigation, with more questions than answers.

Mr G.W.K.Ford: There was this debate about, if you stamp out smallpox, do you or do you not stamp out the final laboratory strains? That must be a general question applying to all these things?

Sir Gustav: I had the great good fortune, in relation to this question, of sitting next to Frank Fenner at a dinner a few weeks ago. Frank Fenner is the doyen of Australia's virologists, who has been multiply honoured for his role in the smallpox eradication campaign, which in large measure was based upon his model work with both myxomatosis and mouse-pox, the ectromelia virus. His belief very strongly is that, once eradication has not only been certified, but has also been documented by experience, you know, that after the certification nothing's happened, that all stocks should be destroyed.

He justifies that on the following basis: should it ever be necessary to re-create the virus, the virus has been completely sequenced, all of its genetic code is known, and should there be some secret encrypted in there, some kind of genetic engineering could re-create it anyway, so that there is no excuse for keeping the actual specimen. Now that is not a universal view, but it the view that the World Health Organisation has adopted, and it is now a question of the Russians signing off. Because I think, from memory, there ace three depositories, and these three parties have to agree: I think there's one in Washington, there's one in Moscow, and I think there may be one other one under the control of the WHO.

President: Thank you very much, Sir Gustav. I'll call upon Dr Norbert Kelvin to move the vote of thanks to our speaker:

Dr Norbert Kelvin: Sir Gustav, it gives me great pleasure to propose this vote of thanks. I think that this work just shows haw important human endeavour is to making our lives more enjoyable, more fulfilled, longer. I think that we are truly blessed in this country to have a man of Sir Gustav's stature working on these kinds of ventures. I must say that, as a chemical engineer, I'm fascinated by the prospect of chemical engineers around the world looking at better ways of delivering these drugs, not just manufacturing them, but delivering them, and I think that there is an enormous opportunity for engineers and chemists, and scientists generally, to improve the methods of delivery, as he has shown: this is a quite unique opportunity. Well, without any further ado, I'd like you all to join me in giving our usual expression of thanks for your wonderful talk.

(applause)

Closure: the President invited Sir Gustav, and visitors, to sign the Society's Visitors' Book, which was commenced in 1876: a year after the French lady, mentioned by Dr Potter, was born!

Sir Gustav Nossal FRS Director, Walter and Eliza Hall Institute of Medical Research, The Royal Melbourne Hospital, Victoria 3050, Australia

(Transcript prepared from a tape-recording by Mr G.W.K.Ford, Hon.Sec.RSNSW, and checked and amended by the speaker prior to final editing)

133 Wattle Road, Jannali NSW 2226 Australia

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