was born on November 16, 1926 in Vienna, Austria, where I had my first 5 years of schooling. When I was 11 years old my family moved to Sydney, Australia, where my father had a business appointment as manager of the Australian branch of an Austrian company that marketed fine steels. I went to school in Sydney and then, from 1944 to 1947, to Sydney University where I majored in biochemistry (First Class Honors B.Sc.) and then did an M.Sc. in biochemistry in 1948. Both my thesis work and my M.Sc. work were carried out with Prof. Jack Still. I purified the hydrogenase and the nitrate reductase of Escherichia coli and using then relevant Warburg manometry techniques carried out detailed enzymological studies involving the identification of activators and inhibitors of both enzymes with a view to identifying their prosthetic groups, and constructed a hydrogenase-nitrate reductase system involving either dyes or flavoprotein as carrier between the two enzymes. This work provided excellent rigorous training in biochemistry and more specifically in enzymology/enzyme chemistry that I always viewed as my fundamental base for further studies.

The Introduction to Virology: Doctor of Philosophy Thesis Research, Sir William Dunn School of Pathology, Oxford

During this time I became very interested in and did a lot of reading on yeast genetics. This was the golden period of yeast genetics with Lindegren and Winge laying the groundwork. I also became very interested in the work on the T bacteriophages of E. coli being done at Cold Spring Harbor by the group headed by Delbruck, Hershey, Luria, and Cohen; so much so, that for my Doctor of Philosophy I went, in December of 1949, to the Sir William Dunn School of Pathology in Oxford, which was headed by Nobel Prize winner Sir Howard Florey, to work with Sir Paul Fildes on the biochemistry of bacteriophage T1 (and to a lesser extent, T2) multiplication. The William Dunn School was an impressive place; the Nobel Prize for Medicine had, after all, been awarded in December of 1946 to Howard Florey and Boris Chain, both of the Dunn School, and to Alexander Fleming. Three years later, the School still basked in its glory (1). Florey, born in Adelaide, was an Australian who had been in Oxford for 2 years as a Rhodes Scholar and who was appointed to the Chair of Pathology and Head of the Sir William Dunn School of Pathology in 1935 at the extraordinarily young age of 37. By the time I arrived in Oxford as an Australian National University Scholar, Chain had left, but several key members of the team that isolated and characterized penicillin were still there. There was Edward Abraham who had (working next door with the famous chemist Sir Robert Robinson) crystallized lysozyme in 1937 and in 1943 been a key member of the team that elucidated the β-lactam structure of penicillin. There was also Norman
Heatley, an extremely ingenious microbiologist and biochemist who developed and supervised the production of penicillin as well as its extraction from culture fluids by countercurrent distribution and who also developed the cylinder plate method of assaying penicillin; Gordon Sanders, a pathologist who was often Florey’s right-hand man; Margaret Jennings, who, together with Florey, conducted the biological tests; Lady Ethel Florey (who was also an M.D.), who organized the clinical trials; and Jim Kent, Florey’s highly skilled and valued technician.

Sir Paul Fildes, a most delightful crusty old gentleman, was generally regarded as the father of British microbiology. Although a medical graduate, he had never practiced medicine but found his niche in the laboratory. He had been in on the discovery of bacteriophages with Twort in Bullock’s laboratory. He had an outstanding career in bacterial physiology, formulated the Woods-Fildes theory of inhibition that explained the role of sulfonamide as an antagonist of p-aminobenzoic acid, and at the time I joined his laboratory, was characterizing Bacterium typhosum bacteriophages. My work, on E. coli bacteriophages T1 and T2, fell into two areas. First, I measured adsorption kinetics as a function of the concentration of monovalent and divalent ions and one-step growth curves as a function of the multiplicity of infection. Second, I became interested in an aspect of virus multiplication that had as yet received scant attention, namely the nature of the changes in host metabolism induced by infection. I measured oxygen uptake using a wide variety of substrates 1 h after infection and found that oxidation of certain substrates was not affected whereas that of others was greatly inhibited; when the ability to use a specific substrate was adapted, adaptation was inhibited (2). This was one of the first demonstrations that host-specific synthetic reactions are rapidly inhibited following virus infection. I obtained my Doctor of Philosophy in 1952.

Interlude

For my postdoctoral work I continued my biochemical training. At the beginning of 1953 I went to Copenhagen to the Laboratory of Cytophysiology headed by Herman Kalckar where I teamed with Paul Berg, and together we isolated and characterized nucleoside diphosphokinase, the enzyme that exchanges the gamma P between nucleoside triphosphates and is now implicated as functioning in signal transduction pathways (3).

At the end of 1953 I returned to Australia to join the Department of Microbiology in the John Curtin School for Medical Research of the newly created Australian National University in Canberra where I remained for 9 years until 1962. It was, in the ’50s and ’60s, one of the most outstanding Departments of Microbiology in the world (4). Its Head was Frank Fenner who joined McFarlane Burnet (Nobel Prize in Medicine, 1960) at the Walter & Eliza Hall Institute for Medical Research in Melbourne in 1946 and embarked on a study of the pathogenesis of ectromelia virus in mice (in which it causes fatal hepatitis), which became a classic and has served as a model for such studies ever since. Fenner came to Canberra in 1949 and turned his attention to myxoma virus, a virus highly lethal for rabbits, which had been introduced into the wild rabbit population with the idea of decimating it; it was so large that it was a significant negative factor in Australia’s rural economy. After carrying out model epidemiological studies Fenner turned his attention to genetic studies on orthopoxviruses and played a major role in the smallpox eradication program in the ’70s. He remains an influential spokesman in this area to this day. He celebrated his 91st birthday in 2005.

