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GERHARD SCHMIDT

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A Biographical Memoir by

HERMAN M. KLACKAR

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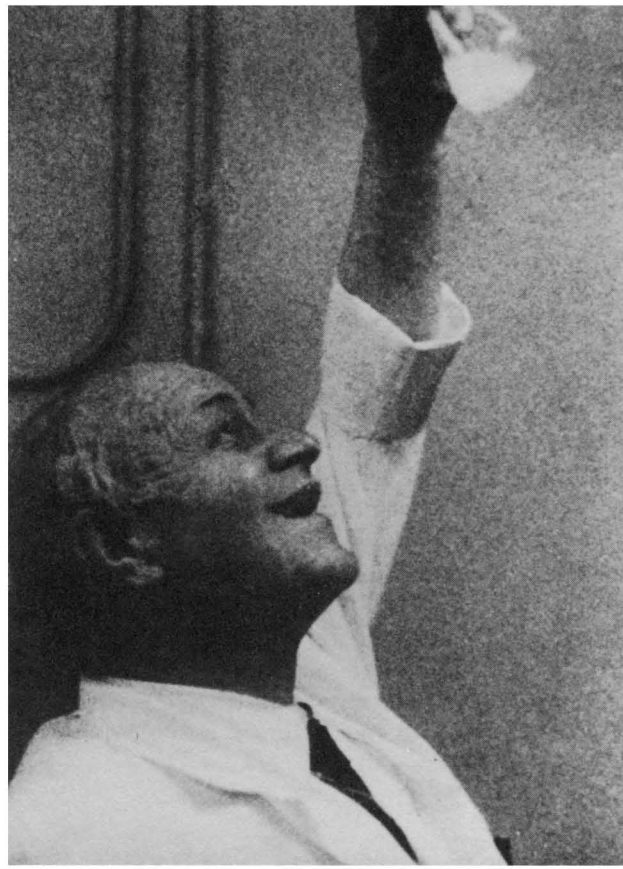

Richard Schmidt

GERHARD SCHMIDT

December 26, 1901–April 30, 1981

BY HERMAN M. KALCKAR

IN THE MID-1920S, during the more hopeful years of the Weimar Republic, Gerhard Schmidt seemed destined for a distinguished scholarly career in biochemistry. In 1926 he received the M.D. degree from the University of Frankfurt am Main, an institution that enjoyed considerable esteem, both nationally and internationally. In that same year, he accepted a postgraduate research fellowship in the biochemistry department there, the first step in a career progression that brought him eventually to the position of *Privatdozent* in the school's Department of Pathology. But Schmidt's career—like those of so many other scholars of Jewish extraction—was suddenly interrupted by the rise to power of the Nazis in 1933. He left Germany, and after a few years of "wandering"—years that took him to Italy, Sweden, and Canada—he finally settled permanently in the United States. There, he continued his work: first, briefly, at the Rockefeller Institute for Medical Research and Washington University School of Medicine in St. Louis, and then, for nearly forty years, at Tufts University School of Medicine in Boston.

Gerhard Schmidt was born December 26, 1901, in Stuttgart, the capital of the kingdom of Würtemberg, which was part of imperial Germany. His father, Julius, was a professor

of chemistry at the Technische Hochschule in Stuttgart and the author of a textbook on organic chemistry; Gerhard's later zeal for sound analytical chemistry was probably influenced by his father's interests and scientific orientation. His mother, Isabella (née Gombrich), was an excellent pianist; her work undoubtedly stimulated her son's active participation in chamber music, an aspect of his life to which we shall return later.

