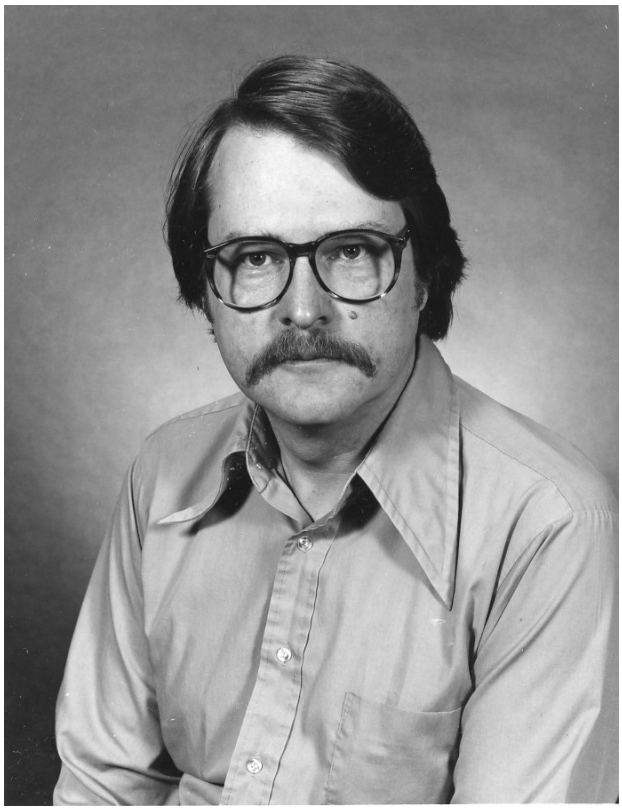
A few memories of Clyde Hutchinson III from the early days and his impact on us all.



Collection of a few letters, photos and awards from Clyde's personal papers together with letters from some of his longtime friends from the early UNC days.

Thanks to Phifer for sending the papers and to his friends who took time to remember how important Clyde and his work has been to all of us. Thanks Clyde, we hope you enjoy this.

THE NORTH CAROLINA AWARDS

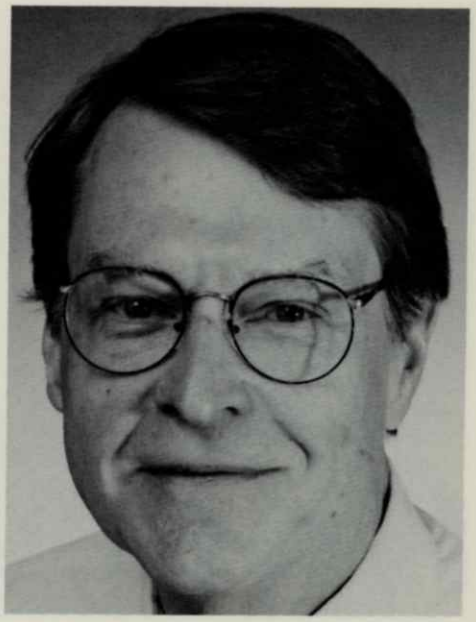
1995

THE AWARD

The North Carolina Awards were instituted by the 1961 General Assembly, which acted on the idea of the late Dr. Robert Lee Humber of Greenville, then State Senator from Pitt County. The purpose of the Awards, as set forth in the statutes, is to recognize "notable accomplishments by North Carolina citizens in the fields of scholarship, research, the fine arts and public leadership." It is the highest honor the state can bestow.

The North Carolina Award was designed by the eminent sculptor Paul Manship and was one of his last commissions before his death.

SCIENCE
Clyde Hutchison III



One of the world's most distinguished scientists and researchers, Clyde A. Hutchison III receives the North Carolina Award in Science for his far-reaching discoveries in the field of molecular biology.

Currently a Kenan Professor in the UNC-Chapel Hill Medical School Department of Microbiology and Immunology, Dr. Hutchison long has worked in close partnership with Dr. Marshall Edgell. Their unique and highly productive collaboration, which began in the late 1960s while both were at the California Institute of Technology (Cal Tech), has resulted in significant scientific breakthroughs in genetics and DNA (deoxyribonucleic acid, the molecule that stores genetic information) research.

Born in New York City but raised in Chicago, Hutchison received a B.S. in physics from Yale in 1960 and a Ph.D. from Cal Tech in 1968. While at Cal Tech, Hutchison first teamed up with Edgell to explore the function of genes. Using restriction enzymes to dissect the DNA genome of a small virus, the two scientists discovered how to purify individual genes in the early 1970s. These findings helped lay the groundwork for gene cloning work in laboratories worldwide.

In 1968, Dr. Hutchison joined the UNC faculty as an assistant professor. While on leave in 1975 in Cambridge, England, he collaborated with Dr. Frederick Sanger and colleagues in determining the first complete DNA sequence of a genome. The genome selected for this landmark undertaking was the same one previously dissected by Hutchison and Edgell.

Following his return to Chapel Hill in 1976, Hutchison worked with Dr. Michael Smith (University of British Columbia) and Edgell to develop a way to mutate DNA deliberately. Called site directed mutagenesis, this technique is now a cornerstone of the newly emerging field of protein engineering.

Hutchison and Edgell have also worked together on the study of so-called "jumping genes" in mammals. This has led to a *Jurassic Park*-like experiment where a functioning, ancient DNA sequence was reconstructed from the sequence of inactive "molecular fossils" found in the modern genome.

Dr. Hutchison became a full professor at UNC in 1978. Today, besides his duties as a Kenan Professor, he is the U.S. editor of *DNA Sequence, The Journal of DNA Sequencing and Mapping.* A prolific writer, he has published scores of articles on various aspects of molecular genetics in *Cell, Science,* and *Nature.*

Hutchison has also been continuously committed to graduate education ever since his arrival at UNC. Scientists who received their doctoral training with him are currently on the faculties of major universities throughout the country.