Several other faculty members were also outstanding. One was Stephen Fazekas de St. Groth, who pioneered quantitative studies on aspects of influenza virus replication with particular relevance to interference by noninfectious virus particles; studies on what are now known as defective interfering virus particles; and studies of the immune response to influenza virus, including exploration of the concept of “original antigenic sin.” Another was John Cairns who came to the Department in 1954; during the next 10 years he worked on the effect of multiplicity on asynchrony of infection and the initiation of vacinia virus infection by autoradiography, studies that revealed that infecting virus particles set up foci of replication that he termed “factories,” a designation that was then applied to several other virus infections. He also pioneered the use of autoradiography to visualize DNA, in particular that of bacteriophage T4, for which he for the first time deduced an accurate estimate of its size. This work created a great deal of interest. In 1965 John became Director of the Cold Spring Harbor Laboratory for Quantitative Biology, preceding Jim Watson. A third outstanding faculty member was Graham Laver who joined the Department in 1957 and initiated a series of biochemical and molecular studies of the two glycoprotein components of influenza virus, namely the hemagglutinin and the neuraminidase. He started this work even before the advent of polyacrylamide gel electrophoresis; he employed electrophoresis on cellulose acetate strips. Using peptide mapping and immunologic assays with carefully prepared antiserum, Laver, in collaboration with Robert Webster who obtained his Ph.D. in the Department in 1963 (see below), formulated the concepts of antigenic drift and antigenic
shift as well as theories of the origin of influenza virus strains responsible for pandemics that postulated the introduction of genome segments from influenza virus strains circulating in pelagic birds, horses, pigs, and chickens into influenza strains circulating in human populations. Laver has been elected to the Royal Society of London and Webster to the National Academy of Sciences. Finally, there was Cedric Mims, who joined the Department in 1956. Mims was/is an experimental pathologist interested in the pathogenesis of viral infections who pioneered many aspects of this field, focusing on the effect of viral infections on lymphoid tissue, the role of immune lymphocytes in arresting viral infections, and the nature of immunosuppression caused by viral infections using as his model systems mice infected with LCM, poxviruses, Sendai virus, and Ross River virus. Mims is the long term Head of the Department of Microbiology at Guy’s Hospital Medical School in London.

This outstanding faculty trained graduate students, many of whom attained positions of eminence. Thus David White was the long term Chairman of the Department of Microbiology at the University of Melbourne; Kevin Lafferty became Director of the John Curtin School of Medical Research after 10 years as Research Director of the Barbara Davis Center at the University of Colorado; Robert Webster (see above) is the long term Chairman of the Department of Virology at the St. Jude Children’s Research Hospital in Memphis; and Joe Sambrook, Ian Holmes, and Ken Easterbrook also became leaders in their fields and acquired international reputations.

This then was the Department that I joined in 1953 as a Research Fellow, and then as a Fellow, and in which I remained for 9 years until 1962. When I came Fenner asked me to work on the biochemistry of myxoma virus replication, but that proved impossible with the techniques available at that time because the titers of myxoma virus turned out to be extremely low, even in the rabbits that it kills. So I spent some time following up loose ends of my earlier work on transphosphorylation and identifying two interesting hitherto unidentified ultraviolet light-absorbing substances in mammalian livers that turned out to be adenine and adenyl succinic acid. The function of these two substances that occur in surprisingly high concentrations at one time considered to be possible intermediates in the transformation of IMP-5’ to AMP-5’ was a matter of considerable debate and conjecture.

The Beginning of Work on Mammalian Molecular Virology, Canberra, 1957

It was around the middle of 1957 that I actually decided to shift my attention seriously to molecular animal virology. It was certainly a good time for a biochemist to begin working in animal virology. Techniques for culturing homogeneous populations of mammalian cells had been developed by Enders in the late ’40s, and in the early ’50s Renato Dulbecco adapted the techniques for working with bacterial viruses to mammalian viruses. The stage was thus set for applying Ellis and Delbruck’s single-step growth cycle procedures to mammalian viruses.

Before I recall and discuss the issues in molecular virology that claimed my attention most intensely over the years, let me provide an outline of where I was located during the next four or five decades.

I remained in Canberra for another 5 years, from 1957 to 1962, interrupted by a fascinating sabbatical year at the NIH in 1959–1960. In 1962 I moved to the Albert Einstein College of Medicine in New York, where I stayed for 6 years until 1968 when I moved to Duke University Medical Center in Durham, North Carolina, where I have been ever since.

My first major interest was poxviruses, from the late ’50s to the late ’80s; then reoviruses, from the mid-’60s into the new millennium; and in the ’70s just after I moved to Duke, I also worked with retroviruses for a decade or so.

My overarching interest has always been molecular virology. I worked on the nature of the genetic material of these viruses, on its replication, on the nature of the mechanisms that express the information that it encodes, and on the nature of this information. I isolated many virus-encoded proteins and characterized their enzymic functions, if any, and how they interact with each other and with their genomes in studies of viral morphogenesis. I was always looking for reactions involved in virus replication that could be inhibited in order to prevent/abort viral infection. Among the agents capable of inhibiting virus multiplication on which I worked were: interferon, for which I established its primary antiviral mode of action; IBT, a methylated derivative of which was an important factor in eliminating smallpox virus from human populations in the late ’70s; and ribavirin, which is now used as an antiviral agent to control respiratory syncytial virus infections in children. Thus my central theme was to find out as much as possible about how viruses replicate and to use the knowledge gained to inhibit/abort viral infections.

Research on Poxviruses

In starting work on poxviruses I proceeded along two lines. The first was to study the incorporation of adenine into normal and vaccinia virus-infected HeLa cell monolayers. The rate of incorporation was increased relative to that of uninfected cells; the peak rate was reached when the first progeny virus particles were observed. Interest-
ingly, although vaccinia virus contains DNA, all incorporated adenine was located in RNA. This was not without significance; this was in the days preceding knowledge of messenger RNA.

My second interest was elucidation of the mechanisms involved in the fibroma-myxoma Berry-Dedrick transformation. It was in 1936 that Berry and Dedrick reported that active myxoma virus could be recovered from rabbits injected with mixtures of heat-inactivated myxoma virus and active fibroma virus. The term “transformation” was suggested by Griffith’s studies on the transformation of pneumococcal pseudotypes. However, Berry soon recognized that reactivation of the heat-inactivated myxoma virus by the presence of the active fibroma virus was a possible alternative explanation. The study of this phenomenon was taken up by several of us in the Department in Canberra in 1959, and we soon showed that it could be reproduced with other poxviruses like heated rabbitpox virus being reactivated by active vaccinia virus. Further, we were soon able to show that the reactivation phenomenon involves a non-genetic mechanism because virus, the DNA of which had been inactivated by nitrogen mustard, was still able to “reactivate” heat-inactivated virus.

I became very interested in this phenomenon and worked out techniques for assaying the phenomenon, demonstrated that the ability to reactivate resides in the central portion, namely the core, of the poxvirus particle, and studied the fate of reactive poxvirus particles within the cell prior to reactivation (5). I concluded that the most likely mechanism of the Berry-Dedrick reactivation is that denaturation inactivates a protein that is essential for the viral genome to express itself within host cells. This protein can, however, be introduced into the cell by any other poxvirus particle, which may itself be damaged in the genome (6).

