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Sir Gustav Nossal AC CBE FRS in Interview with Dr Max Blythe
Melbourne, Australia. 7 March 1987

MB Sir Gustav, looking down the road of your career I'd like to go back to consider when and what turned your views to a career in medicine? Why this avenue?

GN I've got a pretty precise answer to that one. Actually, I wasn't born in Australia. I was born in Austria in 1931 and very unusually for those times, I had a father of Jewish extract and a mother who was a true blue cath, like most Australinsience. That became quite a dilemma for them at Ausdiluss in 1938 because there probably wasn't the imperative need to migrate there would have been if both had been Jews. In the crazy logic of Hitler's Austria, being so called Mischlinger, like I was, conferred a degree of protection on the parents. Of course we didn't realise that only became known much later.... so the decision was taken, to emigrate, and in my early childhood there was one Jewish figure who was always held up to the children as the model of what a person should be - and, of course, you've guessed it, he was a medical man, a professor of paeds. He was called Professor Knupfermacker, and Professor K was held up to us as a hero and really I wanted to be a doctor from as long ago as I can remember - to that seven year old boy who left Austria in 1938.

MB You came to Australia and your career course never challenged neutrally? you maintained a medical course....

GN Yes - well I had, for me, 9 happy and supportive years, being trained and by the Jesuits in primary and secondary school in Sydney in Australia - and in fact.... it is interesting this business of how religion goes with the mother.... that was how it was in our situation, and they were extremely supportive of me. I suppose I could have been termed a bright kid or whatever phrase you want to use, and when the classical interview as it so often did with bright kids, well my son do you want to be a priest, would you, too, like to be a Jesuit? and I revealed that it was my ambition to be a doctor, they backed off very quickly. So, I went to medical school at the University of Sydney at the ridiculously young age of 16 - we only had eleven years of education in those days.... So, I was much too young to be starting medical training. That is then where my elder brother comes into the story? Do you want me to tell what all this was about?

MB Yes please....

GN My elder brother was 6½ years older than I was and he was a biochemist in point of fact, he moved to Adelaide to a lectureship round about the time that I moved to University. I suppose a bit of hero worship came into the situation and I thought, oh gosh, I'll just wait for this biochem business - and he was in fact a student of the Nobel laureate in Oxford, Hans Krebs. He did his PhD with Hans Krebs (when he was in Stuff).... and so of course to this young 16 year old lad, what glamour, my brother actually knows a N? Laureate. No one had ever thought in those terms from Australia before - So I thought I might become very interested in bioch - and when I did my third year 'med' the possibility arose of doing a back of med School (degree) - taking a year off and sort of getting that familiar taste of what research life might be like - and I went up to see the Dean of the Medical School and said, 'Well, Professor Dew, what would you think of me taking a year off to do biochem? and this

wise old man who had seen so much more of the world than I had said 'well look there are plenty of good science students who'll be doing PhDs in biochem and yes it is an important discipline, but you really should do something that harnesses your medical knowledge a bit more and I have this colleague - De Bey - at that time a senior lecturer in micro-biology - who was a virologist - and he said viruses are the simplest form of life and knowing about their reproduction will teach you a lot of biochem.... Why not do that instead? Why not complete your fourth year, learn your Path(ology), bacteriology - get into the wards a little bit, and if you still want to do it - not at the end of year 3 but year 4 and do viral with Pat deBey - and honestly, that one conversation was, in a sense, the beginning and the end of my professional life as the rest rolled forward very very simply.

MB The great moment....

GN The great moment, so indeed I had the good fortune of studying under this brilliant young man Pat deBey - who s?.... became professor of bact, towards the end of the year I was with him, and had this very wonderful entry point, at that very low level of being a student for a year, into the world of med.... research.... And of course, if your an Australian, and if you are working in virology, and if you're casting you're mind back to the very early '50s, (1951-52) you would very rapidly appreciate there was only one name that would spring to the foreground of your mind, the name of Sir Macfarlane Burnett - And Pat deBey had this very smart idea. He always had one or two such students and each year he trotted them down to Melbourne for a week to spend a week with not only with Burnett lets say two or three days with Burnett and a couple of other days at ?, and I had the good fortune, as a very impressionable 21 year old, of meeting this famous figure and actually going home for lunch - people are very impressionable at that age, and of course the ambition to come and work at the W and EH Inst, in virology(!) was born at that very moment.

MB Macfarlane Burnett must have been an incredible man. Did you feel it at this first meeting?

