CHAPTER V

PROBLEMS AND OPPORTUNITIES

1953-1973

1953-1963

Personal Research

The next few years passed rapidly as I settled into my new responsibilities as a very junior faculty member. The work on chymotrypsin went well and in 1957 resulted in a published proposal for the detailed chemistry of enzyme catalyzed peptide hydrolysis. The underlying question was "Exactly how do enzymes make possible the reactions that go on in the body?" In this case how could a protein molecule, chymotrypsin, both recognize a particular peptide bond in another protein and then cause its hydrolysis, all at body temperature and in a near neutral environment. Our answer invoked a specific interaction between a histidine and a serine widely separated in the polypeptide chain but brought together in the specific folding of the native protein. This pH-dependent interaction chemically "activates" the oxygen of the serine for an attack on the carbonyl function of the substrate peptide. This was generally accepted almost immediately as the structure of the "active site" or "catalytic site" of the enzyme. It was definitively confirmed in 1968 by David Blow at Cambridge who, through the application of x-ray crystallography, determined the three dimensional structure of this protease which clearly

showed the proposed imidazole-serine hydroxyl interaction. Blow kindly sent a reprint along with a note referring to our prediction of 1957. Perhaps, alas, had we pushed it earlier in Seattle, we could have been first rather than second in reporting the catalytic mechanism of any enzyme. A scheme for ribonuclease had the priority although it was later found to have problems.

Later Brian Hartley and others showed that an aspartic acid residue was an important supportive component of the histidine-serine complex that we had shown to be the focus of catalysis. Others were to show later that this triad was the common catalytic center of a very large group of enzymes now designated as the "serine proteases." The key discovery in the story of the "serine proteases" was, however, accomplished at Vanderbilt.

The overall "biochemical" environment at Vanderbilt during these years was made pleasant and stimulating by the presence in other basic science departments of the School of Medicine of several biochemically trained or interested colleagues. Victor Najjar, Sidney Colowick and Sidney Harshman in Microbiology; Rollo Park, Jane Park and Robert Post in Physiology; and Allan Bass, Vas Aposhian and Milton Bush in Pharmacology were active in research in related areas. We began meeting as an informal group, the Biochemistry Club. All in all this made for a quite viable environment with only a relative handful of investigators. This, too, encouraged and stabilized the unique cooperative spirit that became a hallmark of the biomedical sciences at Vanderbilt.

In later years this group enlarged and became the Enzyme Club that met monthly in the evening to discuss research. One such meeting in October of 1970 heard William McElroy from Johns Hopkins discuss firefly luciferase. Faculty invited included; Galen Lenhert (Physics), Sidney Harshman, William Mitchell, John Hash, Sidney Colowick (Microbiology), Oscar Touster, Sidney Fleischer, Leonard Lerman, Rose Litman, Herbert Wiesmeyer, Giovanni di Sabato (Molecular Biology), Tadashi Inagami, Stanley Cohen, Leon Cunningham, Conrad Wagner, Jan van Eys, Robert Neal, David Puett, Gareth Mair, Frank Chytil, Harry Broquist, Robert Brady (Biochemistry), Robert Post, Tetsuro Kono, Charles

Park, Jane Park, Earl Sutherland (Physiology) and Thomas Martin (Chemistry).

Faculty

Jan van Eys

After completing his Ph.D. under Darby in 1955, van Eys spent two years in Baltimore with Nathan Kaplan and then returned to Vanderbilt in 1957 as Assistant Professor of Biochemistry. He developed a strong program in enzymology, often related to erythrocyte metabolism and foreshadowing a lifelong interest in hematology. As near contemporaries in age, we became close friends.

This was cemented quite early when I received an NIH travel award to attend the 4th International Congress of Biochemistry in Vienna in 1958. My wife, Jean, and I flew to Amsterdam where we met Jan and his wife, Catherine, at his family home in Hilversum. We then drove together from Holland to Vienna, a trip that still brings smiles when it is recalled. In those less frantic days, Darby was famous in Nashville for his multiple forays abroad (It was even rumored that American Airlines would hold a flight for him at the Nashville airport when he was running late.). A trip to Europe was, however, an absolutely unanticipated dividend of the academic life in 1958 for an Assistant Professor. I confess that the scientific aspects of that meeting in Vienna are a bit of a blur, but my memory of attending a performance of Die Zauberflote at the newly renovated (after Russian occupation) Wiener Staatsoper is crisp and wonderful. After driving back to Holland, Jan and I visited the laboratory of J.A. Cohen at the Medisch Biologisch Laboratorium (MBL), Dutch National Defense Organization in Rijswijk. There we met Rein Oosterbaan whose group had done important work on a problem closely related to my interest in the chymotrypsin mechanism, the reversal of the alkyl phosphate inhibition of chymotrypsin. These alkyl phosphates are "nerve gases" as a result of their inhibition of acetyl cholinesterase and the same reaction occurs with proteases. The regain of normal catalytic

activity was of more than academic interest in cholinesterase, but the chemistry was more easily approached through the proteases. This contact with the MBL, facilitated by Jan, was to play an important future role for me.

Van Eys moved easily between basic enzymology and nutrition. His early interest in clinical activities led him in 1964 to take a leave of absence from Vanderbilt and complete his medical education at the University of Washington where he received the M.D. in 1966. He then returned to Vanderbilt as Assistant Professor of Pediatrics and Associate Professor of Biochemistry. He continued his active program of research and clinical practice, finally leaving Vanderbilt in 1973 for a leadership role in pediatric practice and research, first as Chairman of Pediatrics at M.D. Anderson and later at the University of Texas Medical School in Houston. After retirement, he returned to Vanderbilt and, in 2003, continues an active role in pediatrics and in medical ethics.

Stanley Cohen

The next recruit to the faculty was one who brought special recognition to the Department in later years. Stanley Cohen joined us in 1959 coming from a post in the Department of Zoology at Washington University in St. Louis where he had been doing "interesting" work with Victor Hamburger and Rita Levi-Montalcini. I believe that Herb Pahl, a recently appointed faculty member, first suggested Cohen's name. Pahl had joined the Department as Assistant Professor in 1957 bringing specific expertise in nucleic acid research and teaching into the Department for the first time. Herb was a congenial colleague, and we were disappointed when he elected to leave in 1960 to accept an administrative post with the National Academy of Sciences.

As for Stan Cohen, those of us most interested in strengthening the small group in the Department not directly involved in nutrition or in toxicology were anxious to have new ideas from the "outside" and actively lobbied Darby to hire him. His "recruitment" seminar was held in the old general-purpose classroom T-2208 in the original

medical school building (now Medical Center North). It dealt with the discovery of a factor in snake venom and in mouse salivary gland which would make nerve tissue grow. One of his slides showed a piece of nerve tissue with axons radiating out in all directions, rather like a flower, in response to added "nerve growth factor." I was to see this slide often over the next 30 years. I'm not really sure what the overall general reaction to Cohen's talk was that afternoon in T2208. I was impressed but a bit bemused as to whether his basic observations could ever be reduced to biochemistry. He was offered an Assistant Professorship and joined the faculty in 1959. His first laboratory was the old "constant temperature" room of 1925. This ancient device, powered by a compressor in the courtyard, required a severely dropped ceiling in the lab. He was given this small laboratory because it was the only one deemed suitable for tissue culture. He still claims he had to share this "laboratory" with Gil Meier, an experimental psychologist from the College of Arts and Science, who had gained access to this space because of its complex of pipes, which he used as a "maze" for his rats! I frankly think this joint use idea is apocryphal.