Although we were unable to identify specifically the protein that is inactivated in reactive virus particles and that is supplied by reactivating virus particles, these studies taught us a great deal about the early stages of poxvirus infection and helped me focus my developing interests in animal virology. Before starting seriously, however, I had a sabbatical coming up in 1959, and the nature of that sabbatical greatly influenced my subsequent career.

**Sabbatical in the Laboratory of Cell Biology, NIAID, 1959–1960**

I spent the second half of 1959 and the first half of 1960 in the Laboratory of Dr. Harry Eagle at the National Institutes of Health. Eagle was at that time in the process of putting the finishing touches to his monumental studies defining the nutritional requirements of cultured malarian cells; his was the top laboratory in the world for tissue culture (4). My reason for joining his laboratory was that availability of reasonably large amounts of log phase suspension and monolayer mammalian cells of various types was a prerequisite for the sort of biochemical and molecular virology that I was hoping to get into.

Eagle was one of the most respected scientists of his generation. He was highly articulate and wrote extremely well; and he knew more people than any scientist I ever knew. At the NIH he had been the first Scientific Director of the NCI; at the time I joined his laboratory he was Chief of the Laboratory of Cell Biology in NIAID. The staff consisted of Leon Levintow, Bob Krooth, Norman Salzman, Jim Darnell, Ed Cohen, and Jake Maizel. I made the fifth virologist. Jim Darnell and I teamed up in a project to unravel the earliest stages of poliovirus infection. We adsorbed highly purified poliovirus labeled in either protein or RNA to suspension culture cells and followed changes in the disposition of the label (7). The results were clear: some virus was uncoated, and some was eluted. It was the success of this approach that encouraged me to carry out similar studies with the structurally much more complex poxviruses when I returned to Australia. As for the sabbatical, I enjoyed it enormously. All members of the Department of Cell Biology and many others I met for the first time became lifelong friends; and we (my wife and two children, aged 3 and 1) did a lot of traveling on the East Coast at what was a fascinating time.

**The End of My Australian Career: Canberra 1960–1962**

Once back in Canberra I worked out techniques for the purification/isolation of poxviruses, the last step being sucrose density gradient centrifugation (8), and applied the technique to poxviruses labeled in the DNA or in the protein coat. I then isolated poxvirus DNA and characterized it chemically and with respect to size by measuring its sedimentation coefficient. This work indicated that half-length molecules (molecular weight, 80 million) of poxvirus DNA could be isolated readily.

**Moving to the United States: The Albert Einstein College of Medicine, 1962–1968**

Dr. Eagle left the NIH at the end of 1960 to take the Chair of Cell Biology at the Albert Einstein College of Medicine in New York; when he did so, he asked me to join him as an Associate Professor in his Department. I did, for although the Department of Microbiology in Canberra was outstanding with a variety of faculty members with worldwide reputations, scientific opportunities were clearly much greater in an arena 10–20 times larger. Thus
in 1962 my family (my wife Judith, my son Richard aged 5, and my daughter Vivien aged 3) and I moved to New York to the Albert Einstein College of Medicine. This caused us no culture shock. Not only had we all been in the United States in 1959–1960, but there are surely no two countries that are more similar than Australia and the United States; both are young, huge, with booming economies, ample amounts of entrepreneurship, and loads of welcome for immigrants. The move was, therefore, for us no different from moving from one city to another in Australia. I received a good size laboratory next to Jake Maizel, who had also just moved to the Albert Einstein and started work.

The work I carried out at the Albert Einstein followed half a dozen or more avenues all focused on critical events during the rabbitpox/vaccinia virus infection cycle. They can be summarized in the following paragraphs.

Studies on the Uncoating of Rabbitpox Virus—First, I continued the work I had just started in Canberra, namely observing the fate of poxvirus following infection, that is its intracellular uncoating, using for this purpose highly radioactively labeled rabbitpox virus (8). The results were far more complex than what Jim Darnell and I had observed for the simple poliovirus. It turns out that the uncoating of poxvirus DNA is a two-step process. The first is effected by enzymes present in uninfected cells. Its products are viral cores and the viral inducer protein. The second, namely the breakdown of cores to liberate the viral genome, requires de novo synthesis of the uncoating protein induced by the inducer protein (9). The relevance to the studies of the mechanisms operative during Berry–Dedrick reactivation is obvious. We also carried out a series of studies of the intracellular fate of rabbitpox virus rendered noninfectious by a variety of reagents and treatments.

Studies on the Genesis of Rabbitpox Virus-specific Polyribosomes—Yechiel Becker and I characterized both viral and host cell mRNAs in infected cells. Viral mRNA transcription, which occurs in the cytoplasm, is easily detectable by 30 min after infection and decreases rapidly at about 7 h after infection. Host cell mRNA tends, on the average, to be larger than poxvirus mRNA. Viral and host mRNA can be distinguished by their quite different base ratios: A+T/G+C for cellular mRNA is 1.24 and 1.75 for rabbitpox mRNA. Hybridization to host and viral DNA was also demonstrated and used. The genesis of polyribosomes was then investigated. Messenger RNAs combine first with 40 S subribosomal particles (the free half-life of mRNA being about 30 s) and then with 60 S subribosomal particles to form polyribosomes. 40 S and 60 S subribosomal particles are always present in strictly equivalent numbers; they are made in the nucleus and enter the cytoplasm as individual entities (10).

Studies on the Replication and Coating of the Vaccinia Genome—Yechiel studied the formation and coating of the vaccinia virus genome by examining the size and nature of the structures, complexes, or aggregates (factories?) in which the newly formed DNA is located. During the early stages of infection newly replicated viral DNA is associated with large structures; later on it is released from them and becomes coated with protein. The final stage of maturation occurs at 5–6 h and results in the incorporation of the viral DNA into immature and mature virus particles.

Studies on “Early” Enzymes in HeLa Cells Infected with Vaccinia Virus—Chris Jungwirth and I found that DNA polymerase activity in the cytoplasm begins to increase at about 1.5 h after infection. The host cell and viral enzymes differ in several properties like saturating concentrations of DNA primer, pH activity curves, etc. The kinetics of formation of virus-specific DNase and thymidine kinase were also studied. The mRNAs encoding “early” viral enzymes are remarkably long lived (11).