GN Yes, I can tell you one impression of Burnett that stays with me to this very day. We're talking now about 1951-52.... right, - (I was the fourth year student in '51).... Now he came down in 51 (up to Sydney) towards the end of the year and he gave us this lecture on the poliomyelitis virus vaccine because he'd just been overseas and he had just spoken to Enders and here were we each summer, frightened to death about catching polio and here was a man not telling us about a vaccine that existed - but telling us about a vaccine that was about to exist, and you can imagine in far away Australia - we'd never met anyone that had been an eye witness to something as historic as that. That someone could actually tell you about a discovery that was about to happen f? my investigation - and then in 1952 when I had this much more personal couple of meetings with Burnett you can imagine the impression. Let me tell you about B.... as a person.

MB Please.

GN He was a very shy man. He was a person who without considerable exaggeration - actually described himself as a bit autistic. In his autobiography he uses that word. He as a person who was awkward with his fellow human beings and he expressed that awkwardness by a certain sternness. So he was actually quite a stern, bordering on formidable, kind of boss but I very quickly declined (and I am perhaps going a tiny bit ahead of the story, , I'll come back to the main thread in a moment), I very quickly realised that if you met this sternness (by) a respectful address, by a respectful veneer almost, I would say, you could

very quickly access his mind. So supposing Burnett said something I though was nonsense, there might be another person who would say, 'Sir Mac', which was what we called him, 'Sir Mac this is nonsense'. Now I would say Sir Mac what a very interesting idea but do you happen to have read this recent paper by so and so - and have you considered the vague possibility of such and such.... and if you look at it in that light, might not the conclusion be slightly different. He responded to that. (You might almost think this a bit hypocritical) - He responded to that form of intelligent reaction which didn't threaten his acknowledged primacy - which in some curious form of way needed constantly reinforcing.

MB So that was one of the keys to the lock of your long term collaboration and long term friendship.

GN Absolutely, and I think that to the day of his death he never once asked me to call him Mac. It was Sir Mac to the day he died. We were comfortable and friendly and I really think we became as much as any one could to such an aloof and rather introverted person. I think we became good friends and a great deal of mutual respect for each other - but it was a relationship based on the continued protection of this primacy of his - but I'll come back to Burnett in a moment because you'll be interested to know about my passion for virology and what happened to it....

MB Of course.

GN So I had my little year of the B Medical School and went back to medical school like a good little boy, did my two years as a resident at the Royal Prince Alfred. That was very good for me for I learned how to deal with patients. I loved medicine - I always think of myself as a doctor first!

MB And you like people?

GN I do and I loved all of the work with the patients in a predominately rather poor area of Sydney where you were in act the interface between that impersonal hospital system and the 'honourary' as we called them in those days - the visiting specialists. They were far too busy to talk to relatives. If someone died it was my job to explain why they died. If someone got better it was my job to say - well watch them do this and that over the next little period. I loved that, but in point of fact, when that second year was over, I came to the following decision fork, either to go ahead and complete as it then was my membership of the College of Physicians.... We've since changed into a longer degree which is called a Fellowship - but I could either go and do my MRAPC, which would have taken a further two years or I could embark upon what all of my colleagues thought was this stupid dream of becoming a virologist - apart from anything else where would a virologist get a job. There might be one lectureship become vacant now and again - but there weren't jobs for virologists growing on trees in the 1950s. And I got married in my year off being an intern - and I said to my wife this is what I want to do.... It'll mean motoring down to Melbourne and she said - Give it a go. What have we got to lose for two years, and I can honestly tell you - our thought in moving down to Melbourne in 1957 after my senior residency year would be that we'd do a two year stint with Burnett and then we'd trot back to Sydney and maybe Pat deB, my mentor, could have organised a senior lectureship for me (by their and I would have been happy as a bird to have that sort of career, but there was one big disappointment for me at that time - because I wrote in the dying days of 1956 explaining my wishes and my hopes - I said Dear Sir Macfarlaine, you will remember meeting me on the such and such - and I now want to become your student, and he said, 'Nossal, we'll fit you in somewhere, (I think he

mentioned the sum of £700 a year as a fellowship) but, I've one thing to tell you and that is that I'm switching my whole interest from virology to immunology. Now of course, for a moment, the bottom dropped out of my world. We had in fact, had lectures in immunology. It is quite difficult for today's student to believe that years on, but really immunology was really a dead subject. Immunology was something that Pasteur had invented and then there were a few Germans that had done something with it and then these here Yanks called Cabot and Heidelberger who that turned it into a biochemical sort of thing.

MB Right.