Stan's first exploratory venture involved addition of a cell extract that included what we now call messenger RNA to frog eggs. The idea, about 30 years ahead of its time, was to influence the development of the embryo. Unfortunately, technology at that time was not up to the needs of Stan's ideas. Eventually he returned to an observation he had made while working on nerve growth factor in St. Louis, the premature opening of the eyes of newborn mice when exposed to their snake venom and mouse salivary extracts. He began the long and fruitful isolation and characterization of this "epidermal growth factor" (EGF) and of its mechanism of action. These studies ranged from amino acid sequence determination of EGF to its interaction with specific cell surface receptors and to the intracellular signaling pathways activated by the EGF-receptor interaction. This pioneering work laid the foundation for the subsequent worldwide interest in growth factors and the mechanisms regulating the growth and survival of cells of all kinds. It has been of particular relevance to new approaches to the study of cancer.

Cohen also took a substantial and effective role in teaching and all other departmental activities. He was a gifted teacher and a favorite of the medical students. He accepted the usual committee assignments cheerfully, at least in the early years. Later, even after international recognition came, and as the inevitable committee work of academic life palled, he could still be persuaded to accept an assignment which he was convinced would be helpful in raising research standards or was essential for Vanderbilt's future. He was generous with his counsel and helpful to all whose standards were high. He would, however, only share his equipment with those whose skill and responsibility he trusted. His standards of laboratory work were very high, and relatively few graduate students tried to meet them. One bright graduate student, who later became a patent lawyer in a prestigious New York firm, was jokingly accused of fleeing the pressure of Stan's lab by joining the Marines and going to Viet Nam. In truth, however, Stan's students, postdoctoral fellows and colleagues are unanimous in their appreciation of "life with Stan," both before and after he received the Nobel Prize for the discovery of growth factors (more on this later). He received a series of national and international awards for his creative insights and skill culminating in the Nobel Prize for Physiology or Medicine in 1986. He continued on in research until his retirement to Tucson in 2000. He did tell me in late 2002 that the National Institute of Child Health and Human Development is still after him for a final report on his grant which, under the same number, he held for 36 years.

George Mann

George Mann came into the Department in 1958 from a post in nutrition and medicine at Harvard. An M.D., Mann was the recipient of one of the early and relatively rare Lifetime Career Awards of the NIH. His area of interest and expertise was in human nutrition and over the years, he carried out a wide variety of studies, including participation in the famed Framingham Study. He preferred working with a small group of associates and did not

"integrate" himself into broader departmental activities. He had very definite ideas about integrity in the use of human subjects in research. This brought him into occasional conflicts, most famously with his chairman, Bill Darby. They disagreed about some ethical aspects of a study involving humans in Egypt but managed to do it in print in a national journal! He seldom attended faculty meetings and was usually unavailable for teaching other than in specialized courses in human nutrition. Here, however, his experience and enthusiasm for the subject found him an appreciative audience. His dedication to research and his originality were widely acknowledged, but his overall contribution to the development of the Department was regrettably limited.

Conrad Wagner

The appointment of Conrad Wagner as Assistant Professor in 1961 was a decisive event in the long-term development of biochemical nutrition in the Department. After receiving his Ph.D. at the University of Michigan in 1956, Wagner spent three years at the Naval Medical Research Institute in Bethesda and three years at NIH with E.R. Stadtman in the National Heart Institute. His appointment at Vanderbilt was a joint one with the Veterans Administration Hospital Research Service, and he has maintained this joint responsibility very effectively until the present. Indeed, he served as Associate Chief of Staff for Research at the VA for over 15 years, a rare accomplishment for a Ph.D. His research interests in the field of biochemical nutrition ranged from bacterial studies to human folate requirements. His work on the complex enzymology of methyl group transfer has been especially productive and important. In 1983, he received the Borden Award of the American Institute of Nutrition. His teaching role in metabolism and nutrition was central to both the medical and graduate curricula in the Department, and he has taken a leading role in committees devoted to improvement in both areas. His solid contributions to the biochemical aspects of nutrition research were of great importance in continuing the early nutrition thrust of the

Department and defining its biochemical focus. In 1992, he served as Acting Chairman of the Department during the search for a new chair.

Guilford Rudolph

Gil Rudolph joined the department fulltime as Associate Professor in 1960, having served on a part time basis as Instructor and Assistant Professor since 1949. In the earlier role he was part of a small group of biochemical investigators working in the Thayer Veterans Administration Hospital then located off campus on White Bridge Road in Nashville. When he became fulltime, he was Frank Blood's choice to direct the Clinical Chemistry Laboratory of the Hospital. He carried out this task under the difficult conditions of the changing role and status of clinical labs in hospitals and created a first class clinical chemistry unit. He carried on research in several areas associated with his clinical responsibilities and was later selected as the Chairman of Biochemistry at the Southwest Louisiana School of Medicine in Shreveport.

Medical Education

In addition to the "canonical," comprehensive lecture course in Biochemistry which was given to both medical and graduate students in a shared effort by several of the Biochemistry faculty, there was a very strong laboratory. Here medical students were given experimental opportunities in a variety of important medically related areas that involved "hands on" experience with some of the newer tools of biochemistry. These included the analysis of an unknown amino acid mixture using the then new technique of resin column chromatography, the isolation in pure form of the impressive amount of cholesterol in a single hen's egg and the preparation and study of peptidase enzymes from bovine intestine. Later it involved longitudinal studies of chemically-induced diabetes in mice and similar quasi-clinical projects. Since most pre-medical students then, and now, have limited exposure to laboratory, it

seemed useful to give them, at least once, some direct experience with concepts and methods they would rely on, if not actually perform, during their years of practice. It had the added benefit of helping identify those medical students most interested in a research career so that special accommodation could be made for them. This proved very effective with the Vanderbilt class that always included several especially bright, research-motivated students. It contributed significantly to the later development of a very successful school-wide joint M.D./Ph.D. program. Of course, despite their generally high level of scholarly attainment in college, most first year Vanderbilt medical students are not exactly motivated for a lengthy laboratory experience at a time when they are anticipating exposure to "real medicine" and patients. Biochemistry always faces the reality that it is not destined to be the most agreeable course for most beginning medical students. Talented and understanding teachers like John Coniglio and, in the 1990s, Neil Osheroff can, however, have a very considerable moderating effect. The development of an advanced section of the medical biochemistry course for the increasing number of students who had been exposed to some biochemistry in their college experience was also helpful. Nevertheless, Biochemistry typically only comes into its own for 4th year students and residents who come face to face with the reality that Biochemistry is increasingly an essential language of medical practice.

Sabbatical!

In 1961-62, emboldened and encouraged by Touster's experience, Cohen, Coniglio and I took overlapping sabbatical leaves. In retrospect, it is humbling to realize that our other colleagues felt they could spare the three of us for a year with no difficulty. In June of 1961 I began work with Professor J.A. Cohen and his associates at the Netherlands National Defense Laboratories, T.N.O, in Rijswijk and Leiden, The Netherlands. Coniglio initiated his year of study with Professor George Popjak at the Hammersmith Hospital in London, and in 1962 Cohen began his research at the

Instituto Superiore di Sanita in Rome with, again, his colleague from St. Louis days, Rita Levi-Montalcini, and with whom he later shared the Nobel Prize. Despite the variety of destinations, we managed to locate one another in Europe. The Cunninghams paid a visit to the Coniglios in freezing weather in London in January 1962, and the Coniglios returned the visit in more temperate weather in The Hague in April. The Cunninghams welcomed the Cohens to Europe and to Holland at the dock in Rotterdam in May 1962, and after a brief visit, saw them off by car to Rome. These sabbatical years were extremely valuable to these three, then young, investigators as well as to the Department. It is unfortunate that the pressures of competitive research and funding make such extended stays in important laboratories in other countries next to impossible today. No doubt, the present ability to make frequent trips abroad, together with the dominance of the United States in much biochemical research, makes longer stays less useful.