Inhibition of Vaccinia Virus by Isatin-β-thiosemicarbazone (IBT)—IBT and N-Me-IBT were used during the smallpox eradication program in the ‘70s. Bruce Woodson and I were able to show that IBT affects the ability of late vaccinia virus mRNA to express itself normally. Late vaccinia virus mRNA is formed normally and forms polyribosomes, but within less than 5 min the size of these polyribosomes decreases, thus greatly reducing the functional half-life of late viral mRNA and therefore the amount of protein that is formed. The functional half-life of early viral mRNA is not affected (12).

Studies on the Mechanism of Action of Interferon—Tom Merigan and I were able to show that in interferon-treated cells viral mRNA and ribosomes do not combine to form polyribosomes. Infected interferon-treated cells tend to disintegrate at 3–4 h after infection, whereas untreated infected cells are still in reasonable shape at 21 h after infection (13).

Hybridization and Sedimentation Studies on “Early” and “Late” Vaccinia Virus mRNAs—Kin Oda carried out a superb analysis of early and late vaccinia mRNAs, using hybridization and density gradient sedimentation. He found the following. 1) Early mRNAs are smaller than late mRNAs. 2) Early mRNAs are also transcribed late. 3) The pattern of transcription of early and late viral mRNAs in HeLa and L cells is quite different. In HeLa cells much more late mRNA is made than early mRNA; in L cells the
reverse is true. 4) At 5 h after infection the mRNA molecules in polyribosomes contain all sequences characteristic of early mRNA; by 8 h after infection mRNA in polyribosomes is very significantly depleted with respect to early mRNA. 5) The large mRNA molecules transcribed late contain sequences also present in small early mRNA. Some small mRNA molecules are also transcribed late; they contain at least some sequences characteristic of late mRNA. 6) Early mRNA is very stable in HeLa cells. Late mRNA is significantly less stable, but late mRNA that contains some early sequences is as stable as early mRNA itself (14).

Structural Proteins of Vaccinia Virions and Cores—John Holowczak undertook the first detailed analysis of the structural proteins of vaccinia virus particles and cores. He calculated their molecular weights from the amount of radioactive label in each. The principal component (VSP4) accounts for about 28% of the total viral particle mass. Nonidet P-40 liberates the second most abundant protein component (VSP6), which accounts for about 19% of the total viral particle mass. John followed up this work by measuring the kinetics of synthesis of groups of viral structural proteins by pulse-labeling infected cells at intervals throughout the multiplication cycle. This provided a highly valuable and fascinating picture of the functional relationships between the various vaccinia structural proteins (15).

This work was continued by Izzy Sarov, who showed that 5 proteins are located near the virus particle surface; that 17 proteins are present in cores; that 2 proteins contain glucosamine and are therefore glycopolypeptides; and that 6 proteins are phosphoproteins, the major phosphoprotein being VP11b, a major virus particle component.

Izzy also characterized intermediates in the uncoating of vaccinia virus DNA and intermediates of vaccinia virus morphogenesis. He found complexes that contain newly replicated DNA, spherical particles about 280 nm in diameter that exhibit a highly characteristic layer of capsomers about 5 nm in diameter at their surface (immature particles), and two types of particles that contain DNA and resemble virus morphologically but sediment at only 0.6 and 0.8 times their rate in sucrose density gradients.

Vaccinia Virus Poly(A) and RNA Polymerases—Joe Nevins, who actually joined my laboratory when I was already at Duke, examined the nature, mode of addition, and function during translation of the poly(A) sequences of vaccinia virus mRNA and also isolated and characterized three poly(A) polymerases from HeLa cells infected with vaccinia virus (16). Two were cellular enzymes, whereas the third was present only in infected cells. The latter is a heterodimer composed of two subunits (57,000 and 37,000) and is able to use both RNA and oligo(A) as primer. It is identical with the poly(A) polymerase present in vaccinia virus cores except for somewhat different chromatographic properties caused, possibly, by a charge difference. Its two subunits differ from those of the two host poly(A) polymerases as well as from those of the vaccinia virus-specified DNA-dependent RNA polymerase that Joe also isolated and characterized. This enzyme is different from all other known DNA-dependent RNA polymerases including the two HeLa cell polymerases that Joe also characterized. It is composed of 7 subunits ranging in size from 13,500 to 135,000. The three largest subunits migrate in gels at the same rate as core proteins VP1c, VP1d, and VP2c. The enzyme may therefore be the same as the vaccinia virus core-associated RNA polymerase.

Nature of Terminal Loops of Vaccinia Virus DNA—David Pickup, who also joined me at Duke, carried out a detailed analysis of the nature of the terminal loop of poxvirus genomes. First, he identified the arrangement of repeated and unique sequence elements in the terminal regions of cowpox virus DNA; second, he cloned an EcoRI fragment of vaccinia virus strain WR that contained the terminal “flip-flop” sequence into pBR322; and third, he found that the genomes of 9 out of 10 white-pock variants of cowpox virus DNA possess spontaneous deletions and duplications in their terminal regions; they had lost regions from their right-hand ends that had been replaced (presumably by nonhomologous recombination or by random nonreciprocal sequence transfer) by inverted copies of regions from the left-hand end of their genomes (17).

Dhaval Patel isolated cowpox virus A-type inclusions (ATIs) and characterized their major protein component. One aspect of the pathogenesis of the Brighton Red strain of cowpox virus is its production of hemorrhagic lesions. David Pickup established that the hemorrhage is caused by a viral protein that is related to plasma protein inhibitors of serine proteases (18).

Studies of Vaccinia ts Mutants—Claudio Basilico isolated several vaccinia virus ts mutants and characterized one that is an early mutant. It exhibits decreased mRNA transcription and delayed and decreased DNA replication at nonpermissive temperatures. This mutant has only one-half the normal amount of RNA polymerase associated with it, and the DNA polymerase encoded by this mutant is twice as heat-labile as normal vaccinia virus DNA polymerase. Virus particles formed by this mutant at 39 °C are normal in appearance and possess the normal capsid protein complement and normal amounts of DNA but are only 3% as infectious as wild-type virus particles.
Research on Retroviruses

In the '70s shortly after I moved to Duke, there were several postdoctoral fellows in the laboratory who were interested in retroviruses. They carried out some cutting edge research, the highlights of which are described in the following paragraphs.

