I begin this essay with a brief account of the personal and social aspects of my career, followed by the science.

Early Years

I was born in New York City in 1933 to Jack and Florence Stark, the third of three children, 5–7 years after my sisters, Edna and Bernyce. Because my father was in the restaurant business and doing well at the time, there was a big party to celebrate the blessed arrival of the long awaited boy child. The restaurant business is treacherous, the silver spoon got bent pretty quickly, and my first career choice was made: not the restaurant business. At the beginning of World War II, Dad moved us to the Washington, D.C. area and opened a luncheonette at 15th and H Sts., N.E., “Stark's Beef and Beans,” which sustained us through the war and early postwar years. We lived in semi-rural Maryland, where I went through most of secondary school. Mom worked as a bookkeeper in D.C., and my sisters were away all day in high school, then college, so I had to fend for myself much of the time. Saturdays were spent helping out in the restaurant, perfecting my emerging skills in chemistry and manual dexterity by preparing and flipping pancakes. Between rush hours, I played pool with the streetcar drivers relaxing in the pool hall next door (it was the end of the line) and got a chance to become pals with Albert, the jolly black cook who showed me a very different perspective on life. I have been very fortunate to have made friends with many different people, helping me to appreciate their varied approaches to living and to learn how to adapt to new situations, in life and in science. Angling for catfish in Georgetown with Albert was a highlight. Whites socializing with blacks was not common in D.C. at that time. My dad was devastated when he had to refuse to serve a wounded black veteran in the restaurant. In our segregated nation’s capital in 1945, to have done so would have been the end of the restaurant and our livelihood. When I go to D.C. now, usually to visit NIH, I am thrilled to see how well so many black people are doing, with the shame of segregation long gone. How far we have come!

Grammar school was uneventful, but my three years in Hyattsville (Maryland) High School were not. I had inspiring teachers in biology (Mr. Owens) and chemistry (Mr. Lauer) and did a couple of fun projects in science fairs. For “How Dangerous is a Kiss?” I had the school beauty queen press her luscious lips to a Petri dish, causing their imprint to be immortalized as a thriving culture of bacteria and mold. Why she wouldn't dance with me at the prom I have no idea.

In 1950, we moved back to New York. My dad, who had little formal education but read widely and deeply, was determined that I should be a scientist and insisted that I needed to be in the right place for a good education so, with the pull of a relative who was a New York state senator, my way was wangled into the elite Bronx High School of Science for my senior year. After the relative peace and quiet of Hyattsville, here was a challenge!
Columbia and Rockefeller

I managed to survive Bronx Science well enough to gain admission to Columbia College, where I was to spend 8 wonderful years as an undergraduate and graduate student. Earning money was essential at this time, so summers I rented out seat cushions at Lewisohn Stadium (allowing me to enjoy the full program of wonderful classical concerts free), and during the academic year, I perfected my demon touch typing at the Columbia Scholastic Press Association, working for Col. Joseph M. Murphy, one of the kindest people I have ever met. Columbia College was a revelation, from enjoying the physical activity of lightweight crew to eye-opening, life-changing exposures to the humanities, contemporary civilization, the fine arts, and music. I was a premedical student until I took comparative anatomy, which convinced me to find another road. Chemistry was challenging and fun, as was my advisor, Charles Dawson, whose laboratory included both organic chemists and biochemists. I joined them as a graduate student, working on ascorbate oxidase from yellow crook-necked squash. Because the enzyme was concentrated in the skin, we got a great initial purification by peeling many bushels of squash in the cold room, accompanied by lots of graduate student raucous humor. Charles Dawson was the first serious scientist I had encountered up close and personal, and his wisdom and camaraderie with his students and fellows made a deep impression on me. Unfortunately, none of the rock songs I composed with my labmate Eddie Grossman (the brother-in-law of Neil Sedaka) made the hit parade, but I did finish a thesis and went on to become a postdoctoral fellow in a famous laboratory at Rockefeller University.