GN I wondered what in the hell was Burnett on about - but you see this man had seen a wave that was about to crest and break and had the good fortune to see it before it broke. So in the immunology boom, that really hasn't in a way receded, I had this incredible good fortune of coming in by happen chance, - by the sheerest accident, because I wanted to work with Burnett, onto a wave before it had crested - and a bit like a pretty inept su? that can't do anything but be there in the foam - I was brought along on this wave and I consider that pretty good fortune.

MB Enormous. You came then with your wife and began living in Melbourne.

GN Yes, we came here to Melbourne in 1957.

MB Sir Gustav, perhaps we could mention your wife at this point?

GN Well, my wife at that time was a speech therapist. Interestingly enough, I always prided myself in the fact that while most of my colleagues married nurses I married a speech therapist but I didn't meet her through the Royal Children's Hospital - where she worked. I, in fact, met her because we lived in adjoining suburbs and had mutual friends together. We were a very happy, up and coming young couple. I suppose it would be fair to say that we had Sydney at our feet - she was and is very beautiful and I was for better or for worse, I was ? ? of my medical school class and President of the medical students society.... We were what would have been called in today's world medical yuppies.... and I can tell you, we weren't too pleased in one respect about going down to Melbourne where we knew no one and where in fact this idea of a two year contract was one which sustained us - we'd get back to allow friends and the lovely life we knew in Sydney before too much time was over.

MB But that was not to be.

GN And now I'll explain to you why that was not to be and how I've been doubly blessed and double fortunate in my early life in the lab and its my abiding desire to create the same opportunities for my young students as Burnett prepared for me.

GN Well now, I'm going to have to get a wee bit technical, but in a way that will be useful. Burnett's passion was to try to understand how cells made antibodies. We have this immune system - as in a sense I'd like to ascribe the discovery really to Loui Pasteur who understood the microbial nature of infectious disease, who understood the process of alternation (he didn't know it was due to mutation) but he understood that he could alternate germ and that the alternated germ could still make you specifically immune. And then Emil von Behring, in 1901 discovered it was due to substances called antibodies. That was the beginning of the great saga of the puzzle of antibodies. How could a human being or an experimental animal make antibodies against virtually anything in that microbial world - as

the great Carl Loudstecier discovered, and even against substances manufactured in the test tube - that had never existed in nature before. How could that be? How many bacteria bugs are there. Would there be a million different bacteria? I wouldn't know how many bacteria would exist, but each of those bacteria would have many foreign substances on its surface - many antigens as we call them - and these antigens unfailingly cause antibody formation except in those instances where a person has an immunodeficiency of some sort. So that was the puzzle that set Burnett set himself in someway to solve. And the whole background of the time was that the antibody was so precise, it fitted so beautifully, like a finger into a glove, like a hand into a glove, it fitted so beautifully into the antibody combining site that really, guided by Laudsteiner, everybody believed that the antigen had to act as sort of a template. Laudsteiner didn't actually com the word template - that distinction actually belongs to a still living scientist called Felix Harowicz, who together with Mudd and Linus Pauling, created this so called direct template hypothesis of antibody formation. The concept was very simple antigen comes into the body, protein-synthetic machinery sees something interesting and new ? begins to create a protein on the template of the antigen, so it is in fact not like a hand in a glove, it is like a plastic mould, a plastic being moulded against a template, like a piece of hot metal being forged on a template, and that was the theory of antibody from that held away for many decades. Now, Burnett had read the beginnings of what is called the Crick dogma, he'd realised something big was going on in molecular biology, but didn't have it absolutely straight and then he also read a paper by a man called Yerner, Neils K Yerner, who was subsequently to win a Nobel Prize for immunology, and Yerner had put together a totally different view of antibody formation. Let me tell you about what Yerner's shocking theory was. He said we have 10^{17} molecules of antibody in our blood per ml (10^{17} molecules!) He said we could to afford to have in existence 10" different sorts of antibody and there would still be a million molecules of 10" species and that surely should be enough to recognise any antigen that could exist in nature or that could be synthesised - because 10" is a very very large number. Yernev didn't precise at all how these antibodies would be made or why there should be 10" different antibodies. He did say, he did introduce, one incredibly important notion. He introduced the notion of a selective immune response. The immune response was not going to be instructive - with an antigen instructing the body how to make antibodies. It was going to be a selective thing. The antigen would fossick around in the body and find those rare molecules which would attach to it and then - and this is where his theory went a bit wrong - and then he said macrophage or scavengercells would eat up this complex that had formed - and somehow, the antibody molecule would perpetuate itself, would act as a template for its own production - and that contravenes every rule of the Crick dogma - and is of course incorrect. But Burnett took this and, as it were, twisted it around in the following manner. He said - the selection notion is going to be right, there are going to be a large number of antibody molecules, but they have got to be seen as receptors on lymphocyte cells, so that the role of the antigen is to select a lymphocyte with a receptor molecule on it that fits the antigen, and then to cause that lymphocyte but no other to multiply to differentiation, perhaps, - which was a very deep insight, to mutate further, to give better and better antibodies, as more and more antigenic molecules hit that cell. So that was his great insight in 1957 and it turned out, in a way I'll describe a little later on, to be essentially correct in most of its details. Now that was the situation half way into my first year in the lab - and I had really thought this was pretty crazy. He'd shown me Yerner's paper first and said what did I think of it - but let's be frank, but he'd also shown me many other papers - and I didn't warm to this Yerner thing at all - perhaps a reflection of my lack of imagination, but I didn't think much of it. And so I didn't hear any more for a few weeks - but then one weekend he wrote this little theory which he termed the clonal selection theory and said what do you think of that? I said let me take it away and read it, and I came back a few days later and said, 'well Sir Mac, I can't really tell you what I think