Internationally respected by colleagues for his accomplishments and research skills, Clyde Hutchison received a career development grant from the National Institute of Allergy and Infectious Diseases in 1978 and a National Institutes of Health MERIT Award in 1987. This past April, he was elected to the National Academy of Sciences.

A highly distinguished professor and researcher, Dr. Hutchison has brought great honor to the university and to North Carolina. The potential of his scientific discoveries is all but unlimited.

A resident of Chapel Hill, Dr. Hutchison has one son.

CALIFORNIA INSTITUTE OF TECHNOLOGY

PASADENA, CALIFORNIA 91109

DIVISION OF BIOLOGY

19 August 1964

COPY

Dr. A. Kleinschmidt
Virus Laboratory
University of California
Berkeley
California

Dear Dr. Kleinschmidt:

I am writing concerning my visit to you at the Virus Lab, arranged with Dr. Sinsheimer in your phone conversation last Friday. I have a reservation on a plane arriving SF airport midmorning Tuesday 25 August so I will be at the Virus Lab by early afternoon of that day. I plan to stay a few days (till Thursday or Friday) if this is okay with you.

In addition to the virus you asked for (1 mg of phi X) I will bring several nucleic acid samples I am interested in looking at. The most interesting are probably a) an RNA-ase resistant intermediate in MS2 infection and b) single stranded DNA of the rod phage M13.

I am looking forward to seeing you Tuesday afternoon.

Yours truly,

Clyde A. Hutchison

Clyde A. Hutchison

UNIVERSITY OF CALIFORNIA

VIRUS LABORATORY
BERKELEY 4, CALIFORNIA

Room 427
Phone No. 848-1851

August 20, 1964

Dr. Clyde A. Hutchison
Division of Biology
California Institute of Technology
Pasadena, California 91109

Dear Doctor Hutchison:

I received your letter of August 19, and am glad that you will be able to make a three-day visit to the Virus Laboratory, and that we will be able to try some preliminary work on electron microscopy of single-stranded DNA (ØM 13) and double-stranded RNA.

I have obtained a hotel reservation for you, August 25th to August 28th, at the Carlton Hotel, 2338 Telegraph Avenue, Berkeley; telephone number 845-5964.

The amount of preparations we will be able to prepare mainly depends on the success during the first trials. Don't expect too many good micrographs for valuation because our present state may be in the range of 20% measurable single-stranded DNA.

With best regards to Doctor Sinsheimer and thank you both for the promised 1 mg of ØX phage.

I am looking forward to your visit to the Berkeley Campus.

Sincerely yours,

A. K. Kleinschmidt

AKK:mh

FIRST EM IMAGES OF SUPERCOILED DNA

Among Clyde's personal papers Pfifer sent to UNC was a Kodak box of ancient glass electron microscope plates. These plates, 6x9 cm have a photographic emulsion on the surface and were the early means of capturing images in an electron microscope prior to the use of modern film.

Seeing these it was clear to me (Jack Griffith) that they had been taken on a Siemens 1A electron microscope and examining them one could see fields of DNA molecules. Not as good resolution as present-day images but clear, nonetheless. Combined with my memories of from my time at Caltech in the 1960's and the letters to Clyde from Albrecht Kleinschmidt in Germany (letters were sent from UC Berkeley where he was visiting), it was clear that Clyde had visited Germany and together with Kleinschmidt they obtained what must be the first images of circular double stranded DNA (ϕX174 phage replicative form) in both open nicked and closed supertwisted forms.

I scanned the glass plates, and we have had two 20x20 inch prints on metal done. One will be displayed with a description in the Microbiology and Immunology Department at UNC and the other in the Biology Department at Caltech.