But before we get to that, let me introduce you to Mary Beck, a winsome physics major at Michigan who lived in New York. We met the summer after her freshman (my sophomore) year in college and got married as soon as we could after she graduated. Mary worked as a radiation physicist, paused to raise our two children, Robert and Janna, and then joined my laboratory for many years. In a short essay, what can one say about the glue that holds one's life together?

When I joined them at Rockefeller, Stanford Moore and William Stein were famous protein chemists, having invented the amino acid analyzer and sequenced bovine pancreatic ribonuclease, work for which they were to be awarded the Nobel Prize. In their laboratory I discovered that cyanate, formed from urea, could carbamylate the amino groups of proteins and, together with Derek Smyth, I used carbamylation as the basis of a new method to determine the amino-terminal residues of proteins. I also worked on the mechanism of action of ribonuclease, and extension of this type of work to aspartate transcarbamylase followed at the beginning of my independent career at Stanford. Bill Stein and Stan Moore were wonderful scientists, wonderful gentlemen, and wonderful to me, and we maintained close friendships until each met an untimely death. I could not have had better teachers.

Dennis Shaw, a labmate at Rockefeller, had come from Fred Sanger's group at Cambridge. Shortly after Dennis left each laboratory in which he had worked, the laboratory head won a Nobel Prize: the first prize to Sanger, Moore, and Stein; the second prize to Sanger, Gerald Edelman. I don't want to think about how much Dennis was offered to work in his fifth laboratory, but the streak was broken.

Stanford

After 4 happy years at Rockefeller, I was recruited to the famous Department of Biochemistry at Stanford by Arthur Kornberg to bring protein organic chemistry to the department, together with Lubert Stryer, who was responsible for protein physical chemistry. There I was to spend 20 wonderful years before moving on. My personal and scientific life was enriched immeasurably, initially by Arthur, Lubert, Paul Berg, Dave Hogness, Dale Kaiser, Bob Lehman, and Buzz Baldwin, joined later by Doug Brutlag, Ron Davis, and Jim Rothman. What a group! What an environment! We worked as individuals but with constant exchanges of ideas and information in a system propelled by Arthur's wisdom, for example, in establishing journal clubs and faculty research meetings several times each week. Space for students and fellows was assigned nearly randomly, so that a single small laboratory might have people working on completely different projects from four different groups. Reagents and ideas were shared freely; we were truly a community of scholars. I learned metabolism and bacterial, phage, and Drosophila genetics and was right next door to key discoveries in molecular biology, for example, the creation of the first recombinant DNA in Paul Berg's and Dale Kaiser's laboratories. My own background in chemistry helped us to figure out how to attach RNA and proteins covalently to paper, establishing the Northern and Western methods as derivatives of...
Ed Southern’s pioneering work in transferring fragments of DNA from gels to nitrocellulose. Two sabbaticals in London, in 1970 with Lionel Crawford at the Imperial Cancer Research Fund (ICRF) and in 1977 with Ian Kerr at the Medical Research Council laboratory at Mill Hill, helped to transform my laboratory from protein chemistry to cell and molecular biology. The Cold Spring Harbor course in animal cells and viruses, taught superbly well in 1970 by Tom Benjamin and Howard Temin, paved the way for my work on SV40, initially with Lionel Crawford in London and later in my own laboratory at Stanford.

Ian Kerr’s experiments with 2’,5’-oligoadenylates and interferons led to a collaboration with his laboratory that began with a second sabbatical in London in 1977 and remains in place today, with Ian visiting my laboratory in Cleveland. Ian and I first met in 1963, when he joined Bob Lehman as a postdoctoral fellow, and I have profited enormously from our friendship and scientific association. In 1983, after 20 years at Stanford, I made the difficult decision to move to London, where Ian and I developed a close collaboration to study interferon-dependent signaling.