of the theory - I'd like to think of that some more, but sure as hell I can tell you how to disprove it', or I wouldn't have said sure as hell - I can say that to you but I would have very respectfully said 'Sir Mac, well there is a way that I think I could disprove this theory' - and he said, 'how?' I said, - I happened to have been reading the virus literature - there was some little part of me that still wanted to be a virologist, and I said 'well viruses can be grown in single cells and there are very tricky ways now of culturing cells in capillary tubes and having one virus turn into a hundred viruses by living inside that single cell. I said I don't see why we couldn't immunise an animal with three or four vaccines and take out the single cells (we know that the animal as a whole would be making three or four different antibodies) but would one cell always be making one antibody or would it be making two or three? I was pretty confident in my own mind that if we could do the experiment they'd be making two or three. I can't tell you why I thought that - but I suppose I had been so steeped in this direct template business you see. And so I said why shouldn't we do such an experiment. Why shouldn't I drop what I'm doing...

MB Which was?

GN Good steady beginning work - in immunology - nothing very fancy.... Why can't I drop what I'm doing and do this? And Burnett said now look that's a very interesting idea and he said furthermore, I know who can help you. So now comes the second chapter of my teaching and the second really big event in my life - because there was at that time something called the Fulbright Scheme and this brought visiting Professors to Australia.... from the United States - and Burnett had been expecting for the three months visit in his lab the very find young bacterial geneticist, Joshua Le? - who was then working at Madison, Winconsin, Joshua Le? and his wife Ester had in my book virtually created the science of bacterial genetics. Joshua was a student of Beadle and Tatum's and he had worked on Neurospora genetics with them as a student - but he had said, well bacteria multiply even faster than Neurospora (which is a yeast) and he said why can't I develop bacterial genetics - and he had become a very famous man in ten years - as the father of bact genetics and he in fact won the Nobel Prize at the age of 33 - which is pretty young. So this great man was coming and Burnett said - Oh, he can help teach micromanipulation and so that is in fact how it happened.
GN Indeed it was. Now there was one big difference between Burnett and Lederbey as afar as I was concerned, and from a human point of view its quite interesting. Burnett was 32 years older than me, he was a man with a monumental record of achievement when I first met him. Lederbey was a mere six years older than me when I met him - or something of that order of time and it was, from the point of view much more easy to identify, even though he was incredibly much more achieved than I was, and secondly, I suppose I would describe myself as a fairly verbal person. I love debating. I sort of think on my feet, reasonably quickly. Burnett wasn't at all like that, but Lederbey was the most brilliant person in the thrust and pony of scientific debate that I've ever known. That would still be the case. He is an extraordinary versatile and lightening fast brain and made a massive impression on me and I remember.... You mentioned Lynn my wife - I remember in our little flat in Melbourne, Esther Lederbey and Josh on the floor (I don't quite know why we should have been sitting on the floor because we did have a few chairs) and getting stuck into debates about everything in the world, mainly science but also other things - and they would go home (they had a Ritzier flat that the visiting Professor could afford - and they'd go home to their Ritzy flat and I'd say to Lynn what an extraordinary thing that this chap has befriended me in the way that he has and I really think I'd like to go and work for him when we're finished here. So the next phase of this association was for me quite pivotal, quite centrally important and it related to the fact that Lederbey had moved or was in the process of moving from a good but in a sense somewhat lower key University in Madison, Wisconson, to a bright new, brand