Ken Stone and Ralph Smith investigated the nature of changes in the protein complement of plasma membranes of avian (chick embryo fibroblasts (CEF)) and mammalian (normal rabbit kidney (NRK)) cells following infection with avian sarcoma viruses RSV and B77. Infection of CEF led to morphologic transformation and simultaneous changes in the rates of formation of several proteins. Infection with ts mutants at the nonpermissive temperature caused only one of the observed changes. Identical membrane protein changes were observed in NRK cells at permissive, but not at nonpermissive, temperatures.

Amnon Hizi isolated and characterized the α, β, and αβ forms of the RNA-dependent DNA polymerase of avian sarcoma virus B77 from duck embryo fibroblasts. The α and αβ forms were already known; the β form was a new form that could be isolated from duck embryo (but not chick embryo) fibroblasts because the former contain very little retrovirus genetic information (less than one genome) so that certain precursor cleavages proceed more slowly in them than in other cells like CEF. Amnon compared the three forms of the enzyme with respect to a variety of parameters, including catalytic properties. He also showed that the β subunit is a phosphoprotein (19).

Amnon also isolated and characterized a protein kinase from the Prague-C strain of RSV.

Michael Perdue isolated and characterized a large hairpin segment from avian retrovirus RNA. When subjected to limited digestion with pancreatic RNase, it was an almost perfectly double-stranded hairpin about 350 bp long. It was located in the region between 5,000 and 6,000 nucleotides of viral RNA, close to the terminus of viral RNA, close to the junction of the pol and env genes. The RNA of the helper-free Bryan high titer strain of RSV lacks most of the env gene; it also failed to yield the above hairpin segment.

The Move to Duke, 1968

In the summer of 1968 I moved to Duke University Medical Center in Durham, NC, as Chairman of the Department of Microbiology and Immunology. The Department at that time was small, with only 6 faculty members, but I was given the opportunity to enlarge it; when I retired in 1993 we had 33 faculty members and the Department was then split into a Department of Microbiology and a Department of Immunology.

Research into the Molecular Biology of Reovirus Replication

I started work on reovirus in 1966 while I was still at the Albert Einstein College of Medicine. Gomatos and Tamm had just reported that the genome of reovirus comprises a new form of RNA that could be interpreted as being dsRNA, which caused considerable excitement; furthermore, the laboratories of Kleinschmidt and of Shatkin had presented results that suggested that the reovirus genome is either extremely fragile or comprises several genome segments arranged in three size classes.

This was the situation when we decided to characterize more closely reovirus genome RNA (20). We found no evidence of complete large molecules and concluded that it was segmented. We found the segments to be dsRNA by all available criteria. We then showed that reovirus mRNAs are transcribed in the form of three size classes that are the same size as denatured genome segment strands (21). We also found that reovirions contain about 3,000 molecules (15–20% of total RNA) of short (3–20 nucleotides) ssRNA molecules that are very rich in A (more than 85%). The significance of these molecules, which are not free in the cytoplasm but are present only in virions, was subsequently elucidated by Jack Nichols, who showed (by sequencing them) that they are the products of abortive transcription within virions from which they fail to escape (22).

Following careful definition of the nature of the protein components of reovirions, top component and cores, we devised the assignment of λ, μ, and σ for the members of the three protein size class groups, an assignment that has stuck. The sizes of all capsid proteins were measured, as was the number of each of the proteins in each of the particle classes. It was noted that the sizes of the λ, μ, and σ size class proteins were very close to the proteins that could be encoded by the l, m, and s size class mRNAs.

Studies on the intracellular synthesis of reovirus proteins followed. Core proteins tend to be formed early; outer shell components tend to be formed later. Host protein synthesis does not decrease until late during the infection cycle. At the same time we developed an in vitro protein-synthesizing system derived from mouse L fibroblasts that is capable of translating either mRNA or denatured dsRNA that performs very efficiently and that we have used extensively (23). In particular, we have used it to identify definitively the protein encoded by each of the 10 dsRNA genome segments, measured the relative translation efficiencies of the 10 species of reovirus mRNA (24), and demonstrated that regions upstream of initiation codons control reovirus mRNA translation efficiency.
Reovirus mRNA is transcribed in cores; and we were interested to determine whether cores were capable of transcribing mRNA in vitro also. John Skehel found that they do so very efficiently for long periods of time (25). There is an absolute requirement for magnesium. The products of the reaction are intact single-stranded copies of all 10 genome segments; the number of copies of each segment made is inversely proportional to its size.

While these studies were ongoing, a variety of careful morphological studies were carried out (26). One concerned virions and cores, the emphasis being on discerning capsomer interactions and the geometry and morphology of the 12 core projections or spikes (27). Another study focused on the effect of chymotrypsin on reovirions (28). At low enzyme concentrations virions are converted to cores via several stages, individual components of the outer capsid shell being removed one by one. At high enzyme concentrations a variety of particles are formed that possess full infectivity and no transcriptase activity and lack about one-third of their capsid protein complement.

Over the years a considerable amount of effort was devoted to characterizing a series of reovirus ts mutants that had been isolated by Bernie Fields using nitrous acid, nitrosoguanidine, and proflavine as mutagens (29). He studied 35 mutants, identified 5 recombination groups, and classified them according to their ability to induce the formation of virus-specific RNA at nonpermissive temperatures. Others then characterized these mutants further. For example, Ito determined the patterns of gene expression of mutants of recombination groups C, D, and E and then identified group D (“RNA-negative”) mutants as being μ2 mutants; and Tadao Matsuhisa identified the mutated protein of the group C mutant ts447, a mutant that we often used in a variety of studies (30).

As an aside and because I have long been interested in interferon, we tested a variety of forms of reovirions for their ability to induce interferon, examined mechanisms of interferon induction by UV-irradiated reovirus, and studied the mechanism of inhibition of reovirus replication by interferon. Wild-type reovirus, cores, top component, and various ts mutants were tested for their ability to induce interferon. Top component and cores did not, and most ts mutants induced significantly less interferon at nonpermissive temperatures than wild-type virus. UV irradiation not only did not inhibit the ability to induce interferon but often greatly increased it (31): 200-fold for wild-type virus and 104-fold for ts 447 at 38 °C! The reason is that UV irradiation labilizes the inner capsid shell and causes some dsRNA to be liberated into the interior of the cell. As for the reason why reovirus replication is inhibited in cells treated with interferon, the explanation is that in such cells the translation of early reovirus mRNA, particularly that of the mRNA that encodes protein λ1, is suppressed (32).