ICRF

By the time I got to London, Ian had moved to ICRF in the center of the city at Lincoln’s Inn Fields. In addition to running my laboratory, I gradually assumed some administrative duties as Associate Director of Research. We were fortunate to be able to have a house, complete with garden, about 2 miles north of the ICRF, in Camden Town. Walking everywhere, including back and forth to work every day, was a pleasure. London is a fairyland, probably my favorite city. Part of the laboratory worked on mechanisms of gene amplification, derived from our previous work on aspartate transcarbamylase (as you will see), and the rest worked on mechanisms of response to interferons, eventually using a genetic approach that we are still developing. The years at ICRF taught me many things. Because the laboratory was fully funded, I had the liberty and luxury to concentrate fully on the science. I appreciated this most after returning to the United States, having to deal again with the nitty gritty of NIH funding. At ICRF, the method of funding facilitated an outstanding system of central services, which provided everything a scientist could wish for to make research easy and productive. In moving to Cleveland, I brought as much of the ICRF-style central services with me as I could, including Derek Duke, who single-handedly and heroically set most of them up at the Cleveland Clinic.

Cleveland

A couple of years short of age 60, I discovered that retirement at age 62 was mandatory at ICRF, meaning that very soon I would have to begin to scale down my laboratory. No way! I had to move on. At the Cleveland Clinic Foundation (CCF), my interferon friends and colleagues Bryan Williams, Ganes Sen, and Bob Silverman were helping to look for a new head of research, a position vacated by Bernadine Healy when she left to become head of NIH under the first President Bush. CCF was anxious to build further upon the excellent foundation that Bernadine had established and offered to provide appropriate resources, including a new building. This new challenge was most attractive, as was the opportunity to join the interferon mafia in Cleveland, and so we moved once again, in 1992. In Cleveland, I spent 10 years helping to build the Lerner Research Institute to its present status and size (eight full departments and about 130 principal investigators), with the tremendous help of the department chairs and Derek Duke, who did the lion’s share of the administrative work, leaving me free to help develop the scientific enterprise and to continue my own research. After 10 years, CCF internal politics encouraged me to step down as chairman, but I remain involved in building joint research programs between CCF and its academic partner Case Western Reserve University, where I am currently a Professor of Genetics. The laboratory has maintained a strong interest in mechanisms of interferon action and in the development of novel genetic methods and has explored new projects in interleukin-1-dependent signaling and in other aspects of NFκB-driven gene expression. We also continue to work on aspects of p53 activation and function.

What I Have Learned

Treat everyone with kindness and respect. Learn to work with and get the best from coworkers—bright scientists come with many different personalities, and tolerance for differences in background, cultures, and lifestyles is essential. A good sense of humor helps a lot! Be
daring in choosing new scientific projects and stick to them as long as you continue to feel that the direction is positive. (Unfortunately, the current system of NIH funding does not encourage projects that develop slowly or are somewhat risky, no matter how important they may be. Enterprising investigators often figure out a way around this problem and, hopefully, the system will change.) Think mechanistically, not descriptively. Try to discover how things work.

From Urea to Gene Amplification via Aspartate Transcarbamylase

Wohler reported the reaction of ammonia with cyanic acid to give urea (Fig. 1) more than 150 years ago. At Rockefeller, I found that this reaction is reversible and that the cyanate formed in the 8 M urea commonly used to denature proteins reacts with the amino groups of lysine residues to give homocitrulline residues (Fig. 1), with the elimination of positive charges and profound effects on the ability of the protein to refold when the urea is removed, helping to explain the irreversible denaturation of proteins in urea, which was something of a puzzle at the time (1). The $\alpha$-amino groups of proteins also react with cyanate and, upon exposure to acid, cyclize to give hydantoins, which can be used to identify the amino termini (2). These discoveries, made in the Moore-Stein laboratory, stimulated my interest in cyanate chemistry, leading to later work at Stanford on aspartate transcarbamylase. Work at Rockefeller on the mechanism of ribonuclease action also stimulated my interest in enzyme mechanisms in general, and I began to wonder whether cyanate might be involved as an enzyme-bound intermediate in the transfer of a carbamyl group from carbamyl phosphate to aspartate, catalyzed by *Escherichia coli* aspartate transcarbamylase (ATCase; Fig. 2). However, a variety of approaches showed that cyanate was not an intermediate and that the transfer was likely to be direct, leading Kim Collins and me to think about the structure of the transition state intermediate in this reaction (Fig. 3).