Jack Griffith

FIRST IMAGES OF SUPERCOILED DNA

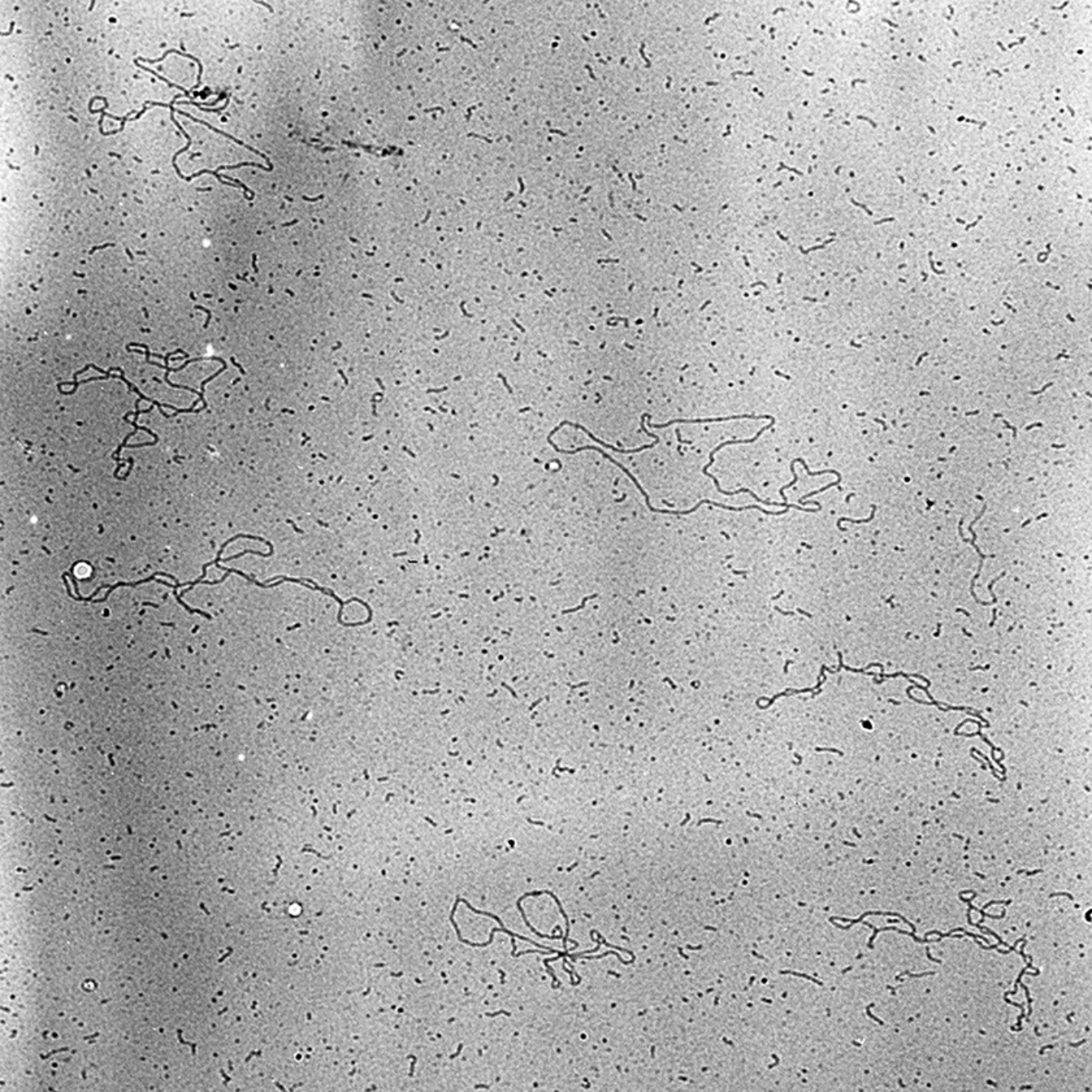
Until the late 1950s, “seeing” DNA molecules in the electron microscope was nearly impossible due to the low resolution of the instruments and the very thin (20 Angstrom) width of the DNA helix. However, in the late 1950’s Albrecht Kleinschmidt in Germany discovered that if DNA was mixed with a protein (he used cytochrome C) and spread on the surface of a Langmuir trough, the DNA became coated with a ~200 Angstrom sheath of denatured protein. This thickened the DNA enough for it to be seen in the EM. The stiffness of the protein coating and spreading out on the air/liquid interface made it much easier to follow the contour of the DNA strands. DNA trapped in the film could be picked up on plastic films covering EM grids and visualized following metal staining or coating. This opened the door to the first examination of small, purified DNAs whose nature was suspected but not directly demonstrated.

The laboratory of Robert L. Sinsheimer in the Biology Department at Caltech had discovered the small bacteriophage ΦX174 and was examining its biophysical properties. When Kleinschmidt visited Caltech, they were able to image ΦX174 single strand DNA and show it to be circular. Images of the double stranded replicative form of ΦX174 also revealed circles, but the images were poor, and Kleinschmidt invited Sinsheimer’s graduate student, Clyde Hutchinson III to visit his lab in Germany to obtain better images.

The ΦX174 DNA was prepared and imaged in a Siemens 1A EM. These instruments were pumped with a mercury vapor diffusion pump and gave off a significant amount of X rays. Photos were taken on glass plates coated with a photographic emulsion and exposure was by eye. The striking images they acquired showed both open (relaxed) circular double strand DNA (molecule in the center of the print) but also many DNAs that were strangely twisted about themselves to form long loose rods.

Today we readily accept the images of supertwisted DNA, understanding that these circular DNAs are coiled about themselves in a direction opposite the helix and this imparts energy to the circular DNA facilitating helix breathing and other structural changes. However, for some time the coiling was passed off an EM preparative artifact until the studies of Norman Davidson and Jerome Vinograd in the Chemistry Department at Caltech using gradient centrifugation put supercoiling on a firm footing.

Image prepared by Jack Griffith (Ph.D. Caltech Biology Department 1969) from an original glass plate provided by Clyde Hutchinson III.



MRC
Medical Research Council

MRC Laboratory of Molecular Biology
University Postgraduate Medical School
Hills Road, Cambridge. CB2 2QH
England

1st July 1974

Dr Clyde A. Hutchison III
Department of Bacteriology and Immunology
School of Medicine
University of North Carolina
Chapel Hill
Carolina 27514

Dear Clyde,

Many thanks for your letter and for the talk that you gave in Cambridge. We certainly very much enjoyed your visit and found it very useful.

I would certainly like to have you spend your sabbatical year in this laboratory and it is pretty certain that we will be able to find space for you from May 1975 - though the space may be a bit limited. I expect that our main interest at that time will still be concerned with ØX DNA, and especially with trying to develop techniques for sequencing, and I suggest you either join in with this work or some related problem.

With best regards,

Yours sincerely,

Fred

F. Sanger

THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

J. CARLYLE SITTERSON, *Chancellor*

July 12, 1968

Dr. Clyde A. Hutchison
Department of Bacteriology
School of Medicine

Dear Dr. Hutchison:

I am pleased to inform you that President William Friday and our Board of Trustees have confirmed your appointment as Assistant Professor, beginning August 1, 1968, on a twelve months' basis, with a salary of $14,000.

You are invited to review the "Rules, Regulations and Policies" of the Division of Health Affairs, copies of which may be obtained from your dean, department head, or the Division Library.