new medical school in Pallo Alto, California, the Stanford University Medical School, which had been in existence but as a small annexe to Stanford University and based in San Francisco. OK Why is that important? It is important to me for the simple reason that Lederbey asked me to come and be a young assistant Professor there in his Department - and it's important for a second reason, in that Stanford University made this move to this very wonderful and brilliant designed new medical school to create really an absolute paragon of excellence in medical education with a panoply of Professors that had been asked to found the School - who really in a sense were historic figures. Take for example the Department of Biochemistry.... headed by Arthur Kornberg, containing within it Paul Berg, Dave (Hogeness Hoagness), Dale Kaiser, Buzz Baldown, Bob Lerman, - all figures to have reached to US Academy of Science in their own right - Paul Bey of course to work the NP, Kornlery to work with NP - around about a year or two after Lederberg. Think of the Department of Radiology with Henry Captan, probably the world's best known cancer researcher - it would be between him and George Clive. Henry is dead now - but to Bell.... A magnificent opportunity for a young man - and here was I, a young assistant professor, 27 or 28 years old, I had to teach the freshmen medical students - but they were 64 selected out of 6,100 - a tremendous challenge - a wonderful thing to happen in your young life. Now I have to say one thing about Ledenberg over those Stanford years. He was so preoccupied with the building up of his Department and with the building of the medical school that unfortunately we never collaborated again. I mean - he was always wonderful to debate things with - but really those golden three months, I now recognise, in hindsight, they were golden for him to because he could work in the lab 8 or 9 hours a day - What Chairman of a Department can do that. I missed very much that close personal contact with him, but he gave me that opportunity and those years 1959 - 1961 were actually crucial to my formation. Let me tell you why. It predominantly has to do with feelings of adequacy or otherwise - that people from Australia have when they contemplate the international scene. You see we are a very small company of scholars here in Australia and really before you've moved out you don't really know that you can stack up. You might be the brightest medical student in your class - but do you really believe that you can mix it with those people who write the text books and those people who own the NPs, and those people who essentially make world medical science in the USA, UK and Scandinavian countries and so forth. The answer is 'of course you can', but someone's got to explain that to you and one of the happiest things in my life, now, is to see student after student, post doc after post doc go through this same heady experience. We train our people well at the W & E Hall Institute and they go off and they go to NIH, or to Oxford or to wherever and they succeed and see that they can compete, but you have to live through that - there's no way anyone can explain that.

MB But you were in a pioneering stratum, that must have confined something on Australian scholars of this generation.

GN Well indeed it did - and in a very direct way because it would be fair to say that Lyn and I were very popular at Stanford - a lot of that I ascribe to my wife. We were a couple that people liked to ask to dinner parties and we met all these great and famous people - and they became my colleagues - though I was only an assistant professor - but in California that doesn't matter. That was another refreshing thing to learn, by the way, that here in Melbourne things are still a bit hierarchial - less so than then, but you were on first name terms very quickly with all these people and in some ways we think of those 2½ years as sort of the happiest of our lives because you're free - There's something wonderful about being as free as that. You know that nothing that goes on within the politics will ever really touch you - so you can get stuck into political debates and it doesn't go as close to the heart as it would

if someone's taking Australia to pieces - and you're beginning to put together the little planks in the platform of your career - and you're in that lovely stage of being just young.

MB Turning to that career, you'd set off to tackle the 'Burnett problem' - the problem you'd said you'd handle. How did that work go - Did you take it to Stanford with you?

GN Right. Yes indeed I did.

MB So, apart from it being the happiest time of a lifetime, this must also have been one of the most fruitful times.

GN Yes it was. We took the let's say one cell one antibody situation to Stanford, built on that, saw that it was absolutely correct, began to apply it in various situations such as cousid9 it's implications for immunological tolerance - which is this very big puzzle of how does the body know how not to form antibodies against itself. We developed certain ideas how that might work - and, in fact, here's an excellent note for me to introduce a second major topic - and that is what was happening to immunology generally around about that time, because I mentioned a wave that was cresting. I would not like to leave your viewers with the impression that I think that Burnett was the total wave - very far from it.

MB Now in your books you have described a second golden age of immunology - you to some extent were a fulcrum in this field - a turning point.