The experience in Holland was pleasant and very broadly educational. The traumatic effects of the recent war had been largely but not totally overcome. The laboratory, a branch of the Dutch National Defense Organization (we were after all working with nerve gases, though not for that purpose), was quite modern, and my colleagues, Hendrick Jansz, Frits Berends and Rein Oosterbaan, were helpful and supportive in every way, save one. Since everyone in the laboratory wanted to improve their English, my efforts to learn Dutch were met with amusement and no help at all. My technician or "analiste," Anne Marie Schepman, made my research possible by her skill and her knowledge of "how things were done" in that lab. In later years, she received her Ph.D. in bio-organic chemistry at Utrecht under Hans Vligenthart, returned on the research staff at the TNO in Rijswijk and made an outstanding research career there. As Anne Marie Fichtinger, today, she and her husband, one of Holland's top architects, remain our close friends. Unfortunately, Professor J.A. Cohen, the head of the TNO lab, died at an early age in 1967. My connection with Hendrick Jans, however, continued. He became Chairman of Physiological

Chemistry at Utrecht where I was Visiting Professor on two occasions. He also visited Vanderbilt several times. My repeated exposure to his research on phage DNA in the 1960s and 1970s turned out to be especially valuable. It made me appreciate much earlier than I might have otherwise the advancing molecular genetic revolution. This had a strong influence later when I was in a position to help direct faculty development at Vanderbilt.

During this year in Europe, from the base in The Hague, several visits important for "education" and for the formation of important professional contacts were possible. These included the Fifth International Congress of Biochemistry in Moscow in August of 1961. In London at St. Mary's Hospital, I visited Michael Green, an old friend from Seattle, who was working with Albert Neuberger. I flew to England with Martin Rodbell, another friend from Seattle days and much later a Nobel Laureate, who was also working in Holland in 1961. I was also able to visit the Marseilles group of yet another friend of Seattle days, Pierre Desnuelle, and the Carlsberg Laboratory in Copenhagen, a long time obligatory visit for protein chemists where Martin Ottesen had recently taken over from one of the founders of modern protein chemistry, K.U. Linderstrom-Lang.

Although the research component has dwindled in recent years, I have continued frequent visits to Holland and maintain ties there. Introduction to the Dutch in 1961 added a special dimension to my life, scientifically and personally.

Research-Glycoproteins

Research on my other major research interest, glycoprotein structure, had begun before I left on sabbatical in 1961. Our studies of the chymotrypsin mechanism had largely ceased because the obvious next steps would involve structural studies such as x-ray crystallography that required equipment and expertise that were simply not available then at Vanderbilt. The decision to leave the chymotrypsin story was painful but seemed rational. My naïve understanding of the grants process in those early days of NIH

also contributed since I thought one could only have support for one project! And I had become aware that practically nothing was known about the composition and structure of the carbohydrate that co-isolated with certain proteins, known generically as "glycoproteins." There was also the intriguing question of the almost necessarily novel linkage between the peptide chain and the sugars. And finally, there was also the ultimate stimulus that the biological function of these carbohydrate "prosthetic groups" was totally unknown. It seemed a promising area to pursue with, at that time, very few competitors. So I sought and received NIH funding for this new project. Shortly thereafter, the Director of the NIH Study Section that had funded my chymotrypsin project was passing through Nashville on his way with his family to a Florida vacation. He stopped by for a chat and in the course of the conversation asked why I had not reapplied for support! This cozy, familiar interaction between investigator and NIH has certainly changed drastically as the bureaucracy and size of the process has grown.

My first graduate student, Richard Nuenke, began in 1956 a re-examination of the chemistry of the "model" glycoprotein, ovalbumin, with the view to characterizing its reported small carbohydrate component. Prewar studies by Albert Neuberger had suggested the presence of an undefined complex of amino acid and carbohydrate in digests of ovalbumin, and we set out to determine the existence and nature of any linkage between the two. We were successful and reported briefly on the novel acyl-glycosylamine linkage of aspartic acid to N-acetylglucosamine in 1957. Unfortunately, this proposal ran counter to the dogma of the day, that carbohydrate units were linked to protein through an amide link involving the amino group of glucosamine. So we had to wait some months for this idea to fade away before the publication of our full paper. During this interval, Neuberger unexpectedly returned to this problem after a fifteen-year hiatus, and we had to share with him this first demonstration of a covalent linkage of carbohydrate to protein in glycoproteins. This completely novel acyl-glycosylamine linkage turned out to be one, and probably the most common, of the three chief links between peptide chains and carbohydrate in mammalian systems.

Facilities

Leadership of the School of Medicine passed from Dean John Youmans to John Patterson in the mid-fifties. Patterson, an "outsider," had a completely different managerial style that led to considerable unhappiness among many department chairs, including Darby. At the assistant professor level, however, Patterson was greatly appreciated for his successful efforts to break what had been almost a multi-year freeze on faculty salaries. His overall situation was untenable, however, and he left Vanderbilt in 1961. There were several active local candidates to succeed him as Dean, and eventually the Chancellor named Randolph Batson from Pediatrics. At about this same time, Alexander Heard succeeded Harvey Branscomb as Chancellor of the University.

Throughout these years "space wars" raged throughout the School of Medicine as the very limited availability of space always failed to keep up with the needs of rapidly growing research activity. Biochemistry laid claim to increasing bits of Learned Lab and took over part of the old 1925 medical library when the library was moved to the new A-north wing in 1964. In a famous effort, van Eys managed to capture and add to his laboratory the restroom on an adjacent corridor but failed in his attack on a nearby financial management area.

Beginning in 1959 the six additional floors of the A.B. Learned Laboratory were opened, and the Department of Biochemistry, among others, gained valuable new space. It was quite exciting and motivating to be among the first to actually occupy new, fully modern research quarters. About that time, through the connections of Ray Meng in Physiology, who had a United States Army research contract in parenteral lipid alimentation, we obtained a new Spinco (the pre-Beckman company) analytical ultracentrifuge. I had been fortunate as a graduate student at Illinois to participate in setting up the second production instrument. This instrument played a role in my research over the next several years. The mere presence of such an expensive, state of the art tool of the trade helped us feel that protein chemistry at

Vanderbilt was making progress. Its use as an analytical tool has almost vanished in recent years but it was essential for the primary demonstration of homogeneity and molecular weight of proteins. Rapid determination of these parameters today with gel electrophoresis and similar tools rely on these earlier standards.

John Coniglio was also enjoying newfound modernity in his radio-labeling studies of lipids. At last, special lab design features aimed at reducing exposure to radioisotopes were possible. Some weeks later, however, Coniglio was observed with a puzzled look on his face standing before one of his expensive laminar flow hoods. In contrast to the simple chimney draft mechanism of the hoods in the older building, these were actually exhausted by fans. He was standing before one of the hoods with a small burning paper in his hand. The smoke from the paper was wafting gently out from the hood rather than in. The fans had been installed backwards, so that for some weeks whatever radioactivity had been in use was directed into the lab rather than up the stack. Fortunately, in those days only very small amounts of isotope, usually carbon 14, were available, so no real damage was done. The fans were reversed.