We followed Linus Pauling’s reasoning that an analog of the transition state would be a potent reversible inhibitor, binding much more tightly to the enzyme than substrates or products. Thus we synthesized N-phosphonacetyl-L-aspartate (PALA; Fig. 3) and were delighted to find that it was a very specific inhibitor of ATCase at nanomolar concentrations (3). It turns out that, fortuitously, PALA can readily enter mammalian cells to inhibit ATCase potently and specifically and thus block the *de novo* biosynthesis of pyrimidine nucleotides. More of this soon. PALA proved to be useful in helping us to unravel the catalytic mechanism used by *E. coli* ATCase and in helping Howard Schachman’s laboratory to unravel the allosteric mechanism. Much productive work on the catalytic mechanism followed in our laboratory, using a variety of methods ranging from chemical modification to nuclear magnetic resonance. Toward the end of this period, my first sabbatical at ICRF put me in contact with mammalian cells in culture, and of course I tried out some of our precious supply of PALA on them. Although significant inhibition of growth was seen, I didn’t yet realize that the uridine present in serum allowed the cells to bypass the *de novo* pathway and survive. When I used dialyzed serum, the true power of PALA to kill cells was revealed. However, about 0.001% of the cells survived and formed colonies. These new cell populations stably maintained their resistance to PALA and had elevated levels of ATCase activity. Furthermore, by using higher and higher concentrations of PALA, we could continue to select ever more resistant cell variants, with truly remarkable enzyme levels, up to 5% of the soluble protein (4)! From these cells, we purified mammalian ATCase to homogeneity, leading us to discover that it was one of three enzymes covalently linked in a single giant polypeptide (CAD) that also included the first (carbamyl phosphate synthetase) and third (dihydro-orotase) enzymes of the *de novo* pyrimidine pathway (5). Meanwhile, Geoff Wahl and Rick Padgett undertook to find the cause...
of CAD overproduction in PALA-resistant cells. These were early days in mammalian molecular biology, and many of the methods had to be developed and adapted along the way. First we found that the levels of CAD mRNA were elevated and then that the number of CAD genes was higher in the resistant cells (6). Together with independent work from Bob Schimke’s laboratory showing that methotrexate resistance was due to increased copies of the dihydrofolate reductase gene (published a few months earlier than our paper), the work provided the earliest evidence for gene amplification in mammalian cells. Because increased gene copy number is a hallmark of cancer cells, it seemed important to investigate the mechanism of amplification, which we did for many more years (7–9).

PALA is quite specific for ATCase since, in cell culture and in animals, its toxic effect is completely neutralized by uridine, which provides an alternative route to pyrimidine nucleotides through salvage biosynthesis. Together with Randall Johnson, we initiated tests of PALA as an antitumor agent in mice, with initial spectacular results in which mice bearing two different types of transplanted tumors could be cured by PALA as a single agent (10). Unfortunately, as is often the case with agents that are effective in mouse models, for reasons that are not yet clear, PALA is not effective as a single agent in a variety of human tumors and has seen only very limited therapeutic use, mainly in combination with other drugs.

PALA inhibits the growth of both normal and tumor cells in tissue culture, but only the tumor cells give rise to resistant variants through gene amplification. The tumor suppressor protein p53, required to prevent amplification and functional only in the normal cells, is activated by the DNA strand breaks that accompany amplification, and active p53 prevents the rare normal cells in which this event has occurred from proliferating. We are still pursuing two important mechanistic issues concerning the action of PALA on normal cells. What events follow PALA-mediated arrest of DNA synthesis and cause the activation of p53? What is the basis of the stable protective growth arrest of normal human fibroblasts that allows them to survive many weeks of exposure to PALA, in contrast to tumor cells, which are killed within days? Perhaps a better understanding of how different types of cells are differentially affected will suggest novel therapeutic approaches in which PALA can be used for the treatment of cancer.