GN I would sooner put it that I was a conscious eye witness to a very drastic change in a discipline - and I'd like to divide that into, as it were, two parts. There's one part that is a fundamental science part, another part that's a slightly more applied part. Now let me - as I told you, I'm a doctor first and a scientist second - let me therefore deal first with the medical part. There are three areas of medical science that don't have much to do with vaccines - that were beginning to burgeon out at that time. There was the field of autoimmune disease - the field of organ transplantation, and the field of cancer.

MB This was the late 50s now - we're into the late 50s?

GN I'm thinking about the 50s and early 1960s, when in point of fact, really for the first time, people in various parts of the world, Melbourne, yes - but also London, NY and Stockholm, were beginning to ask very deep questions about the involvement of this immune system which, heretofore, had only dealt with defence against infectious diseases. They were beginning to ask themselves ? this system be the total answer to some of these great problems of autoimmunist transplantation and cancer? Do we have time for me to say here a little bit about these three in turn?

MB If you would.

GN Well let's speak about autoimmunist first. We have this deep problem. You, Max Blythe, are sitting there, and I Gus Nossal am sitting here. If you were to donate me a part of your blood something may or may not happen that's very bad, but if you donate me your kidney, something would certainly happen that would be pretty bad if you didn't do something about it. In other words, my immune system has a very vigorous capacity to react to react to reject, your kidney, OK? Now this was beginning to be found out at that time, and people like Medewar and Gover and James Grys in Oxford were very much at the focal point of that recognition - that the rejection of foreign tissue is an immunological event. This is

why Medewar won a Nobel Prize for his insight into the fact that those same cells which have the task of making antibodies, of guarding us through inflammatory responses against tuberculin, - the more cell mediated style of immunity, those same cells are the cells that will possibly reject blood if the blood groups are wrong and most certainly reject the kidney because there's a 1000,000,000 to one chance that your kidney is identical in all its 'blood groupings', tissue histocompatibility types, to my constitution. - I'm now jumping ahead of myself - the transplantation side, but speaking of autoimmunity, the deep puzzle is why don't we form antibodies to ourselves? I've just told you, I'm protected. I'll form antibodies to you - Gus'l form antibodies to Max. Why doesn't Gus form antibodies to Gus. And then of course, nature's experiments.... You know disease as Robert Good has termed it, is the great experiment of nature. Diseases tell us so much about the normal and we do have diseases where you've make antibodies, for example, to the red cells. Now you ponder for a second what happens when I make antibodies to your red blood cells. Instead of having their normal life of a hundred days carrying the oxygen around in the way they do, allowing me to live, those antibody coated red cells live now only 2 or 3 days. A vicious and so called haemolytic anaemia. The red cells are dissolving inside my body and I die, it's simple. With an untreated haemolytic anaemia sort of were the prototype - One organ specific, one more generalised - coming into the orbit of immunology all of a sudden. And lo and behold, everything that you learned by studying again transplants, suddenly now fertilised in a very particular way this new area of medicine. Now we were, with Ian McKay at the Hall Institute and Mac Burnett, amongst the very first to popularise this concept of the autoimmune diseases, at the same time in the late 1950s that Henry Cuckle was doing the same in New York and Peter Meesher w, who was very briefly at New York University and then went back to Switzerland - A few hardy souls were daring to say that these diseases - 'that that disease' was autoimmunist. Now today of course, as we're speaking in 1987, that is trite, that is commonplace - but it was very unpopular at that time to say that a disease might be due to antibodies gone wrong. Yet in the decades intervening, diseases as common and unimportant as insulin dependent diabetes and multiple sclerosis, possibly also rheumatoid arthritis, have somehow fallen into this autoimmune camp. Now that was a wonderful thing to see evolve.

GN Now the second area, organ transplant, - I've almost mentioned that already. The fact that this aggression of my lymphocytes against your kidney had to combatted. Now I can remember as if it were yesterday a chap called Roy Cone, a surgeon, professor of nephology at Stanford University coming to me and saying 'Gus, you are an immunologist, please explain to me why can't I wrap this kidney in plastic' - and if I wrap it in plastic, surely those lymphocyte cells that you speak about won't be able to get in - and why doesn't such a kidney graft work?' I mean that is how primitive the understanding was in 1959 of how the immune system worked. And I can remember Norman Shumway, wonderful man, doing these heart transplants in dogs and brilliantly succeeding in allowing the heart to pump until....