Department of Molecular Biology

In 1963, in an important, if belated, recognition of the significant biochemical developments in the biological sciences related to genetics, the College of Arts and Science of Vanderbilt University created a new department, Molecular Biology. The sudden death of the first candidate for the new chair and some "political" turmoil among the first faculty appointed in the new department required an urgent resolution of leadership. The University administration turned to the Medical School and to one of the Department of Biochemistry's key teachers and investigators, Oscar Touster, as the first Chair of the Department of Molecular Biology. Space was allocated on the top floors of the newly extended Learned Laboratory, and Touster began the creation of this badly needed component of a balanced Vanderbilt program in biological science. At that time the strength of the Department

of Biochemistry was still divided among nutrition, toxicology and "other" areas of biochemistry. It was certainly no secret to Darby that some of us were concerned that the "other" areas were not large enough to really prosper. One thought was that it might be a good idea if the "other area" biochemistry faculty transferred to Molecular Biology. This was, to say the least, not a popular idea at the administrative level in either department, and the idea died. In retrospect, that was undoubtedly the correct decision, not least because the episode emphasized the need to commit to adding strength to broader areas of Biochemistry over the next few years. This was greatly facilitated when Health Sciences Advancement Award (HSAA) funding became available three years later. So, the two departments, Biochemistry and Molecular Biology have gone forward in cooperation and in friendly competition, with the limits of their specific disciplinary "turfs" somewhat undefined.

1964-1973

Personal Research

My own research continued on other aspects of glycoprotein structure. One major result involved the demonstration, largely by graduate students Richard Nuenke and John Rainey, that although the peptide portion of glycopeptides derived by proteolysis from purified glycoproteins could be shown to be homogeneous, there were variations in the composition and structure of the attached glycosidic components. This "microheterogeneity" was a major clue in later studies in other laboratories to both the step-wise synthesis and the function of glycoproteins. The vast structural variety possible through combinations of many sugars and their potential for multiple isomeric forms has found utility in a central role for these complex heterosaccharide groups in cell-cell recognition and related phenomena.

Another study resulted in the discovery of the carbohydrate component of collagens. This work, carried out by my second

graduate student, William Butler, for his Ph.D., produced another unanticipated but now commonly found structure, the o-hydroxylysyl glycosides. Here, too, the persistence and insight of a graduate student was the key to the isolation of the key glycopeptide, that behaved rather atypically in the usual separations.

Thus, the inherent functional heterogeneity of the glycosidic portion of glycoproteins and two of the three known glycopepetide linkages were discovered at Vanderbilt by graduate students. During the next few years, we continued our interest in the significance of the carbohydrate in collagens (Jere Segrest, Paul Morgan, Gayle Jacobs, Jose Aguilar, John Rainey, Wilburn Clouse, John Ford, Hugh Davies), and of the catalytic mechanisms of enzymes by studies of creatine phosphokinase (Joan Clark Stevens, Gayle Jacobs, Diana Trundle, Caroline Scurry Brown) and clostripain (William Porter). Studies of the nature and significance of the chemical reaction of iodine with proteins, particularly sulfenyl iodides, and the potential relationship to thyroid metabolism were a new interest (Ludek Jirousek, Diana Trundle, Soo Il Chung).

Curriculum Changes

The year 1965 saw a major revision in the entire medical curriculum. Under Darby's leadership, a committee of the Medical School recommended, and the Dean and the Executive Faculty adopted, a revised curriculum in which Wednesdays were entirely devoted to an array of new elective courses from all departments. Biochemistry's early development of electives for medical students had now become standard for the School of Medicine. The Medical Biochemistry course was now scheduled on Mondays and Fridays from 8:00 a.m. until 4:00 p.m., with two hours of lecture and the balance in conferences or laboratory. Some additional changes, and an inevitable change in numbering, left the course offerings of the Department of Biochemistry as follows: 321 (Medical) Biochemistry; 322 (Medical) Biochemistry Laboratory; 521 Fundamental Principles in the Use of Radioisotopes; 522 Toxicology; 523 Fundamentals of Human Nutrition; 524 Advanced

Metabolism; 526 Biochemistry and Differentiation; 527 Nutritional Biochemistry; 528 Clinical Biochemistry; 529 Lipid Chemistry and Metabolism; 530 Nutrition Clinics; 581 Research Fellowships in Biochemistry; 582 Research Fellowships in Nutrition; 583 Special Problems in Nutrition; 584 Preceptorship in Biochemistry; 599 Biochemistry Seminar; 323 Special Problems and Experimental Techniques; 324 Use of Radioisotopes in Metabolism; 325 Micro-Physiologic Techniques in Biochemistry; 326 Bio-organic Chemistry; 327 Seminars in Biochemical Literature; 333 Protein Chemistry; 399 Research. Course offerings beginning with 5 were intended primarily for medical students and reflect the proliferation of electives stimulated by the change in the Medical School curriculum. Courses beginning with 3 were primarily for graduate students, though exceptions to these restrictions were frequently made for exceptional medical students.

Faculty (1964-68)

Robert Neal

Bob Neal came to Vanderbilt as a graduate student in 1960 after service in the United States Air Force. He received his Ph.D. under Bill Pearson in 1963 and then spent a year in the Department of Toxicology at the University of Chicago. This exposure to toxicology was to shape his career at Vanderbilt and elsewhere. He returned to Vanderbilt on the faculty in 1964 and remained until 1981. After the tragic death of Frank Blood in 1971, Neal became Acting Director of the Center in Environmental Toxicology. The resignation of Bill Darby as Chairman of the Department in that same year and the insistence by the NIH that we make a national search for someone to succeed Blood as Director of the Toxicology Center only delayed the inevitable. Neal's breadth of knowledge and his administrative talents made him the obvious choice of the search. (It was my pleasure as one of my first acts when I succeeded Darby as Chair in 1973 to appoint him permanent Director of the Center in Environmental Toxicology.) The Toxicology Center

achieved rapid new growth under Neal's leadership. It extended its reach into several other departments, especially Chemistry and Pharmacology, but its "home" in Biochemistry was important to Neal's success in emphasizing the biochemical approach to toxicological studies that became the hallmark of the Vanderbilt Center. His success and national stature led to his selection in 1981 as the President of the Chemical Industry Institute of Toxicology in Research Triangle, North Carolina. After 7 years there, where he further influenced the biochemical approach to toxicology nationally, he retired and returned to Nashville where he had always retained the title of Adjunct Professor of Biochemistry. Later, he "really" retired to his home in North Carolina where the ocean fishing is somewhat better.

Laken Warnock

"Red" Warnock received his Ph.D. in the Department in 1962 under Jan van Eys. After a postdoctoral experience with Roger Koeppe at Oklahoma State, he rejoined the Department as Assistant Professor in 1964. During most of his years at Vanderbilt he was also affiliated with the Division of Research of the VA Hospital. His major research interest was in metabolism and metabolic regulation. He also became an early expert on the proper conditions under which research animals were maintained and became the crucial faculty resource person in that field. He served as Director of the Animal Research Facility at the VA Medical Center for many years and was a consultant to the American Association for Accreditation of Laboratory Animal Care. Another accomplishment, which was especially valued, was the departmental budget computer program that he wrote in its entirety and which was used successfully by the Department of Biochemistry for many years. It was so informative and user-friendly that we fought hard to retain it as long as possible, but, of course, the irresistible tide of school wide compatibility washed over us eventually; a thoroughly opaque auditor-friendly program replaced it. Warnock was a dedicated teacher and greatly enjoyed "fencing" with the medical students.

For many years he was in charge of the Biochemistry Laboratory Course for both medical and graduate students and taught sections on metabolism in the related lecture courses. He has an amazing store of stories about those past years when biochemistry faculty and graduate students worked together to generate a serious and "relevant" laboratory experience for the medical students.