Interferons, NFκB, and Mutant Mammalian Cells

My sabbatical in Ian Kerr’s laboratory at Mill Hill in 1977 stimulated work on 2’,5’-oligoadenylates that was relatively short lived and on how cells respond to interferons (IFNs), which continues unabated today. While we were still at Stanford, Richard Friedman cloned the first cDNAs corresponding to IFN-stimulated genes and went on to identify the first IFN-responsive elements in the promoters of such genes (11, 12). Following the move to London, the work proceeded as a close collaboration with Ian Kerr’s laboratory. We characterized the promoters in more detail and, importantly, described the activation by IFN of a latent DNA-binding protein present in the cytosol of untreated cells (13). What was this protein and how was it activated? Biochemical purification of interferon-stimulated gene factor 3 (ISGF3) in Jim Darnell’s laboratory provided the answers to the first question and, eventually, to part of the second. The novel signal transducers and activators of transcription (STATs) 1 and 2 and the associated protein IRF9 constitute ISGF3, and activation was achieved through phosphorylation of specific tyrosine residues on the STATs. The kinase responsible was identified through work initiated in our laboratories by Sandra Pellegrini. We developed a method, described below, for obtaining mutants of human cells that failed to respond to IFN because of the loss of expression of a single protein, caused by chemical mutagenesis (14). In principle such mutants could be complemented with exogenous DNA encoding the missing protein, thus allowing an unknown signaling component to be identified. Sandra obtained the mutant cell line U1A at ICRF and took it with her to her own laboratory at the Pasteur Institute in Paris, where she cloned the missing enzyme (15). Tyk2 is a tyrosine kinase that associates tightly with the cell-surface receptor for type I IFNs. It is a member of a small family of related proteins that...
kinases known as JAKs and, together with JAK1, is responsible for the activation of phosphotyrosine binding sites for STATs 1 and 2 on the IFN-α receptor and for the subsequent tyrosine phosphorylation and activation of the STATs themselves. Continuation of the mutant hunt led eventually to the isolation of a set of eight cell lines, each lacking a different single protein required for signaling in response to type I or type II IFNs, namely STAT1, STAT2, IRF9, Tyk2, JAK1, JAK2, and the receptor subunits IFNAR2 and IFNGR2 (see, for example, Refs. 16–18). Because the JAKs and STATs are required for signaling in response to many cytokines (19), these mutant cell lines have been broadly useful to the ∼400 different laboratories to which they have been provided so far. Because signaling in response to IFNs involves more than the JAKs and STATs, a major current occupation of the laboratory involves describing the nature and mechanism of action of the additional factors that are required for induction of the full complement of IFN-responsive genes. Furthermore, STATs 1 and 3 can also function as transcription factors in the absence of tyrosine phosphorylation, driving the expression of a set of genes distinct from those activated by dimers of STAT1 or STAT3.

The genetic approach used with IFNs was extended to interleukin-1 (IL-1) by Xiaoxia Li. IL-1 does not activate STATs, using instead another important latent transcription factor, NFκB. Mutants lacking the signaling proteins IRAK or MyD88 were obtained and used to help characterize the pathway (20). In contrast to the simple pathway used by IFNs, mainline signaling in response to IL-1 is unbelievably complicated, requiring over 20 different proteins and still counting! Xiaoxia now continues to unravel this pathway in her own laboratory.