Sincerely yours,

J. Carlyle Sitterson

J. Carlyle Sitterson

cc: President William Friday
Dr. C. Arden Miller
Dr. Isaac M. Taylor

Dr Mark Ptashne
The Biological Laboratories
Harvard University
16 Divinity Avenue
Cambridge, Mass. 02138

Dear Mark,

Many thanks for your letter. Yes, it is true that we are having some trouble clearing up the misconceptions perpetrated by the geneticists and are having to re-write some of their basic dogma.

With regard to the Gordon Conference on Nucleic Acids, I would like to come but do not think I will be able to get there myself. Would it be possible for me to send a representative? The work on the double gene was done by Bart, Gillian Air and Clyde Hutchison. We do not seem to be able to persuade Bart to travel that far, and Gillian is already signed on for the other Gordon Conference that Yanofsky is organising. Clyde however would very much like to come and would present a good story.

All the best,

Yours sincerely,

Fred

F. Sanger

Okeedookie. Send Clyde. We Sometime geneticists shall be amused. Glad to hear that Bart won't desert the sinking ship. Best all around....

Mark

Clyde –

Tom Broker of CSH Labs

516-692-6725

wants to know if he can put ϕx on the cover of the abstract book for the small phage meeting....

Like figure 4 of the November Nature Paper.....

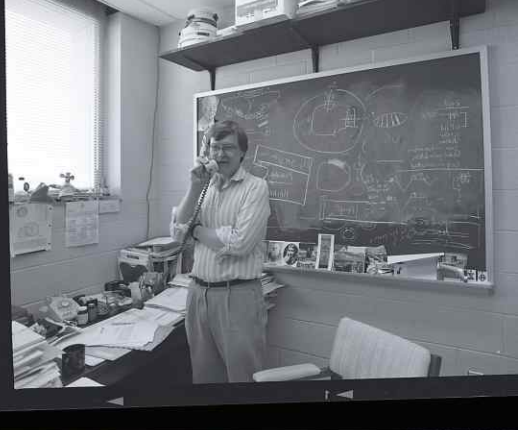
CALL HIM THIS AFTERNOON – he is expecting a call about 5 PM

Why am I hanging onto these?

Damn if I can think of any reason.

Med Illustration can print these 6 x 7 negs

Jack



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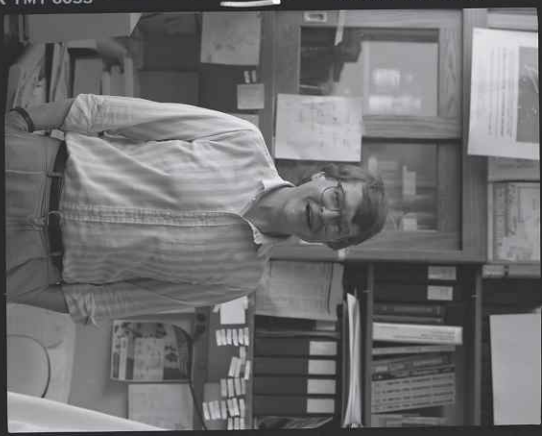


STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Medicine

February 9, 1977

Dr. C. Hutchison, III
University of North Carolina School of Medicine
Chapel Hill, North Carolina

Dear Dr. Hutchison:

I've been hearing for some months about the hybridization procedure you have developed for a manner of mapping overlapping segments of fragments of DNA digested with different restriction endonucleases. Has the procedure been written up at this point?

If a preprint of your paper on this subject is available, I'd appreciate a copy. With best wishes,

Sincerely yours,

Stanley N. Cohen
Professor

SNC:nm

sent receipt sheet 21 Feb 77
Promised ms. to follow.

The Chapel Hill Garden Club

April 7, 2004

Dear Clyde,

Thank you so much for participating in the Chapel Hill Garden Club's 5th Spring Garden Tour.

You will be performing at The President's House, home of Molly and Robert Broad, #6 in the ticket booklet, on Franklin Street. Parking has been reserved for you in the Broad's driveway to the left of the house. You will need the enclosed name tag to get into the driveway. The time you are playing in the schedule is 11 AM. There is a lovely porch in the back garden with cover in case of questionable weather and we will have a chair. Roberta Copeland is the volunteer and will be there to help you.

We have enclosed a complimentary ticket. We hope you will use it to go on the tour or to give to a family member or friend. My cell # is 619-8804 if you have any questions that day or if anything comes up this week please call me at 932-6324.

On behalf of the Chapel Hill Garden Club thank you so very much for your participation in this wonderful event!

Sincerely,

Lynn Gschwind

Lynn Gschwind
Amenities Chair

Post Office Box 10054 • Chapel Hill, North Carolina • 27515

The Royal Society
6 Carlton House Terrace
London SW1Y 5AG
Tel. 01-839 5561 Telex 917876

ext. 261
NHR/LH
6 July 1977

Dear Dr Hutchison,

On behalf of the President and Council I wish to express appreciation and grateful thanks for your contribution to the Jubilee Exhibition and the Royal Society's Conversaziones. The success of the exhibition and of the social occasions was due, in no small measure, to the efforts of you and your colleagues in arranging displays of such interest to our guests.

Yours sincerely,

R. W. J. Keay

Executive Secretary

Dr C. A. Hutchison,
MRC Laboratory of Molecular Biology,
Hills Road,
Cambridge.