Benjamin Wilson

Ben Wilson received his Ph.D. at George Washington University in 1955. He came into academia at David Lipscomb College in Nashville in 1959 after 10 years as Chief of the Microbiology Branch, Biological Warfare Laboratories, U.S. Army Chemical Corps, Ft. Detrick, Maryland. He moved from David Lipscomb to Vanderbilt in 1963 where he brought his unusual expertise to the Toxicology Center. His main area of research was in naturally occurring toxins, such as those produced by bacteria, fungi and higher plants. He discovered several important toxins such as rubratoxin and the ipomeanols that, because of their importance in the handling of many food crops, subsequently became the target of research in many laboratories. His discoveries of the neurotoxic compound penetrem A and another from aspergillus were of major importance. This research often involved collaboration on an international scale, and Wilson, as a recognized authority, was a frequent participant in important national and international symposia.

Tadashi Inagami

Tadashi Inagami came to Vanderbilt in 1966 after postdoctoral research in physical biochemistry under J.M. Sturtevant at Yale. He had earlier received the Ph.D. at Yale and the D.Sc. from Kyoto. My interest in proteases had made me aware of Inagami's studies of trypsin, and I was obviously enthusiastic about his recruitment. At Vanderbilt, Inagami became interested in the proteolytic transformations of the renin system and their relationship to

hypertension. He built an internationally recognized research program in this field, developing a large and excellent group of students and postdoctoral fellows. Later he extended his interest successfully into other areas of endocrine control of blood pressure. He was the key basic science investigator of Vanderbilt's interdepartmental Center for Research in Hypertension and became its Director in 1979. It is a tribute to Inagami's broad expertise and leadership that he has been a highly successful Director of this large and rather clinically oriented Center. This is yet another example of the large contribution of the Department of Biochemistry faculty to the broader development of research at Vanderbilt. Inagami has received wide recognition for his research including the Ciba Award of the High Blood Pressure Research Council of the American Heart Association, the Japan Academy Award, the SPA Award of the National Fund for Scientific Research of Belgium and Vanderbilt's highest scientific award, the Earl Sutherland Prize. He is presently the Stanford Moore Professor of Biochemistry. He has also been active in bringing new developments in instrumentation and expertise to amino acid analysis and peptide sequence determination. In this, he has ensured their wide accessibility to students and faculty. Such cooperation, characteristic of the development of research resources in the Department of Biochemistry, has made possible the early availability of new techniques and the easy familiarity of graduate students with them.

The Department and I, especially, are indebted to Inagami for his thorough and even-handed chairing of the departmental Faculty Promotions and Appointments Committee for many years.

Willard Faulkner

Willard Faulkner received his Ph.D. at Vanderbilt in 1956 under the direction of Frank Blood. His major research interest was in the area of the development and evaluation of new techniques of clinical chemistry and their significance to clinical evaluation of health status. After spending several years at the Cleveland Clinic, he was enticed back to Vanderbilt by Frank Blood at the time

when Blood had been given the immense and difficult assignment of bringing all the clinical laboratories of the hospital up to satisfactory levels. Faulkner took on clinical chemistry and quickly ensured the highest standards. Over the years, he was a leader nationally in clinical chemistry and published key resources in his field. Although his office was physically separate from the rest of the Department, he was an active participant in departmental affairs. The hospital clinical laboratories are "hot spots" of interfacial tension between "science" and "medicine." Faulkner's expertise and dignified demeanor calmed many potential difficulties.

Health Sciences Advancement Award (HSAA)

Life for me in research and teaching in the company of excellent faculty colleagues, graduate students and postdoctoral fellows was too enjoyable to last. In 1967, I was approached by Allan Bass, Chairman of Pharmacology and John Shapiro, Chairman of Pathology, who, with others, had written a major grant proposal to the NIH for a Health Sciences Advancement Award (HSAA). The goal of this NIH program was the rapid development of "a few select" outstanding research oriented medical schools to a "higher level of excellence" in biomedical research. Bass and Shapiro asked me to serve as the acting principal investigator, taking it through the site visit. I was quite skeptical, but, after all, Allan Bass was one of my truest friends and most generous leaders in the Medical School. After his assurances that this was temporary and really wouldn't change my life, I accepted and, of course, my life was changed. Most obviously, despite an awareness of the likelihood and a real effort to thwart it, my time at the bench and in active research took an immediate nosedive from which it never recovered.

We were successful in the competition for this HSAA, and there will be more about its very considerable effect upon biochemistry at Vanderbilt. The great surprise to me was the requirement, unmentioned prior to our receipt of the actual award, that NIH wanted the principal investigator of this HSAA program (by this time the modifier "acting" had somehow vanished) to be

appointed as an Associate Dean of the School of Medicine. Bowing to an NIH "request" is a given when cash is in the offing, so in 1967 I was appointed by the Dean and Executive Faculty as the first Associate Dean of the School of Medicine. It was not at all clear what responsibilities this office of Biomedical Sciences would have other than managing the HSAA. Rather rapidly it included responsibility for grants "management" and "development" as well as for almost anything related to research that originated or came to rest in Dean Randolph Batson's office. Naturally, this precedent opened the door and appointments of other associate deans in Medical Education (John Chapman), Clinical Services (Lloyd Ramsey) and Medical Center Programs (F. Tremaine "Josh" Billings) followed. The office of Biomedical Sciences survives today although, in keeping with academic tradition, the title has now ascended to Associate Vice Chancellor for Research. The duties remain largely the same, although the scale is much larger as a result of the successful development of research in all departments of the School of Medicine over the years. In checking to be sure of the correct current title for this office, I learned how the administration of Vanderbilt University School of Medicine and Hospital had grown. From the three officers of early 1967 (Dean/Director of Medical Affairs, Hospital Director and Director of Finance), there are now more than forty officers at comparable levels listed in the "Facts 2002" bulletin of the Medical Center.

The increasing responsibilities of my role as Associate Dean dominated my personal activities during the period 1967-1973 and severely impacted my interaction with graduate students and research overall. In fairness to the students, with the help of colleagues, I took what steps I could to reduce my commitments. Bill Mitchell, a faculty colleague in Microbiology, guided Bill Porter and John Rainey to the completion of their Ph.D. studies of clostripain, and some specific research problems were "exported" with the help of equally generous colleagues elsewhere. Rex Montgomery at the University of Iowa undertook a detailed structural analysis of the ovalbumin glycopeptides, initially using samples which we provided and with the participation of one of

our M.S. graduates, Cheng-Chung Huang, who later received his Ph.D. at Iowa.

Although the vicissitudes of life in medical administration during the years 1967-72 are not the subject of this history, a few comments may be relevant as they reflect on broader issues affecting the Department of Biochemistry. These years encompassed many crucial changes in the School of Medicine and included some financially very tough years at the NIH, and, in turn, at Vanderbilt. One quote from a letter to Rex Montgomery, a colleague at the University of Iowa, will give a taste, with leeway for my usual hyperbole, of financial concerns during the Viet Nam period.

Rex had mentioned his plan on his return from a sabbatical in Australia to initiate some studies of metal ions with proteins. I replied, "I am always thoroughly uncomfortable because I know so little of the fundamental chemistry of such complexes. Perhaps I can get you to clarify these things for me when you return and I get out of this administrative morass. Mr. Nixon has really brought science to a grinding stop. If no other source of support for medical schools is quickly forthcoming, there will be some spectacular disasters. The tides and eddies in Washington are so poorly defined, however, that we are all still hopeful, but a cold-blooded analysis gives only one answer—financial crisis."