MB Total rejection

GN Total rejection by the lymphocyte cells of the body. And I can remember Rose Payne working on the histocompatibility system - because Gover, of course, and Gover and Snell had found that there were certain antigens that we call histocompatibility antigues - tissue-type antigens that you could match for ?. She was one of the real pioneers of that matching - All that happening, there at Stanford University and of course we now know that Norman Shumway stuck with it and we do have heart transplants working better because of cyclosporin. He was able to make them work reasonably well with less elaborate immuno-suppressive treatment. Now thirdly, I said I'd say a few words about cancer. That's more controversial. That's been less spectacularly successful. Two words about my time at

Stanford. I had the great good fortune - as I mentioned, Henry Caplan, I had the great good fortune also of having George Clive as a colleague there, one of the great fathers of tumour immunology. He spent a six months mini sabbatical with Lederbey, you see. Lederbey had the power to draw these people to him. He had also Avrion Micheson, one of Britain's most famous immunologists come and spend time in the lab while I was there. So why is the cancer side of it more controversial? There is no doubt that lymphocytes and macrophages, the intelligent cells and the scavenger cells have the potential to kill cancer cells. There's no doubt about that. There's the potential of the immune system to kill cells that are cancerous under some circumstances. Where there is grave doubt - very grave doubt - is whether the potential exists to kill the last cancer cell. Debulking of a tumour we can already achieve, can't we, we can already, through radiation and cytotoxic chemotherapy, and for that matter, through surgery, remove the great mass of tumour tissue. The trick in cancer treatment is to remove that last malignant cell - and as we sit here in 1987 it is still not given, with a few exceptional situations, like chorionic carcinoma, that the immune system has the potential to remove that last cancer cell. But the field has progressed, the field has not gone away and still people like Stephen Rosengerg, at the National Institute of Health, who are acting on the belief that properly trained, properly schooled, properly helped by soluble molecules like Interlukon 2, lymphocytes can do the job.

MB Is it possible in fact that they do the job on certain low developing cancers?

GN Well, that was going to be the second thing I was going to mention. There was this wonderful man Lewis Thomas - and I also met Lewis Thomas during those years. He was at that time at New Zealand University, a Chairman of the Department of Pathology - or maybe of medicine, I'm not sure which. But Lewis Thomas was keen on this immunological surveillance notion and he said how do we know that this immune system didn't actually evolve to constantly patrol the body and find cells that were a bit aberrant and knock em off, and well only seeing the organ transplant nuisance then of the immune system - as a side function.

MB - and the cancers that got away....?

GN .... the cancers that got away. The few that remain after the immune surveillance has done a good job and dishing of root of the pre-cancerous centres. Now Burnett took up this thought of immunological surveillance actively and wrote some brilliant papers about it, but I do believe the primacy of the notion is Lewis Thomas. I think that notion hasn't quite survived in as clear cut away.... for example, we now know that the immunosuppressed people who have had too much therapy for their kidney grafts or their liver graft - they don't really come down with a bewildering variety of cancers. They do get an excess of lymphoid malignancies - of lymphomas and leukaemias - but in point of fact, it would be pretty doubtful as to whether Ca of the stomach, of the cervix uterus, cancer of the lung, have much to do with immunology/surveillances but in point of fact, there were three big disease areas that came into the orbit of immunology as I was a young man growing up - and I think its been very heady to watch the separate, parallel, strong evolutions as subdisciplines. Now, I have to get back to the basic side. Don't forget that really all we knew about antibodies in 1957, when I started, was that they were proteins that could be separated electrophoretically and then we used to talk about big antibodies, the 10s, the macroglobulins, and the smaller antibodies.

GN The 70s; now all of this beautiful work on the structure of the antibody molecule, which we can now, with X-ray crystallographic precision, see at 1.5 A^{o} resolution - all of that was still in the future. Even more in the future was the knowledge of the genetics of the immunologi? genes. This extraordinary system that indeed allows us to create inside our own bodies, this genetic-translocations, genes for millions and millions of antibodies. So, even though I have never, despite my 16 year old ambitions, never done any biochemistry, here I am as a cellular immunologist, of shall we say some note, with a box seat to watch people like Rodney Porter, Gerald Edelman, Leed Hood, progressively uncover the secrets of the structure of the antibody molecule, and then as it were to come along from a still better perspective, as a Director of a large immunology research institute - to watch the likes of Tonagowa and Fileader come in and dissect for me, display for me, the genetics of the immune system. So from that point of view, I feel that I have been terribly lucky Max, in the colleagues that I have had over the years.

MB Can I just go back to that impression of a second golden period of immunology - can I just extend that - for we might just look down the next ten years very briefly and consider where those years will take us. It has gone a long way in your three now massive fields come to change all that early defence and immunisation field into one that is so, much more ambitious in terms of body defences. Where's the future.