The Provost & Fellows of King's College

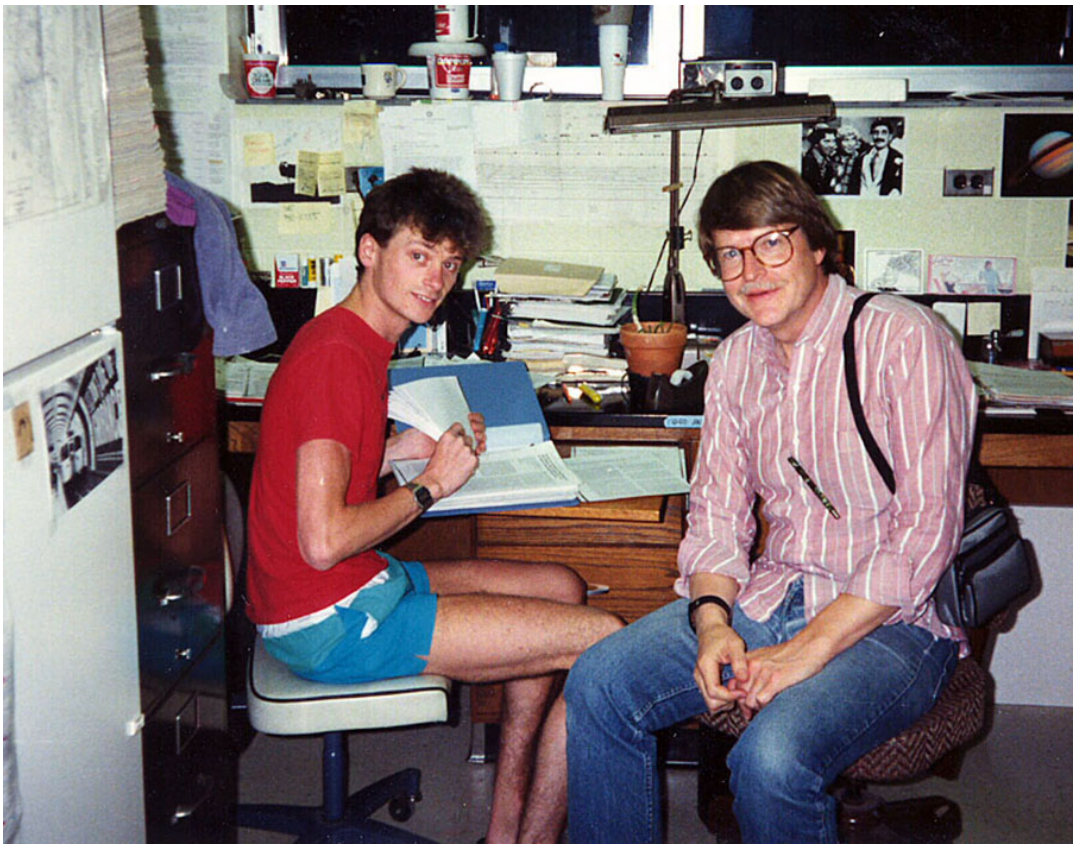
request the pleasure of the company of

Clyde

for dinner in the Beves Room

on Wednesday May 26th, *7.30 for 7.45 p.m.*

~~*An answer is requested addressed to*~~



5 Apr 2025

Dear Clyde,

Since moving into a retirement community on Mt Carmel Church Rd, close to where you lived for a number of years, I often think of how tough it was of you to bicycle along this 6 miles of hilly, curvy road on your way to your lab at UNC!

It was wonderful to see you here again in Chapel Hill when you recently came for Marshall's memorial gathering at UNC. I was so glad to see you! When you got up to speak, I found myself remembering the autoclaving films you used to amuse us with at various lab gatherings in the 1970's.

Your visit also called to mind the significant suggestions you had made to my dissertation. It meant a lot to me at the time because I had been working without an active advisor in those days.

It's nice to have so many of your original Cal Tech buddies here in Chapel and to be included in some of their social get togethers. We don't get to see you often, but you're often the topic of the guys' fond rambling memories of the "good old days" at Cal Tech. I trust you enjoy such memories too.

Warmest regards,
Cora-Jean

April 7, 2025

I am writing to express my profound appreciation for Professor Clyde Hutchison, whose pioneering work and enduring impact on molecular biology have contributed immeasurably to our University and science.

I first encountered Professor Clyde Hutchison in 1968, shortly after he and Marshall Edgell arrived in the Microbiology department at UNC. The pair brought an exceptional level of Molecular biology to the campus and were instrumental; in developing molecular biology at UNC—in this regard, I should acknowledge the vision of the then chairman of microbiology, Fred Sparling who had the vision to look for and hire such faculty. From the start, it was clear that Clyde's intellect was exceptional; his creative research approach revolutionized the tools we use in genetics and molecular biology.

Early in his career, he isolated and utilized restriction enzymes at least as early—if not earlier—than the scientists who were ultimately awarded the Nobel Prize for that discovery. Though his findings were not yet published, he generously shared preprints, allowing others to benefit from and build upon his groundbreaking work.

Further, he carried out in vitro mutagenesis in ΦX174 well before this technique took root in other laboratories, and even in his initial publications, he showcased a deep understanding of its significance for genetic manipulation and molecular research. Had circumstances differed, these remarkable advances could have earned him not one, but two Nobel Prizes.

His influence extended beyond his laboratory bench: He mentored countless students and faculty, bringing rigor, passion, and generosity to every collaborative project he touched. His dedication to nurturing young scientists and fostering open communication of research findings exemplifies the collaborative spirit upon which our University prides itself.

Let us not forget Clyde's enduring legacy His contributions elevated the reputation of our University and, more importantly, transformed molecular biology in fundamental ways. I wholeheartedly urge our community to honor him in whatever manner possible—through tributes, symposia, or formal acknowledgments—so that his name and discoveries remain an inspiration for future generations.

Thank you for your time and consideration. If there is anything further I can provide to facilitate a proper tribute, please do not hesitate to let me know.