A broader but more tempered sense of anxiety in the Medical Center during these difficult years is partly illustrated in excerpts of the summary report I, as Chairman of the Building Committee of the School of Medicine, sent to Dean Batson in April of 1968. This group had been appointed with the charge to look deeply and critically into the status of present and planned new construction in the Medical Center. It had broad representation from clinical and basic science areas.

"The uncertainty of funding of all parts of the Medical School Building Plan (the Todd-Wheeler Report) and the equally obvious retarding effect of this on planning and program development throughout the University have led us inevitably to a consideration and re-evaluation of construction priorities in the belief that we might help define urgent and irreducible goals. Such goals should,

indeed must, be within the immediate financial resources of the University if deterioration of the programs of the School of Medicine is to be avoided. The completion of Phase I of the Todd-Wheeler plan on schedule in 1970 appears to be totally beyond the present financial resources of the University. It seems to this committee that this very ambitious plan, though desirable in many aspects and generally satisfactory as a long-term guide, is acting to inhibit more modest increments of construction. This, in turn, is producing a situation in which it becomes increasingly difficult to retain present faculty and to recruit new faculty."

An additional excerpt is of interest as an indicator of the sense of the faculty in 1968 of the future of American medicine.

"One aspect of the School of Medicine's plans for future construction has become increasingly important in our view. This is the unbelievably rapid change in attitudes and policies of the public and the state and federal governments toward health care. These developments were clearly not in sight during the Todd-Wheeler study. In direct terms, we believe now that the viability of Vanderbilt Hospital depends upon the rapid development of a modern, innovative medical care facility which can serve as a base from which the clinical faculty of the School of Medicine can attract a patient population adequate for the education of medical students, interns and residents. The building of the West Tower project would permit many developments of that type. In addition to creating modern and competitive bed facilities for medicine, pediatrics, and obstetrics and gynecology and new operating rooms, it would permit the early location and development of the Stallworth Rehabilitation Center and the establishment of a Children's Medical Center in the round wing."

After extensive discussion among the faculty, this report was forwarded in 1968 to the Chancellor in the hope that it would spark an early release from the confines of the 1925 building and the growing number of minor accretions to that structure. For various reasons, financial and managerial, this was not to be until many years later. The clinical departments, especially, struggled onward under extraordinarily difficult limitations of facilities. The

basic sciences including Biochemistry under Bill Darby also moved onward toward their goals of increasing strength and quality but always under the pressure of inadequate space. This is perhaps a good place to emphasize the excellent support Bill Darby and I, and indeed all the preclinical chairs, enjoyed from clinical chairs over the years. They understood our role in the School of Medicine in teaching and research and were strongly supportive of our needs for space and dollars for that purpose, even during these years when their own clinical programs were suffering from a truly major and depressing need for a modern clinical facility. Perhaps this served to strengthen us all as a faculty, but we were all relieved and more than delighted when a new hospital was finally completed many years later under Vice Chancellor Vernon Wilson's leadership.

Faculty (1968-72)

On Thanksgiving Day, November 28,1968, the Department lost one of its most beloved members. William Pearson was killed in an automobile accident. Pearson had been instrumental in the development of the Division of Nutrition and was the leader in a series of novel and important Nutrition Surveys made by Vanderbilt and other institutions for the United States Department of State and the National Institutes of Health.

A number of new appointments were made during 1968-71 in the Department of Biochemistry largely in collaboration with the Health Science Advancement Award. These included Harry Broquist as Professor, Bert O'Malley as Associate Professor and Robert Brady, Kenneth Lembach, Gareth A. Mair, J. David Puett, Frank Chytil, J.T. Davis, and Samuel DiMari, as Assistant Professors.

David Puett

Dave Puett came into the Department of Biochemistry in 1969 as a part of the HSAA program after several years at the Chemstrand Research Center in North Carolina. His research interest was in the structure and conformation of proteins, including tetanus toxin,

Tamm-Horsfall glycoprotein and acetylcholine receptor. His particular interest, however, was in protein hormones, including luteinizing hormone, growth hormone, gonadotropins and epidermal growth factor. His interest in the endocrine hormones led him to the post of Associate Director of Vanderbilt's strong Population Center where he developed an outstanding research and graduate training program. Puett was a fine teacher as well as an accomplished scientist and a skillful administrator. He was interested in and successful in all aspects of graduate education. His leadership as head of the departmental Graduate Education Committee took our program to new heights. It was a painful but understandable loss when he accepted a challenging post at the University of Miami. From there he later moved to the Chair of the Department of Biochemistry at the University of Georgia at Athens.

Kenneth Lembach

Ken Lembach joined our faculty in 1969 coming from a post-doctoral fellowship at M.I.T. with John Buchanan. He was appointed under the HSAA program and developed a research program around the biochemistry of growth initiation, utilizing the induction of ornithine decarboxylase in cultured cells as a key "marker." He exploited this metabolic indicator in studies of the effects of several growth factors and proteases that seemed to point toward exciting new understandings of cell growth regulation. In the process, he established a departmental cell culture facility that both found and stimulated wide use. He was a strong and universally admired teacher. Despite his success in these several areas, he left the Department and academia in 1979 for a Senior Research position at Cutter Laboratories, where he has continued his research. This loss, too, was very keenly felt as Lembach had great potential as a colleague and leader in teaching and research.

Wayland Hayes

"Jack" Hayes joined the Department in 1968 at the invitation

of Bill Darby. He came from the senior position of Chief Toxicologist at the National Communicable Disease Center and added both breadth and strength to the Center in Toxicology. He had received his Ph.D. in 1942 in Zoology and Physiological Chemistry from the University of Wisconsin and an M.D. from the University of Virginia in 1946. His main research interest was in pesticides, and he wrote and edited several authoritative volumes on the toxicology of pesticides. He was a consultant to the World Health Organization, the Pan American Sanitary Bureau, the American Medical Association and the National Research Council. He was a past President of the Society of Toxicology. His strong focus on less biochemical features of toxicology reduced broader contact with graduate and medical students, but he was an active participant in the specialized toxicology course for graduate students. One of the reasons Darby had been able to convince Hayes to leave his important government position to join Vanderbilt was the family connection. His father had been a well-known member of the Vanderbilt faculty. Hayes became Professor Emeritus in 1982.

Robert Brady

Bob Brady joined the Department in 1969 under the HSAA program. His postdoctoral work with Esmond Snell had been on the biosynthesis of sphingolipids. At Vanderbilt he used his familiarity with these and similar lipids to jump quickly into the early race for the isolation and characterization of membrane receptors. He targeted the acetylcholine receptor protein and went head to head with Jean-Pierre Changeux who was tackling the same protein in Paris. Brady faced an acute shortage of the source for isolation of the receptor, *Torpedo nobiliana*, which we only partly jokingly ascribed to the hoarding of this creature by the competition at Woods Hole. So we made a special trip to Dauphin Island, Alabama where, with the help of my brother-in-law who was head of the Alabama Marine Fisheries, we convinced the shrimp boat captains to save the normally discarded electric fish, *Narcine*

braziliensis. We returned to Nashville with enough raw material to carry forward several decent sized isolations. Shortly after this, however, and in the knowledge of almost certain success in the competition with Changeux, Brady heard the call of his church and left the Department to go fulltime into other activities.