Some time later we examined the mechanism of the antiviral activity of ribavirin, a broad spectrum antiviral agent active against 12 DNA- and 40 RNA-containing viruses, against reovirus (33). Ribavirin inhibits ssRNA and dsRNA formation, protein synthesis, and viral multiplication, the prime target being ssRNA formation. When the effect of ribavirin triphosphate was tested on core-catalyzed transcription, elongation was inhibited to the greatest extent; initiation was 2.5 times less sensitive and cap formation/methylation were unaffected. Remarkably, the transcription of plus strands into minus strands by immature virus particles, the replicase reaction, was unaffected. We proposed that ribavirin triphosphate binds to a site close to the catalytic site of the transcriptase, thereby inhibiting its helicase function (which is not necessary for the transcription of plus strands into minus strands) and lowering its affinity for template RNA, thereby greatly increasing premature replication.

The next stage in our elucidation of the nature of reovirus was the crucial one of sequencing the genome segments and characterizing the proteins that they encode. The work was started by cloning all 10 genome segments into pBR322 (34). The first genome segment to be sequenced was the ST3 S2 genome segment (35), which encodes the 331-codon long protein α2, and for which we also sequenced the corresponding genome segment of ts447, the ts lesion of which is in this protein. The two sequences differ in three locations. The mutation at position 581 (Ala to Val) causes significant reduction of the size of an α-helix and may be that which is responsible for its phenotype. This was followed by the sequencing of the three serotypes of genome segment S1 (36), the three serotypes of S3 (37), the three serotypes of M2 (38), the ST3 L3 genome segment (39), the ST3 M1 and M3 genome segments (40), and the three serotypes of the L1 genome segment (41). We thus sequenced 8 of the 10 reovirus genome segments. In all cases where all three serotype genome segments were sequenced, a detailed analysis was carried out concerning their genetic relatedness. Particular attention was paid to nucleotide changes in first or second as opposed to third base codon positions, few of which entail amino acid changes. For genome segment S3, the figures for the first, second, and third base codon mismatch comparisons for the ST 1:3, ST 1:2, and ST 2:3 pairs are 10, 23, and 24; 4, 7, and 7; and 86, 71, and 69. Thus most mis-
matches are in third base codon positions. For all genome segments STs 1 and 3 are the most closely related as judged by nucleotide homology (more than 85%), whereas serotypes 1 and 2 and 2 and 3 are somewhat less closely related (about 75%). The only exception is genome segment S1; here ST1 and ST2 exhibit 28% nucleotide base homology, whereas STs 1 and 3 and STs 2 and 3 exhibit 5 and 9% homology, respectively. As for changes in terminal sequences, many of which had been known for some time from sequencing of terminal regions prior to complete genome segment sequencing, it was noted that they tend to be conserved, even in the case of genome segment S1. Terminal regions may include recognition signals for ribosomes, RNA polymerase, and encapsidation (42). As for the antigenic relationships of the proteins encoded by the three serotypes, Gaillard had shown some time before that these are highly conserved, even those encoded by ST2. The only exception is provided by the three σ1 proteins which display type specificity (43).

There remained the problem of identifying the functions of the proteins encoded by the reovirus genome. These proteins were expressed in large amounts by cloning the relevant genome segments into the thymidine kinase gene of vaccinia virus strain WR, which was then grown in HeLa cells or in strain 143 osteosarcoma cells. Each protein was then isolated and characterized. The following results were obtained. 1) Protein A2, the major component of the 12 icosahedrally located core projections/spikes, is the reovirus guanylyl transferase, that is it is the reovirus capping enzyme that forms the GpppG caps at the 5’ termini of reovirus mRNAs (44). It possesses no methyltransferase activities. 2) Protein A3 is a poly(C)-dependent poly(G) polymerase, that is it transcribes poly(C) into poly(G). It is thus the reovirus RNA polymerase. Neither protein A1 nor protein A2 enable it to transcribe RNA; the ability to exercise this function is presumably provided by a host protein (45). 3) Protein σ1 is the cell attachment protein (46). It modulates tissue tropism and the nature of the antiviral response. It is present in reovirus particles in the form of 12 trimers anchored to the projections/spikes. It is formed in very small amounts only in infected cells, but Akhil Banerjea devised a mammalian expression vector system that produces large amounts of it (47). 4) Protein σ2A is a nonstructural protein that exists in the cytoplasm of infected cells in significant amounts in the form of large complexes that contain both it and ssRNA, including I, m, and s reovirus ssRNA species. The complexes can be dissociated with salt. Protein σ2A forms complexes with poly(A), poly(C), poly(G), and poly(U). Neither its function nor that of its complexes with ssRNA are known (48). 5) Protein σ3 is one of the two major components of the reovirus outer capsid shell (900 molecules/particle, 28% of the reovirus particle’s protein complement). It possesses high affinity for dsRNA. It binds to poly(AU) and poly(IC) (48).

Before going on to the last chapter of this account of almost four decades of work on the nature of reovirus, I would like to describe two rather interesting techniques: one for dealing with the functions of reovirus proteins during the actual reovirus multiplication cycle and the other with reovirus genome segment reassortment into progeny genomes.

The first of these techniques operates as follows. When cultured cells are injected with mixtures of cores of two different reovirus serotypes, a high proportion of the resulting assortants are monoreassortants, that is virus particles that contain one genome segment of one parent and nine from the other parent. We isolated complete sets of these monoreassortant viruses. These viruses can then be used to determine which protein controls replication cycle parameters. Applying this analysis, we established that proteins A2, μ1/μ1C, and σ3 control yield size and extent of RNA and protein synthesis; proteins μ2 and σ1 control severity of pathogenic effects; and proteins σ1, μ1/μ1C, and μ2 control plaque size. Identification of monoreassortant phenotypes is very useful for identifying which viral proteins are functionally involved at the various stages of the reovirus multiplication cycle (49).