The same cells used to select mutants unresponsive to IL-1 can also be used to select mutants in which, abnormally, NFκB is constitutively active, and chemical mutagenesis was used to generate such mutants (21). Further work revealed that these, and also many cancer cell lines with abnormal constitutive activation of NFκB, achieve this state by secreting factors, including TGFβ, that activate NFκB by binding to cell-surface receptors (22, 23). Because activated NFκB contributes importantly to the resistance of cancer cells to apoptosis, it is important to identify the proteins whose lost expression in the mutant cells allows NFκB activation, and this effort continues in the laboratory today.

Some Methods

I have always tried to find better ways of doing things in the laboratory, and we have been fortunate enough to develop several methods of broad utility. To investigate the oligomeric structure of ATCase, Gregg Davies perfected the use of bifunctional imidoesters to cross-link the lysine residues of proteins. We realized that intra-oligomer cross-linking was highly favored over inter-oligomer cross-linking and that the resulting products could be seen in denaturing gels as a series of bands, with the band of highest molecular weight representing the full oligomer (24). Thus CAD, with three bands, was shown to exist as a trimer (5).

We had learned to couple DNA covalently to diazotized cellulose before attempting to analyze mRNAs by the then current method of running a tube gel, cutting it into many slices, and hybridizing each slice with a radioactive probe. Once through this cumbersome procedure was enough, and we reasoned that RNA could be transferred from a slab gel to diazotized cellulose, where it would be bound covalently and would still be available for hybridization with a labeled probe, as in the Southern procedure in which DNA is bound non-covalently to nitrocellulose, a procedure that did not work for RNA at the time. Thus the Northern procedure was born (25). Perhaps more original was the development of the Western method. Because we knew that diazonium groups would react with proteins as well as nucleic acids, we
reasoned that proteins could also be transferred from slab gels to paper, with detection through the binding of tagged antibodies (26). Later, both the Northern and Western methods were improved by others to eliminate the need for covalent linkage to paper.

Finally, I want to discuss the origin and development of methods for forward genetics in mammalian cells, which has the major goal of discovering hitherto unknown components of signaling pathways. In the initial experiments noted earlier, we used an IFN-regulated promoter to drive the expression of the selectable marker protein guanine phosphoribosyl transferase. Xiaoxia Li later developed a more flexible and generally useful selection, using Herpes thymidine kinase to select unresponsive mutants with gancyclovir and a protein encoding zeocin resistance to select cells with restored function (20). Chemical mutagenesis gave unresponsive mutants at workable frequencies. All of these were recessive, lacking expression of a single protein required for signaling. Although Sandra Pellegrini’s heroic effort led to the complementation of mutant U1A with genomic DNA encoding Tyk2, using the HAT selection, functional complementation of most of the mutants obtained in the IFN and other pathways has been very difficult, with a low rate of success, for reasons that are not completely clear.

Current work in the laboratory aims at eliminating the pesky problem of functional complementation by using retroviral insertion to mark the mutated gene, which can then be identified directly (27). If the retrovirus carries a strong promoter, its insertion into or near a gene can generate dominant mutants, in which the overexpression of a full-length or truncated protein or an antisense RNA from a mutated allele blocks the function of the normal protein or mRNA expressed from the unaffected allele (28). This method and related ones are being used to identify proteins involved in regulating the activation of NFκB or in regulating the activation or function of p53. Forward genetics has contributed immeasurably to our current understanding of pathways in bacteria and yeast. Its potential to contribute similarly to analysis of mammalian systems has hardly been tapped. Hopefully, novel methods being developed in several laboratories, including my own, will soon help to open these new frontiers further.

This account of my career is already too long, and thus I must omit much important work carried out over many years by many bright, hard working, and dedicated students, fellows, and technicians. I hope you are all willing to forgive me the omissions and to remain friends. I have been unbelievably fortunate to have been paid well for practicing my main hobby of science, so why would I want to stop? Hopefully, the fun and fulfillment can continue for at least a few more years.

This article is dedicated to my teachers and friends in science who have passed on: Charles Dawson, Bill Stein, Stanford Moore, and Ernesto Scoffone.

Address correspondence to: starkg@ecf.org.

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