Bert O'Malley

The appointment of Bert O'Malley in 1970 was a cooperative action of the Departments of Medicine, Obstetrics and Gynecology and Biochemistry, and the HSAA. Although his primary appointment was not in Biochemistry, the impacts upon the Medical Center and the Department of his research group, certainly the largest in the School of Medicine, and his research *modus operandi* were positive and substantial. O'Malley had been recruited along with his group, so that this "operation" brought to the School of Medicine a large research program involving faculty level individuals from several universities. The main area of their research was reproductive biology and biochemistry. This was formalized by the successful competition for an NIH supported Population Center. The success of this program over the next few years led to repeated outside efforts to recruit the group to move elsewhere. Eventually, in 1972, O'Malley and several of his associates did leave Vanderbilt for Baylor where they again established a strong program in reproductive biochemistry. Vanderbilt made strenuous efforts to retain O'Malley and his entire group, but our ability to commit additional space and other resources eventually became limiting.

Frank Chytil

The Department of Biochemistry did retain one special member of the O'Malley group, Frank Chytil. Frank received his Ph.D. in 1952 from the School of Chemical Technology in Prague. His early years were spent in research in the Department of Physiology, Czechoslovak Academy of Sciences. After a postdoctoral year in biochemistry at Brandeis in 1964, he returned to Czechoslovakia

in the Academy of Sciences. Finding conditions of life and science intolerable in communist Czechoslovakia, Chytil, his wife, Lucie, and their children literally escaped to the West in 1966, first to Brandeis and then to the Southwest Foundation for Research and Education in San Antonio. We owe Bert O'Malley for bringing Chytil to Vanderbilt as Assistant Professor of Medicine and Biochemistry but we surely weren't going to let him leave with O'Malley. Chytil has always called the complex separation of people, equipment, programs and money occasioned by the move of several of O'Malley's group to Baylor "the divorce." As Associate Dean at that time, it was my job to sort all this out. It was cordial, but business like, and Chytil's characterization is apt. In any event, Frank remained in Biochemistry at Vanderbilt, becoming Professor in 1975 and General Foods Distinguished Professor in Nutrition in 1984. His research in Vitamin A metabolism has brought him international attention. In 1983, he shared the Osborne-Mendel Award of the American Society for Nutritional Sciences with his colleague David Ong. In 1993 he received the Lederle Award in Human Nutrition of the American Institute of Nutrition for his many contributions to the understanding of the physiological role of vitamin A in tissue development and maintenance, particularly in the lungs. In addition to its major biochemical significance, his broadening of our understanding of the role of Vitamin A has been of great value clinically, especially in newborns. In 1991, he was elected as a Fellow of the American Society for Nutritional Sciences. Frank has recently (2003) written an entertaining and enlightening autobiographical essay for the *Annual Review of Nutrition* entitled *Rough and Rocky Road to the Retinoid Revolution*. He, with Connie Wagner, John Coniglio, Harry Broquist and David Ong, created the strong biochemical character that has sustained and strengthened Vanderbilt's and Biochemistry's leadership role in nutrition.

Harry Broquist

Harry Broquist had already achieved national recognition for his research in nutrition in the Departments of Dairy Science,

Chemistry and Chemical Engineering at the University of Illinois, Champaign-Urbana when he came to Vanderbilt in 1969 as Professor of Biochemistry. Bill Darby attracted him into the Division of Nutrition of the Department of Biochemistry with the aid of the HSAA program. His research, stemming from his doctoral training in microbial nutrition in Professor E.E. Snell's laboratory at the University of Wisconsin (1946-1949), has focused importantly on lysine metabolism in microorganisms and animals and has had broad biochemical, nutritional and toxicological significance. A comprehensive autobiographical summary of these and other aspects of his career appeared in the *Annual Review of Nutrition* in 1997. With his background and interests, he was able to contribute very broadly to all aspects of the educational programs of the Department, particularly in strengthening nutrition input into the biochemistry curriculum required in the training of medical students. He was designated by Darby to be his successor as Director of the Division of Nutrition when Darby stepped down to join the Nutrition Foundation. Broquist's reputation in the field insured that the Division continued to develop as one of the strongest programs of biochemical nutrition in the country. He was a frequent participant in NIH study sections and site visits, a prolific contributor to the scientific literature and a respected member of the editorial board of major journals such as the *Journal of Biological Chemistry*, *Nutrition Reviews*, and *Annual Reviews of Nutrition*. Broquist served as President (1984) of the American Institute of Nutrition, and after retiring as Emeritus Professor in 1987, he received in 1995 the Conrad A. Elvehjem Award for specific and distinguished service to the public through the science of nutrition.

The Graduate Program

The training of graduate students in biochemistry had been recognized as an absolutely fundamental role of the Department since its inception and has been vigorously supported by each new chair. This is hardly surprising since the existence of a strong Ph.D.

program is essential for a strong department. It is impossible to recruit and maintain an outstanding and qualified faculty in the absence of a strong graduate program. The training of Ph.D.s is the basis for the definition and continuation of the discipline of biochemistry. Only those trained in and committed to the discipline and its base in chemistry can adequately develop and transmit it. As biochemical knowledge is absorbed into other disciplines, it is vital that biochemistry itself retains its close ties with chemistry.

The graduate program in Biochemistry grew from fewer than three students in 1950 to more than 47 in 1970 and has fluctuated at other times reflecting chiefly the availability of support. The Biochemistry program and that in Pharmacology have always been the largest in the biomedical sciences. Biochemistry has provided the largest number of "core" didactic course offerings for all basic science departmental programs.

Graduate training in the biomedical sciences nationally, including biochemistry, has developed in a culture since 1950 where essentially all students expected tuition and stipend support. The federal government, through NIH, The National Science Foundation, The Atomic Energy Commission and other agencies, has largely provided this. Similar support by private agencies such as the American Heart Association and the American Cancer Society has been relatively much less but quite important in maintaining balance and standards.

The influx of talented new faculty during the 1960s naturally led to significant growth of the Graduate Program in Biochemistry, both in numbers of students and in the variety of research and course opportunities. A number of graduate course changes were implemented in 1970-71 which reflected this continuing growth in number and quality of Ph.D. candidates in Biochemistry. The name of Course 333 was changed to "Mechanisms of Enzyme Catalysis" and 525 "Mineral Disposition in Man and His Environment" was added. Course 524 "Advanced Metabolism" was divided into 524.1 (331) "Advanced Biochemistry I" and 524.2 (332) "Advanced Biochemistry II." 530 "Nutrition Clinics" was

changed to "Nutrition Rounds" and 529 was changed to "Lipid Chemistry and Transport." Although the inclusion of such prosaic details as course names in a history may seem superfluous, they do provide a record of changing national and departmental interests as biochemistry developed.

The importance of Ph.D. training in biochemistry for the advancement of medical science was recognized early on by the National Institutes of Health through the award of individual fellowships to graduate students. This approach was largely replaced in later years by training program grants covering a substantial number of students and made to individual departments or interdepartmental consortia. This led to a much more organized graduate education program in tandem with the increase in NIH research grants. The latter provided the great bulk of the resources for the actual research as well as for salaries for some graduate students as Graduate Research Assistants. It had the unfortunate side effect, common to all NIH programs, of being very susceptible to sudden changes in the level of federal budgets. This phenomenon is bad enough for ongoing research projects but is devastating to graduate education programs where initial commitments of four to five years of support to a student are common. This problem was exacerbated by the tendency of NIH to regard "bigger good" programs as better than "smaller good" programs, so that continued program growth was taken as a sign of success. When carried to its logical conclusion, it produced larger enrollments both at Vanderbilt and nationally than were sound. This also made the effects of NIH budgetary cutbacks much more severe since the Department was left with excessive long-term commitments. One example may serve to indicate this complicated relationship. In the late 1960s, there occurred a sudden decrease in growth of federal funding for research and research training. Biochemistry had a thriving graduate program supported in large part by an NIH research-training grant. A renewal application was "approved but not funded." John Coniglio, who was in charge of this application, tried to get some understanding of what was going on. A senior official at NIH gave him the following insights. "While

we recognize the concern of you and others at Vanderbilt with regard to your renewal application, it is only fair to point out that a large number of departments or programs across the nation are in similar or worse situations in relation to research training grant support. At the present time, we are funding only about half of the approved training grant applications. Those not being funded include a considerable number of renewal applications. It is certainly not our intent to discontinue training grant support to high-quality, productive programs if that is avoidable. Over the past several years, there has been a decrease each year in the total number of training grants funded by this institute. In view of appropriations proposals, an even more stringent situation is expected for funding grants to begin next July 1."