Gerhard attended the Eberhardt Ludwig Gymnasium in Stuttgart, where he was valedictorian of his class at commencement exercises in the spring of 1919. That autumn he enrolled in the University of Tübingen and elected to study medicine; in 1922, however, he transferred to the medical school of the University of Frankfurt am Main. His early interests included not only chemistry and medicine but also general biology and particularly zoology—one of his favorite books was Brehm's popular zoology text, *Tierleben.*

After he received his medical degree in 1926, Schmidt accepted a research fellowship in the laboratory of Gustav Embden. While preparing for work on the so-called "nuclein deaminase," which was generally thought to liberate ammonia from various purine nucleosides, he selected (among various tissues) skeletal muscle for a special study. Parnas and his group had already described ammonia formation in skeletal muscle after tetanic contractions. Schmidt observed that muscle dispersions or extracts catalyzed the release of ammonia from muscle adenylic acid preparations, a phenomenon recently described by Embden and Zimmerman in early 1928; according to the physical and chemical methods they used for evaluation, the crystals were supposedly identical to the adenylic acid that Levene and his group had isolated from yeast nucleic acid by alkaline hydrolysis. A few months later, however, Schmidt was to revise this view profoundly. He found that the adenine ring in Embden's muscle adenylic

acid was rapidly deaminated by the muscle deaminase, whereas Levene's yeast adenylic acid was not at all deaminated by the muscle enzyme.

The young Gerhard Schmidt may well have had sleepless nights after these initial observations. To reinforce his new findings, he designed the following control. Since Levene's yeast adenylic acid was obtained by subjecting yeast nucleic acid to a prolonged alkaline hydrolysis, Schmidt subjected muscle adenylic acid to the same type of hydrolysis. The deaminase preparation remained equally active on the treated as well as the untreated muscle adenylic acid. Schmidt wrote: "Therefore there can be no doubt about the chemical difference of the two substances (muscle and yeast adenylic acid). This will be illustrated also by physical and chemical methods, in a subsequent report by G. Embden and G. Schmidt."[1]

These crucial enzymatic findings were published in 1928 by Schmidt alone—but with the keen interest and enthusiasm of his mentor Gustav Embden; the chemical data were published by Embden and Schmidt in 1929 in the same journal—*Zeitschrift für physiologische Chemie.* (It is interesting to note that the next yeast adenylic samples sent to Schmidt and Embden were not only sent personally by P. A. Levene but were also prepared by him.) Schmidt's article emphasized that another deaminase in muscle catalyzed the liberation of ammonia from adenosine, regardless of whether this nucleoside originated from yeast or muscle adenylic acid. Hence the position of the phosphoric acid in the adenine nucleotide was essential for the specificity of the muscle adenylic acid deaminase. Although a few specific enzymes (such as urease) had been described several years earlier, Schmidt's new finding in the case of muscle adenylic acid deaminase may be the first example

[1] G. Embden and G. Schmidt, "Berichtigung," *Zeitschrift für Physiologische Chemie*, 197:191–92. This paper corrects one of their mathematical oversights.

of the importance of conformational differences (beyond the local target groups) for enzyme specificity. This principle was to be used successfully by Gerhard Schmidt and later by other investigators for the characterization of nucleic acids and their fragments.

Because inosinic acid, the deamination product of muscle adenylic acid, had been identified by Levene as a 5′ nucleotide, muscle adenylic acid had to be considered a 5′ nucleotide. Conversely, yeast adenylic acid, which is now known to be simply an artifact of the alkaline degradation, had to be assigned a different structure—either as a 2′ or 3′ (or both) nucleotide. Although Schmidt followed further developments with active interest, from the beginning he was careful not to categorize the nucleotides (as 2′, 3′, or 5′) until further chemical and biochemical evidence became available.[2]

Schmidt's and Embden's investigations, however, were soon interrupted, as outside political events began to impinge on scientific research programs and institutions all over Germany. With the rise of Hitler and the Nazis, virulent anti-Semitism began to spread rapidly, and many German scholars and artists of Jewish extraction were forced to leave the country. At many German universities, Nazis began to infiltrate the academic community, and the persecution and harassment of Jewish scholars in the sciences and the humanities began to accelerate. This was certainly the case at the University of Frankfurt where Gustav Embden and Gerhard Schmidt were pursuing their important research. Finally, in 1933, during one of the frequent clashes of Nazi stormtroopers and their opponents in the streets near the university, a