The second technique involves the use of monoclonal antibodies against reovirus proteins. We isolated a complete set of such antibodies against all reovirus proteins (50) and used it, for example, to demonstrate that protein A2 is exposed on the virus particle surface. We then used this antibody set in a major study to identify proteins that associate with reovirus mRNA prior to the generation of progeny dsRNA genome segments and proteins that are components of the structures within which progeny double-stranded genome segments are generated. Three proteins rapidly become associated with mRNA molecules to form ssRNA-containing complexes: μNS, σNS, and σ3. Some complexes contain only μNS, others μNS and σNS or σ3, and others all three proteins. Each complex contains one mRNA molecule and, depending on the size of the RNA, 10–30 protein molecules. Complexes that contain dsRNA, which become detectable as early as 4 h after infection, contain not only the above three proteins but also A2. The relative proportions of the 10 genome segments in the total number of complexes is equimolar. This suggests that genome segment assortment into progeny
Two other interesting studies were the demonstration that reovirus subviral particles of any type are formed in cells infected with various combinations of hybrid vaccinia viruses that express various reovirus genome segments. Thus particles that are very similar to reovirus core shells are formed in cells infected with vaccinia virus expressing genome segments L1 and S2; if also infected with vaccinia virus expressing L2, the particles formed also possess the characteristic projections/spikes; and if also infected with vaccinia virus expressing L3, the particles formed are morphologically identical to those formed in its absence but also contain the reovirus RNA polymerase.

The other study is simply the observation that reovirus exists in the form of 13 particle species that differ in their content of protein α1: from 0 to 12 trimers of this protein at the ends of the projections/spikes.

The final, and potentially most interesting study on reovirus with which I have been associated, is the demonstration by Roner that reovirus RNA is infectious. In brief, single-stranded or double-stranded ST3 RNA is lipofected into L929 mouse fibroblasts together with a rabbit reticulocyte lysate in which ssRNA or melted dsRNA has been translated. After 8 h the cells are then infected with a helper virus, say ST2 virus, and virus yields are harvested 24 or 48 h later. Under these conditions virus that forms plaques by 5 days is produced, all of which is ST3 virus. dsRNA is 20 times as infectious as ssRNA. The primed rabbit reticulocyte lysate is not essential but increases viral yields by 100-fold. Translation of all species of RNA is essential. Whereas no reassortants are formed when ss- and dsRNA of different genotypes are lipofected together, mixtures of dsRNAs of different genotypes do yield reassortants. The same is true for mixtures of ssRNA.

These findings permit the introduction of new or altered genome segments into the reovirus genome. They open the way to the identification of encapsidation and assortment signals on reovirus genome segments, the characterization of functional domains in reovirus proteins, the construction of highly efficient vaccine strains (for pathogenic dsRNA-containing viruses like rotaviruses), and the development of reovirus, a virus nonpathogenic for humans, as an expression vector. Identification of signals required for the insertion of heterologous genome segments into the reovirus genome is already under way; and the feasibility of constructing novel reovirus strains has been demonstrated by the successful introduction of a functional CAT gene into the reovirus genome.

**Comments, Extracurricular Activities, and Background**

I have been very fortunate in always having been well funded and having had bright and enthusiastic young collaborators. I had close to 100 graduate students and postdoctoral fellows. Many among them have done extremely well, like Bernie Fields, who died tragically of pancreatic cancer in 1995 and who was Chairman of the Department of Microbiology and Molecular Genetics at Harvard and a member of the National Academy of Sciences, and John Skehel, who has now been Director of the MRC Institute for Medical Research at Mill Hill for more than 10 years, is a Fellow of the Royal Society, and 5 years ago was knighted by the Queen.

My laboratory has never been large, generally 10–12, because I have always had many responsibilities besides research. For 25 years, from 1968 to 1993, I was Chairman of the Department of Microbiology and Immunology at Duke University Medical Center, which I built up from 6 faculty members to 33 and which in the mid-’80s was ranked as one of the top three microbiology/immunology departments in the country. Not only was it outstanding in research but also in teaching. Our teaching load was large: bacteriology, virology, mycology, parasitology, and immunology, all from both the biological and the molecular point of view. Not only did faculty members lecture to medical students, but they also contributed to writing Zinsser Microbiology, the major, premier microbiology/immunology textbook, which the Department had inherited from Hans Zinsser of Harvard, who initiated it in 1910. We wrote the 15th, 16th, 17th, 18th, 19th, and 20th editions spanning the period from 1972 to 1990. The book, new editions of which appeared every 4 years, was very successful. It generally comprised about 1,260 pages. I acted as Editor-in-Chief and wrote the basic virology chapters, which generally amounted to about 180 pages. Compiling each new edition always involved 18 months of intensive literature research, writing, and coordinating contributions. Each edition comprised about 100 chapters from about 25 authors, about one-half of whom were members of the Department, and 90% were faculty members of Duke University Medical Center.

In addition to my administrative, teaching, and research activities at DUMC I served for many years on review committees. I was Chairman of the Virology Study Section of NIH in the early ’70s; served as President of the Microbiology Chairmen’s Association in 1979; Editor-in-Chief of Virology for 24 years; Editor-in-Chief of Microbiological
Let me review briefly several issues/activities with which I was associated or that I initiated and that afforded me great satisfaction. The first was within Duke and that was my role in founding the Duke Comprehensive Cancer Center. The late ‘60s and early ‘70s were a unique time in biomedical research. Spectacular advances in molecular biology, genetics, and virology were beginning to permit definition of cancer in far more concrete terms than had hitherto been possible. In particular, recent discoveries had shown that certain viruses were capable of transforming normal cells into tumor cells, which permitted detailed examination of the transformation process in molecular terms. The resulting intellectual ferment generated a strong feeling that here was a golden opportunity for implementing an all-out assault on cancer, and in January 1971 President Nixon, in his State of the Union message, declared a “war on cancer,” a key ingredient of which was the creation of a series of Comprehensive Cancer Centers.

This was the situation shortly after I came to Duke in 1968 as Chairman of one of the five basic science departments. I became interested in the new horizons for cancer research for two reasons: Judith, my first wife, had breast cancer (she had had a mastectomy the year before when we were still in New York), and as a molecular virologist building up a department, it appeared to me that Duke was the perfect place for one of the regional Comprehensive Cancer Centers. I prepared a rationale for such a Center and what would be required in terms of staff and facilities and circulated this material in January 1971 among key Department Chairmen. As a result of the keen interest and support that it received I discussed it in detail with Dr. Anlyan and in February 1971 he and I went to brief President Sanford. He also was enthusiastic and fully supportive. As a result I formally proposed to MedSac in April 1971 that DUMC apply for one of the regional Comprehensive Cancer Centers, and MedSac approved. Dr. Anlyan set up a Cancer Planning Committee with me as Chairman and Bill Shingleton as Vice-Chairman. Intensive planning for a couple of years culminated in a successful application to the NCI for a Comprehensive Cancer Center, followed by two applications for facilities, the first for the Jones Building for Basic Cancer Research and the second for the Morris Building for Clinical Cancer Research. As for the Directorship of the new Comprehensive Cancer Center, we decided that the Director of the CCC should not also be a departmental chairman; and Dr. Anlyan, Wayne Rundles, and I decided that the Director of the CCC should be Bill Shingleton, which turned out to be an excellent choice. The DCCC is now in its 34th year and very successful; its five yearly core support grant applications are always approved with high priority.