Sincerely,

Darrel Stafford

UNC SCHOOL OF MEDICINE

THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL
SCHOOL OF MEDICINE
Department of Microbiology and Immunology

O 919-966-1191 | F 919-962-8103

Marsico Hall | 6th Floor | Campus Box 7290
125 Mason Farm Road | Chapel Hill, NC 27599-7290
med.unc.edu/microimm

April 7, 2025

Dear Clyde,

So many memories of the old days at Caltech and here at UNC! I need to begin with a huge thanks to you and Marshall for coming to Chapel Hill and making UNC attractive enough for me to take a chance and move East. When I left Caltech, I moved to Stanford and spent 3 years in the Kornberg lab and then 3 more in an independent position. I then started looking for faculty positions and happened to hear that Joe Pagano and Phil Manire had an opening at UNC in the new Cancer Center. Visiting, you, Marshall, and John Newbold took me to dinner at Bullocks in Durham for Carolina Bar B Que and I was hooked. Not only did UNC have several excellent faculty I knew, but Paul Modrich was nearby at Duke. I have never regretted coming to UNC and over the years the scientific environment has gotten better and better, all built on the foundation you, Marshall and Darrel Stafford created.

In 1990 I ran that scientific meeting in Alaska which you attended, and I was amused that you brought along an electric keyboard to work on your jazz compositions. Fifteen years later my wife Karen and I were sailing in Prince William Sound off the Alaska coast and she also had brought an electronic keyboard. The sea otters must have enjoyed listening to Chopin!

Recalling old memories when I first started in the Sinsheimer group before moving to James Bonner's lab, I remember a day when Reg Kelly was heating a flask of phenol with a Bunsen burner and then dumped in some buffer. That was followed by a blast of liquid in his face. My memory was that you and some of the others shoved Reg's face in the sink and showered him with water quickly enough so that he did not suffer any burns. Reg went on to UCSF and hopefully did not repeat pouring water into superheated phenol!

All the very best wishes and memories to you, my friend.

Dear Clyde,

When I arrived in Chapel Hill in the Spring of 1982 I had no furniture. That was because it came one month later in a truck with Steve Nordeen's and Sandy Martin's furniture. We were all friends in the Bay area and it was great luck for me that we were all moving to Chapel Hill at essentially the same time. This allowed Steve and me to continuing our careers in intramural sports. It also allowed me to become a de facto member/groupie of your lab. I quickly got to know Dan Loeb who was also a sports nut at that time. One of Dan's later mentors once referred to Dan as "A Great American", an irreverent way to comment on how great Dan was to work with, something you and I both had the pleasure to find out for ourselves.

As a new assistant professor I was casting around for new projects. I had gotten some money from Burroughs Wellcome to try to express HIV reverse transcriptase in bacteria to get biochemical amounts of enzyme. I had also managed to get a partial clone of the HIV genome to use for expression but this effort was always a bit fanciful for two reasons. First, I had never expressed a protein in bacteria, and second, I didn't know where the ends of RT were encoded in the DNA sequence. It was another stroke of good luck for me that your lab was dealing with a similar problem. You had figured out that L1 was a mobile element and had reconstructed an intact sequence. Dan Loeb was trying to express L1 proteins in bacteria. We were able to use your expression vector as one improvement but our own assay for RT activity in bacterial lysates was not yielding any positives as we put in HIV DNA fragments of different length. Our friend Susan Lord suggested we do a Western Blot using serum from an HIV+ person to probe for the expression/production of viral proteins. We took several constructs with different fragment lengths the HIV DNA, expressed them in bacteria, then ran the first Western blot ever in my lab using the patient serum to probe the filter. We found one construct that gave the processed RT bands of p66 and p51 - one of the constructs had expressed the RT coding domain but also expressed the upstream viral protease that had dimerized to become active in bacteria and process the protease-RT precursor to give the two products of RT, just like in the virion. There was not enough RT present to give biochemical amounts but we did now have an assay for HIV protease processing in bacteria. We used this assay as a collaboration going forward.

We (you and I and our labs) were fortunate to have Dan Loeb interested in this work. Dan spearheaded an effort to "mutagenize every position in the HIV protease", which we did and measured the phenotype in the bacterial expression assay. Your work with genetics and oligonucleotides led to the strategy of "doping" the oligo synthesis so that there was a mixture of correct and randomly mutated positions in each oligo. We used these oligos in second-strand synthesis of single-stranded phage DNA then screened by sequence and phenotype to build up a library until we had each position mutated multiple times. I still have occasion to refer to that map of mutants covering all positions in the HIV protease. Your lab also did a similar experiment with the much larger RT domain, a tour de force effort.

Several years later my lab was trying to figure out how to avoid the complication of PCR resampling in what was then new deep sequencing platforms in our study of HIV RNA populations. It was a pretty straight line between your earlier doping of oligos during synthesis to creating a stretch of random nucleotides that would each create a "Primer ID" during cDNA synthesis for each starting template. As we were starting to present and publish this approach a company came to UNC and wanted to pay for a patent and license the technology. After 10 years a patent was issued to UNC for Unique Molecular Identifiers (UMI) based on the Primer ID work. The good news is that UMIs are widely used in next gen sequencing approaches to greatly improve data quality. The bad news is that UNC views it as a process patent and is not interested in defending the use of the patent by anyone. I'm afraid our contribution will be lost in history but I know what we did and I also know that it was inspired by our earlier work with you and your insights in genetics, mutagenesis, and tools like oligonucleotides.

When you left UNC we lost our most creative scientist. We also lost our most irreverent scientist and we take ourselves much too seriously now. I have enjoyed my career here at UNC, in the beginning through my direct interactions with you and further on through the success we shared that has been an important part of the research foundation for my lab. I am in your debt.