[2] Soon after Schmidt's discovery of muscle adenylic acid, Fiske, Subarrow, and Lohmann described ATP and ADP. These pyrophosphate derivatives of muscle adenylic acid were not direct substrates for the deaminase. However, the latter enzyme became a crucial tool for this author in the description in 1942 of adenylate kinase (myokinase), the enzyme responsible for the reversible formation of 5′ adenylic acid and ATP from two molecules of ADP.

uniformed stormtrooper was killed. The man arrested for the act, allegedly a "communist," was tried before a tribunal that in its verdicts usually favored the Nazi cause. But the verdict on this occasion was "not guilty" because the coroner's report from the pathology department stated that the victim had been shot in the chest and not in the back, as claimed by the Nazis. (Their story had been that the victim was fleeing and was then shot; instead, the pathology report indicated active aggression.)

The Nazis confronted the chairman of the pathology department, Dr. Fischer-Wasels, and accused the young "Jewish doctor" Gerhard Schmidt of falsifying the findings of the autopsy. Since Gerhard was engaged exclusively in medical research and had no responsibility whatsoever for autopsies, Fischer-Wasels immediately suspected a plot and with deep sorrow urged Schmidt to leave Nazi Germany. At first, Gerhard found the accusations too absurd to be alarmed. But finally, when Fischer-Wasels insisted on accompanying him to the next train for Switzerland, Gerhard became convinced of the imminent danger of the conspiracy. With only a few belongings (perhaps including his beloved cello), he left Germany for neutral Switzerland. (Fischer-Wasels, a conscientious scholar and administrator who abhorred anti-Semitism, is said to have rescued other Jewish medical scholars; apparently, however, Gustav Embden was not one of them. Embden's early death in Frankfurt, after he was forced out of his department by the Nazis at the height of one of his most creative scientific periods, remains a riddle.) Gerhard always felt grateful for Fischer-Wasels's resolute and courageous action, and American scientists as well have the old chief to thank for preserving Schmidt's research and teaching abilities for the scholars—both old and young—of this nation.

Schmidt's flight from Germany marked the beginning of years of displacement, a period that saw him moving among

appointments at universities in Italy, Sweden, and Canada. As a refugee, Gerhard Schmidt preserved his enthusiasm for the study of phosphorus compounds and for the enzymology of the bases of nucleic acids. He and his last pupil in Frankfurt, Ernest Bueding, had been studying guanase, a deaminase of the base guanine that they found to be abundant in the spleen and liver. As a guest researcher in the institute of Hans von Euler in Stockholm from 1933 to 1934, Schmidt was encouraged to continue his studies on guanase in rat livers from normal animals and from rats deficient in vitamin A. On von Euler's suggestion, Schmidt and his coworker I. Rydh-Ehrensvärd investigated the effect of carotenes on guanase levels in the spleens of vitamin A-deficient rats; they found that administration of β-carotene brought about a doubling of the guanase levels. During 1934, Schmidt was able to publish some other results from his research, such as the isolation of a dipeptide phosphoric acid and a study of purine bases in nonfertilized sea urchin eggs. These topics seem to be related to the work of another prominent Stockholm biochemist, Einar Hammarsten, but it is not known whether the two researchers met during Schmidt's sojourn in Stockholm.

In 1934 Schmidt moved to join Pontimalli in the Department of General Pathology at the University of Florence. With tumor research his main focus during this stay, Schmidt's interest in phosphoproteins was greatly stimulated. In the studies he conducted, his findings indicated that chickens carrying Rous sarcoma released phosphoproteins to the blood plasma. In addition, the phosphoprotein fractions were subject to partition.

In 1935 Schmidt obtained a Carnegie Foundation research fellowship for displaced German scholars. With it came his first chance to visit the Western Hemisphere, where he was invited to set up his own research program in the

Chemistry Department of Queens University in Ontario, Canada. There, in 1936, Schmidt initiated his first systematic studies of nucleic acids and nucleohistone, topics to which he would return later in his research career. For the biochemical resolution, he chose a partly purified alkaline phosphatase preparation from calf intestine. Free nucleic acid incubated with this enzyme released the main part of the phosphorus of the nucleic acid; in contrast, upon enzymic incubation, nucleohistone released only 20 percent of its phosphorus, presumably from the fraction corresponding to the free nucleic acid. If, however, the nucleohistone was preincubated with pancreas extract and then incubated with phosphatase, all the phosphorus was released as inorganic phosphate. Purified trypsin had no effect on nucleohistone.