The second such activity was my founding of the American Society for Virology. Viruses were discovered in the 1890s; and it was not long before the unique advantages as model systems of these extraordinarily simple self-replicating biological units capable of inducing most profound changes in the cells that they infect began to attract attention. Molecular studies of bacterial viruses provided the basis for the generation of molecular biology and molecular genetics; Nobel Prizes began to be awarded to virologists; yet by the mid-1960s no Society for Virology existed anywhere in the world, virology being subsumed under the heading of microbiology, which included bacteriology, mycology, parasitology, and virology. The problem was that bacteria, fungi/yeasts, and many parasites are unicellular organisms, whereas the dominant branch of virology by the mid-1960s was concerned with viruses that infect humans and other vertebrates. As a result, virologists no longer felt at home with the American Society for Microbiology (ASM), the annual meetings of which were the only annual get togethers for virologists. Hence discussions began in the ‘70s and gathered momentum as to what should be done to remedy this situation.

In December 1980 I sent a letter to a dozen friends who were leading virologists, suggesting that we might form an American Society for Virology (ASV) and suggested meeting at a central location to discuss such an initiative. Because the response was overwhelmingly positive, we sent the same letter to 180 virologists; of 140 replies, 138 were positive. As a result 40 leading virologists met at O’Hare International Airport on June 9, 1981, where we discussed specifics and finally passed unanimously a resolution to found an ASV. I was elected Interim President. The first annual meeting of the new society, attended by about 900 virologists, was held August 1–5, 1982 on the campus of Cornell University in Ithaca, NY, where the new society was officially promulgated and I was elected first President. This was the first society for virology anywhere in the world; now there are more than a dozen. The ASV now has almost 3,500 members, 600 of whom are citizens from 44 countries outside the United States. This year we...
will have our 24th 4-day long annual meeting; about 1,500 virologist will be present.

The third such activity devolved from my research on vaccinia virus. WHO had mounted a worldwide smallpox eradication campaign in the 1970s and had set up a committee, the Smallpox Eradication Committee, to keep track of it and coordinate it with related activities. I was one of the two United States representatives on it. The campaign terminated when smallpox was officially declared eradicated in 1980. Although eradicated in humans, there was still a great deal of smallpox virus around in the form of samples, isolates, and specimens in many laboratories; and efforts were made to track these down and destroy them. When this goal was within reach, the leadership of the Smallpox Eradication Campaign recommended that all smallpox samples/stocks everywhere be destroyed, so that smallpox could officially be declared to be totally eradicated from the planet. This proposal was brought before the Smallpox Eradication Committee where the United States had no objection, but the Soviet Union objected. We then decided that all smallpox virus stocks worldwide should be destroyed except stocks in two institutes: the CDC in Atlanta and the Institute of Viral Preparations in Moscow, which was later changed to the NPO “Vector” Institute of Molecular Biology in Koltsovo, Novosibirsk region, Russia.

This was fine until, in the late ’80s, the Eradication Campaign leadership renewed their efforts to destroy these stocks also. This did not seem smart to me for several reasons. First, one could not possibly be certain that no smallpox virus whatsoever escaped destruction either by chance (in an unmarked tube or in an overlooked location) or by design. Second, one of the major concerns of the Smallpox Eradication Committee was to follow infections caused by monkeypox virus in Africa. Monkeypox virus, a close relative of smallpox virus, causes a smallpox-like disease in humans but is much less readily transmitted among humans than smallpox virus. The problem is that mutation could at any time increase the rate of transmission of monkeypox virus among humans by several orders of magnitude. Third, there is always the possibility that smallpox virus might be surviving in smallpox patients buried in permafrost; smallpox antigens have, in fact, been recovered from such accidentally exposed patients. Finally, if smallpox virus does appear again for any of these or other reasons and no smallpox virus is available for measuring the potency of old or newly prepared stocks of smallpox vaccine, huge epidemics could result with no way of arresting them. Therefore, at the 9th International Congress of Virology in Glasgow in August 1993 I pointed out, in the course of opening a Round Table Conference entitled “Smallpox: the final steps toward eradication,” how shortsighted and self-destructive destruction of the officially sanctioned stocks of smallpox virus would be. I followed up this talk with three articles entitled “Why the smallpox virus stocks should not be destroyed” (in Science, 1993), “The destruction of smallpox virus stocks in national repositories: a grave mistake and a bad precedent” (in Infectious Agents and Disease, 1994), and “The remaining smallpox virus stocks are too valuable to be destroyed” (in The Scientist, 1996) that elicited a great deal of interest and a deluge of comments. The official United States position vacillated for several years until in the late ’90s the United States officially decided (after urging by Britain) not to destroy its smallpox virus stocks. The wisdom of this decision became apparent during the smallpox virus scare several years ago when the efficacy of smallpox vaccine stocks could be accurately determined.

As for my interests outside the laboratory and the office, I might mention the following. First, because I am equally at home in two cultures (the Austrian/German and the British/American) I am greatly interested in international affairs and love to travel; I have traveled widely. I love classical music and opera, the theater, and reading. I play tennis and golf when time permits. I have devoted a considerable amount of time and effort to two causes in Durham: Caring House, a home-away-from-home residential facility for out-of-town patients of the Duke Comprehensive Cancer Center who are undergoing intensive chemotherapy or radiotherapy, for which I was President of the Board of Directors and directed a successful $2.25 million Endowment Raising Campaign; and the Durham County Public Library, of whose Foundation I am a member, the current objective of which is, once again, to raise an endowment.

My first wife, Judith, an Australian who was the mother of my son Richard and my daughter Vivien, died in 1975. Two years later I married my present wife, Pat, born in Columbus, OH, whose first husband Chuck had died 4 months before Judith. Together we have 6 children and 17 grandchildren (including two sets of twin girls) who range in age from 23 years to 1. What could be better!!!

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