GN I would like to speculate on the future with you and I'm going to begin as a real disciple of Louis Pasteur - Let's go right back to Pasteur. Now Pasteur saw no discrepancy between pure science and applied science. In fact, this man who did his wonderful pure science things, like discovering the true nature of microbial life, like discovering the fundamental principles of immunology. He was also a consultant to the wine industry of France and he was also, which most people don't know, an expert on the restoration of old master paintings, through the application of applied chemistry. There's still a laboratory in the L'Ouvre where he did work. So he was a pure scientist and an applied scientist. Now in the applied science of immunology in the Pasteurian sense, I see a great future in the development of new and improved vaccines. We do not, as we sit here have a vaccine for any parasitic disease of man, including malaria and we do not have, I believe, satisfactory vaccines for the great diarrhoeal diseases like cholera and typhoid. We have unsatisfactory vaccines for these. We do not have a vaccine for AIDS, we do not have a vaccine for hepatitis A, we do not have a vaccine for some of the very important diseases. And I believe impelled by the genetic engineering revolution, impelled by the fact that we can now manipulate these microbes much more cleverly than Pasteur could, I see a great future for vaccine development, both molecular vaccines created through recomb DNA and live, alternated vaccines this the more planned attenuation of microbes than Pasteur could do. I'd like to begin there because I have a very great interest in diseases of the third world. Maybe we could come back to that in a few moments time - but I think the vaccinology has to be the beginning of it. It is not terribly glamorous, you know. It might be more glamorous.... to think of cures for cancer - but I think there is an enormous field here.

MB And there's a massive change in prospect for the third world?

GN Exactly, New vaccines and improved vaccines. Now, I think, turning to the Ca problem, quickly, we're facing an extremely interesting future because I think we are learning more about lymphoid and scavenger cells and how we can make them dance to our tune. Now I'm thinking of part of a new area of research - Lymphokine research. There are pure molecule being made available through recomb DNA technology that act as whips for the immune system. They really act as strong triggers for the individual cells and unfortunately there are quite a few of them. There might be as many as 9 or 10 molecules - some affect

scavenger cells, some affect the lymphocyte cells, some will affect the so called B cells more than the T cells and so we have to learn about all of them. But I believe intelligent harnessing of these cells in the fight against Cancer - there will be particular cancers which immunotherapy will cure. Now the big question is will this include the common cancers? Most of the triumphs in cancer therapy in the recent past have been in malignancies like leukaemia, lymphoma, chronic carcinoma, seminoma of the testis - rather unusual tumours - Now, will we be able to cure metastatic breast cancer, metastatic colon cancer, metastatic lump cancer, by immunotherapy. I think the true answer is the jury isn't in on this one.... but I would look more to a future combining, if you want, cellular therapy with monoclonal antibodies - the missiles that can be homed in on the cancer through an antibody vehicle acting as a bullet. And thirdly, through our knowledge of these lymphokine factors. By the way, I'm not telling you anything very new, here, in fact, the DNA industry - so called - the Genentex and the letuses of this world are investing millions and millions of dollars into the search for the various factors I have mentioned, in the hope that in? a cancer therapy modality will come forward.

MB So the answer lies somewhere in a combination of immunology and biochemistry to provide more prone cells and better and assisted lymphocytes.

GN Yes, Everything we have learned about Ca in these last fifty years of very frontal study points to the need for a multi pronged attach - because don't forget its not really just like the parasite or the influenza virus - which mutates away exclusively to avoid the immune system. We've got the Ca cell on the one hand indeed having the capacity to mutate and change and foil the immune attach - because it can easily spare a few antigues and change its spots, but it is also mutating and changing to avoid every other defence of the body. And you have a tremendous respect for the cancer cell's capacity to change and mutate and - and its been a successful parasite because of its adaptability.. I don't know whether you've ever looked down a microscope at these cancer cells when its gone - completely wild - but you know, you and I have 46 chromosomes - now this Ca cell can have any number of chromosomes - up to twice or even more than twice, the number of chromosome of the normal cell and it chucks out chromosomes, willy-nilly. And it has a fantastic capacity to mutate and adapt. Therefore, please have great respect for its capacity to foil what human intelligence can do.

MB A colossal repertoire of tricks.

GN Exactly, but I'm not pessimistic in the long run. You know, society's merely got to give us time.

MB Thank you very much Sir Gus for this afternoon at this point. I hope that we can meet in ten years time to go through a further decade of this story.

Melbourne, March 1987

Note: arrange editing change and for the part of the Melbourne studio to be acknowledge - Ricky Schwartz etc.