Ron Swanstrom

7 April 2025

Dear Clyde,

I want to write a sort note to reminisce about you as a colleague during the time we overlapped here in the Bacteriology and Immunology (now Microbiology and Immunology) department at UNC.

As a newly-arrived assistant professor in 1975, fresh from my Ph. D. time in Bernard Roizman's lab at the University of Chicago, and a post-doc with Jim Darnell at Columbia University and then The Rockefeller University in New York, I was suddenly faced with the realization that couldn't afford to acquire the restriction enzymes I needed on my extremely small start-up budget. While in the Darnell lab, we could purchase some of them commercially, and also fortunate to have a collaboration with the Sambrook lab at Cold Spring Harbor for enzymes that were not commercially available. I needed these reagents in order to cleave adenovirus and herpes simplex virus DNA, purify the resulting fragments (this was in the pre-cloning days), and use them in my proposed studies of viral mRNA metabolism in infected cells. I had a lot of experience at purifying virion capsids and extracting viral DNA, but even with both a B.S. and a Ph.D. in "microbiology", I had actually never grown any liquid cultures of bacteria, let alone broken open and purified enzymes by column chromatography. There was a wonderful collegial feeling in the department, most of whose members were housed at that time in McNider Hall, which extended to virologists (Newbold, Wertz, Pagano and I) in the Swing Building (now Taylor Hall). With a lot of input from the members of your joint lab with Marshall Edgell and from Ken Bott, I vividly remember the immense satisfaction I had in assaying column chromatography fractions and finding the tell-tale pattern of cleaved ΦX174 DNA I used as a marker of restriction enzyme activity. It was many years before I had to purchase Eco-R1, HindIII or Sma1 from New England Biolabs!

Thanks Clyde for the impact you had by the application of molecular genetic approaches to the research programs of your colleagues both in the medical school and the wider University.

Steve Bachenheimer

Clyde

Jack is organizing a tribute to you, and I am glad to add my two cents.

I'll never forget my first year at UNC, when Eleanor Blackman, my technician, and I were crammed into a 100-foot lab next to Harry Gooder's and yours and Marshall's was just down the hall, filled with bright students and doing science that was beyond me, but clearly was both important and exciting. I was a struggling physician scientist trying to establish a lab, you guys were rolling and on the cutting edge of a new era in science. You were polite, but appropriately uninterested in our search for novel ribosomal mutants of *E coli.* Once Marshall tried to convert me to work on restriction enzymes, but I was unable to see what the future would bring, which seemed clear to both of you. Would that I had listened. Everyone thought you deserved a Nobel for your part in the story.

I also recall learning years later that you had taken up the piano at about 50 and were doing gigs around town. I never got over that and vowed I would do the same thing when I retired. We had a piano. Talk is cheap, I dreamed but that was all. Good on you.

After you left UNC I followed your career at a distance and would have loved talking with you about your work with Ham Smith. Your life after that was lost to me but I'll always remember your droll slow precise speech, the twinkle in your eye, your apparently unflappable attitude to science and life. You did things your way, buoyed by immense ability and confidence, an unforgettable person.

I have happy memories of you and now wish you the very best.

Fred Sparling

My Life with Clyde
Jeff Frelinger

I first became aware of Clyde when I arrived at Caltech in September 1969 as a new graduate student. Clyde and Marshall had already left for UNC by then, but Clyde's legend in Kerckhoff was well established for being really smart (by Caltech standards) but kinda weird, long lived grad student in the Sinsheimer lab. He was reputed to have magic hands. I first met Clyde in peron when I was being recruited to UNC by Fred Sparling in 1982. By then he had already established his own reputation, confirming the Caltech scuttlebutt that he was really smart. Later, my lab became interested in examining the structure and function of mouse MHC class I proteins and Clyde had just returned from Cambridge sabbatical where he had developed the methodology for site directed mutagenesis, a great opportunity for me. Clyde and my student, Rich Murray, worked on the idea of creating large mutant libraries by using doped oligonucleotides that carried random mistakes allow the simultaneous creation on complex mutant gene libraries, dubbed RAMBO, for random mutagenesis by oligonucleotides. Clyde spent many hours with Rich and me working out exactly how this could be done and trouble shooting the process. It worked brilliantly.
Collaborating and watching Clyde made me realize he had devised the perfect strategy for maximizing dong the science that he clearly loved and minimizing academic bullshit. Rule 1- don't refuse committee assignment- just miss most of the meetings. (I adopted this, great idea) 2. Avoid teaching medical students by doing the minimum. People will stop asking. 3. Be really helpful to everyone's grad students. Clyde always had time for grad students, and postdocs. 4. Be really smart and successful in funding your lab and publishing really good papers. I wished I could have emulated him more.

When I became chair of the Microbiology and Immunology Department following Fred Sparling, I realized that Clyde was an institutional gem, who only needed to be left alone. He continued to flourish without attention, and indeed the less I paid attention to him the better he and I both liked it.

I had the opportunity to serve on several thesis committees of Clyde's students. He managed to imbue the same love of science in them, but also the lack of motivation to leave a place where things were going well, that is try not to graduate. I remember one meeting with a 6th (maybe 7th) year student, who had already published a half dozen good papers. The student wanted to embark on a whole new project. In contrast to the usual where the committees need to tell a student what more needs to be done, here we needed to tell the student he could not start a new project, no matter how interesting, and write his thesis. Clyde would have been OK if the student stayed forever.

As a colleague Clyde was everything you could want- smart, funny (although a really dry sense of humor), irreverent and driven. It was a sad day for UNC when he decided to leave for TIGR. We missed him.