In this particular case, the situation was managed with a variety of strategies, but it resulted in a much more cautious approach to the size of the graduate program and in efforts to develop alternative sources of funding. The size of the graduate program is, of course, strongly influenced by the size of the faculty since the training of graduate students and the performance of research by the faculty are intimately related. The growing number of postdoctoral fellows helped reduce pressure for enlargement of the number of graduate students.

One key component of graduate study, the joint M.D./Ph.D. program has long received strong support from medical administration. In later years, support from that quarter came for Ph.D. programs as well when the value of these students to the overall research base and educational environment and to faculty recruitment and retention became more evident and appreciated. The basic foundation of NIH support for educational programs for Ph.D.s and postdoctoral fellows in Biochemistry, however, remains as important as ever, though it changes somewhat in form from time to time.

The critical importance of all graduate programs including the joint M.D./Ph.D. program to the overall health and standing of the School of Medicine is currently (2002) recognized by the direct and continuing allocation of funds from medical

administration for the support of such students. This was first begun in 1971 on my initiative as Associate Dean utilizing General Research Support funds from NIH and, in various forms, has been continued and increased over the years, essentially assuring a base level continuity of graduate educational programs despite occasional sudden changes in federal support. In the early 1980s Dean Chapman, at the request of the Graduate Education Committee of the School of Medicine, created a "graduate tuition fund." This underwrote the "payment" by the School of Medicine of that portion (then 85%) of a graduate student's tuition that was returned "automatically" by the Graduate School to the School of Medicine. This limited program was meant to provide a floor for graduate enrollment in the basic science departments, and we were honor bound not to use it if we had any alternative mechanism for paying full tuition (such as training grants.) Another problem affecting student recruitment was the ability of many universities to supplement the stipends allowed on training grants. To assist us in remaining competitive, Dean Chapman was able to authorize and, to some extent, provide from time to time during the 1980s funds for the supplementation of stipends offered to potential graduate students. All of this was quite necessary to retain a competitive graduate program in Biochemistry. John Chapman deserves great credit for understanding the competitive nature of graduate student recruitment and for providing assistance.

Regulation and governance by the Graduate School of the University, the Graduate Faculty and its Dean has sustained the quality of the graduate programs of the basic science departments. Within the School of Medicine, the Dean of the School of Medicine, until the 1990s, relied on a Graduate Education Committee composed usually of the chairs or senior faculty of all participating departments (Anatomy, Biochemistry, Physiology, Microbiology, Pathology, and Pharmacology). By this cooperative involvement of the Graduate School and the School of Medicine, the various programs were able to maintain their individual professional standards as evidenced by the success of their graduates. Each departmental program was organizationally separate although most

chose to enroll students in several basic biochemistry courses that provided a core of knowledge useful in many fields. In the early 1990s, these departmental graduate programs were collected within the School of Medicine for administrative and student recruitment purposes. The first year curriculum for all departments was merged. Additional financial support was then provided by medical administration.

The overall quality of the Graduate Program in Biochemistry over the years, in terms of national ranking, is difficult to assess numerically. Because of wide variations in specialization, meaningful national rankings do not exist, although it is accepted that the programs of the larger research oriented universities, Harvard, Stanford, etc. lead the pack. Biochemistry has certainly been repeatedly recognized within Vanderbilt as one of the premier programs of the University. Competition for students is now largely national because of the federal training grant programs. The number of national graduate programs in biochemistry and closely related fields (molecular biology, biophysics, structural biology, etc.) available to interested students is quite large, particularly in comparison with other fields. Competition is always influenced by funds available above and beyond the federal programs for the support of the student. This has been rather variable at Vanderbilt, but is currently, in 2002, very good. In early years Biochemistry at Vanderbilt found advantage in recruiting exceptional students in the southeastern section of the United States and in accepting applicants with excellent records but with deficiencies in chemistry or mathematics which could be readily repaired in the Vanderbilt University environment. With time the reputation of our faculty grew, and we began to recruit successfully nationally. It remains a fact, however, that study for the Ph.D. is highly individualized, at Vanderbilt and elsewhere, and the final overall evaluation of a program rests on the very complex assessment of the success of its graduates. In the main, we rely on evaluations by our local colleagues (the Graduate Program Review of 1974), visiting colleagues including site visits by NIH, ourselves (especially new members of our faculty) and our graduates to determine whether our graduate

program is serving our students well. On the whole, such feedback over the years has been very reassuring that we are, in fact, training excellent scientists and teachers, who quickly find a place in the national biomedical environment. Our fine competitive record of NIH approval of our graduate training programs further supports this conclusion.

The M.D./Ph.D. combined degree program at Vanderbilt has existed formally since about 1967 when the Vivian Allan Foundation provided specific support. By judicious use of this resource in combination with research and training grants, a viable program with some excellent students was developed. The initial program ran, generally rather well, on an *ad hoc* basis relying chiefly on Medical School and Graduate School mechanisms for regulation. Although the informal nature of the early years of this program makes definitive statements suspect, it appears that the first M.D./Ph.D. graduate was Jere Segrest who received his Ph.D. in Biochemistry, working in my laboratory, in 1969.

By 1972 the growth of the joint M.D./Ph.D. program and the increased size of the medical class led to a review of the program by a faculty committee chaired by John Coniglio. This review enthusiastically endorsed the program and made recommendations for improved management. This report provided the foundation for greatly improved School of Medicine support for the joint M.D./Ph.D. Program that is thriving in 2002.

Departmental Organization

In early 1970, Darby recognized the growing size and diversity of the Department and attempted to formalize the existence of four interest areas. These were nutrition, toxicology, human biochemistry (clinical biochemistry) and general biochemistry. Although acknowledged as the "basic foundation" of the Department, "General Biochemistry" was not a particularly felicitous choice of name, at least with those faculty assigned to it. It did provide some autonomy to the growing portion of the Department not included in the other three areas, however, and

made possible some strengthening of course requirements and the development of an independent and more focused student seminar series. The student seminar in Biochemistry has always been a feature of the graduate program as a training tool for a professional life that is highly dependent upon clear and forceful presentations of one's work. It is also, traditionally, a valuable resource for bringing the current literature before students and faculty. The vast increase in Medical Center seminars of all types in the 70s and later has not reduced the importance of student presentations.

This formal organization of the Department really did not endure long. The nutrition and toxicology components had already long been explicitly identified as divisions. Clinical chemistry, while an historically important part of the Department, was being steadily eroded as a result of organizational changes in the hospital laboratory. Furthermore, most of the faculty in nutrition and in toxicology saw themselves as much biochemists as the rest of the faculty. For these and related reasons, the definition of "General Biochemistry" as a specific subgroup did not take hold and simply vanished over time. With later changes in departmental and divisional leadership, the nutrition and toxicology programs changed so as to focus even less on non-biochemical approaches. Thus the need originally felt to separate these areas from "General Biochemistry" became moot.

Tragedy again struck the Department on January 31, 1971 when Frank Blood died suddenly. Robert Neal became Acting Director of the toxicology program.