April 2025

Dear Clyde,

I was surprised and deeply saddened to learn of your bad fall and consequent injuries. And I am very grateful to Jack Griffith for asking me to join him and other colleagues in writing some words of personal appreciation and support. It is without question that you remain in very high regard in the UNC community both as a colleague and an outstanding researcher. It was suggested that I try to recollect memories from our shared time at Caltech. And in reflecting back on those years I must add that, like all my body joints, my memory is also somewhat arthritic and likely flawed. But I give my best effort.

It was early in 1965 when I started to work with you on a joint project involving your recently isolated array of ϕx mutant phages. The goal was to isolate genetically recombinant RF DNA from E. coli spheroplasts mixedly infected with mutant ϕx (ss) DNA. As a newcomer to this area of microbiology, you guided and instructed me through the new techniques and methods. Then in 1966, the first recombination deficient (rec-) mutant of E. coli was reported. We acquired that strain and proceeded to show that mutants of ϕx174 did recombine in the rec- cell. At that time Paul Howard Flanders (on leave from Yale) was working in our group, and with his encouragement we went on to show that prior UV irradiation of the input mutant DNA significantly enhanced the amount of recombination. These data were never published, but about a year later, the Tessman lab (at Purdue) did publish equivalent findings using coliphage s13.

With your oversight and interaction, I learned a great deal about designing experiments and evaluating data during that time of our collaboration. Your subsequent research exploits are much better known. However, I will now turn to lesser known aspects of your Caltech time when you were not doing research.

1. The “car” problem

   You lived on campus at rooms in the Athenaeum. Evidently you owned a car – although I never saw it. Your car was a source of major irritation to campus authorities as it remained unmoved in a campus parking space for years. You didn’t drive your car. You walked out every day to access your meals. I recall wondering when you came to Chapel Hill if you would be driving at all.

2. Music

   It is well known that you enjoyed playing the piano and were particularly fond of jazz. But that pastime largely developed post Caltech. I recall that you brought and

played both a clarinet and saxophone at the lab. And one day you showed up with a "Chinese musette". I am afraid I cannot recall how you acquired this odd instrument. You told that it was a double reed woodwind…but it had a flared distal end much like a trumpet or bugle. You did play with it a bit in the lab. I have wondered if Phifer may have come across it in your personal effects.

3. Amateur Movies

Late in the Caltech years you acquired a Super 8 movie camera and became highly motivated at making movies. One movie that I especially remember involved filming the simulation of a grad student (think it was Al Lyon) being rolled on a lab cart into a very large autoclave in the basement of Kerckhoff. Your movies were much celebrated among the students.

4. Athletics

You were not known to participate in exertive activities. Fellow students were adept kayakers, skiers, tennis and soccer players, and rock climbers. But not so Clyde. However, when Marshall was organizing a camping trip to spend days down in the bottom of the Grand Canyon alongside the Colorado River, you signed on. The approximately ten-mile hike down was not challenging. But I still recall how tough it was to hike back up the multiple switchbacks to the South Rim. And Clyde kept the pace with the group. It was definitely an athletic achievement.

I do hope that some of these memories strike a familiar chord and resonate a bit for you. And I apologize profoundly if my recollections do not jibe with your own. It was a long time ago. But I…and I think you did too…loved every microsecond of those Caltech days. And I am so thankful to have shared that time with you.

Best,

John Newbold

Millbank
15615 Millbank Rd.
King George, VA 22485

Prof. Clyde Hutchinson, III April 10, 2025

Hello Clyde,

In the 1970s it was incredibly difficult to work on RNA. I'd come to UNC from a post doc with Mike Levine learning P-22 genetic approaches, after a PhD working on RNA animal virus replication. I was in thrall to the exciting RNA replication work of Weissman and Spiegelman, and wanted to investigate replication of a mammalian RNA virus. There were few techniques for molecular analysis. At the time, we had to label RNA with 3H Uridine in the presence of Actinomycin D, separate it on tube gels, then slice them into 100s of pieces and count the radioactivity in each slice. Agonizingly slow.

The advent of cloning, and learning how to make and use restriction enzymes, from your and Marshall's labs opened a wealth of new avenues for investigation. In particular, the ability to do site-directed mutagenesis to investigate gene function was a game-changer.

Your lab was generous. You shared techniques and reagents with many of us locally and around the world. That had a major impact. I remember hearing about the new technique of "salted oligos" for mutagenesis. You'd figured out a way to use mixed oligos effectively. I went to your lab to ask about it and how to optimize design. I knocked on your door, and the expression on your face when you looked up was priceless: It was " Oh no, not another interruption of work."

But, you swallowed your dismay at being interrupted, and gave me the information on oligo design needed to optimize success. The thing I remember most was your excitement about the power of salted oligos to obtain many mutants rather than having to use one traditional oligo at a time. As you talked, excitement broke through your irritation at being interrupted; your joy at a new way to get ahead was there, and obvious, as always.
I hope you know how much your enthusiasm impacted those of us around you.

I've enjoyed reports of your work at the Venter Institute from your "boss" John Glass, now director of the La Jolla Venter Institute and leader of the JCVI Synthetic Biology Group.
John, was a UNC undergrad who became my technician after I arrived at UNC in 1974, and continued with me for his PhD. Later, after he joined JCVI, and experienced it's relative investigative freedom, his work burgeoned in creativity. He visited last fall and remarked how awkward it felt to him to have you and Hamilton Smith, icons of his time in grad school, now "reporting" to him as you continued to do research in the Synthetic Biology Group.

Sending best wishes and a belated apology for interrupting you that long-ago day,
Gail

Gail Williams Wertz
Professor Emerita
UVA School of Medicine