Schmidt published his findings in 1936, two years before he joined P. A. Levene's laboratory in New York. An additional study (in 1937) on the growth of chicken embryos, and the dependence of growth on egg white (even in rather high dilutions) and on glucose, testifies to Schmidt's interest in general biology. As one of his conclusions, he states that development is resumed after substitution of the inorganic salt solution with egg white.

Schmidt's 1936 studies of and interest in nucleohistone prompted him to apply to P. A. Levene at the Rockefeller Institute for Medical Research in New York. As mentioned earlier, Levene had provided valuable assistance while Schmidt was still in Embden's laboratory in Germany by sending him pure yeast nucleic acid adenylate as a reference compound to muscle adenylic acid. At the time of Schmidt's application, Levene was studying stepwise depolymerization of pure yeast nucleic acid by means of enzymes. Schmidt's exercise of 1936 in this field had already made him familiar with the literature and also with many of the techniques needed for this work. Thus, in 1937, Schmidt left Queens

University and joined Levene as an assistant in the Research Laboratory of Chemistry of the Rockefeller Institute.

Schmidt and Levene first reinvestigated the action of a thermostable pancreatic enzyme preparation capable of depolymerizing yeast nucleic acid. They fully confirmed previous reports of this phenomenon by W. Jones as well as by R. J. Dubos. The heat-stable pancreas enzyme preparation did in fact catalyze a gradual depolymerization of yeast nucleic acid, yielding fractions that were still unable to pass through a cellophane membrane. They termed the digestion product "tetranucleotides of high molecular weight." During this period, Levene held the firm belief that nucleic acids were polymers of tetranucleotides, containing the four different bases (two purines, two pyrimidines).

Another of their joint papers included E. G. Pickels, one of the leading experts in ultracentrifugation techniques and the interpretation of such data. It is in this context and at this point that Einar Hammarsten and his school in Stockholm became standard references. According to Schmidt and his coworkers, the only nucleic acid preparations (from thymus gland and fish sperm) in connection with proteins (histone and protamine, respectively) that they considered "naive" or "genuine" nucleic acids (more specifically, deoxyribonucleic acids) were the nucleic acid preparations from the Hammarsten group. They quote the Stockholm group's assessment of the molecular weight of the native nucleic acid (the term DNA was not in use at that time) as of the order of 10^6. Schmidt, Pickels, and Levene also assessed the so-called Neuman preparation—termed the "a" form of nucleic acid—and determined that it had a molecular weight of 2×10^5 to 10^6. Finally, they confirmed R. Feulgen's suggestion that the enzymatic conversion of the "a" form to the "b" form is a depolymerization.

The year Schmidt spent in Levene's laboratory was prob-

ably profitable in several respects. However, Levene's conclusion that the so-called tetranucleotide was the basis for nucleic acid structure gradually came to have less validity for Schmidt, and in later years he discreetly dismissed it.

In 1938 Schmidt received an invitation to join Carl Cori, professor of pharmacology at Washington University School of Medicine in St. Louis. Carl and Gerty Cori by that time had discovered α-glucose-1-phosphate and the enzyme glycogen phosphorylase, and they felt they were at the beginning of an exciting scientific development. Carl Cori had visited Gustav Embden in his laboratory before 1933 and had admired his work and that of his associates, including Gerhard Schmidt. So Schmidt went to St. Louis, and the year 1939–1940, which he spent in the Cori laboratory, must have reminded him of the exciting years with Embden. During the year Schmidt was fortunate enough to work with Carl as well as Gerty Cori, and also with a gifted young doctoral student, Sidney Colowick.

In St. Louis Schmidt became involved in studies of the enzymatic fission of glycogen by muscle phosphorylase, as well as the enzymatic resynthesis of polysaccharides. The Coris had found that muscle adenylic acid was needed for the enzymatic action of muscle phosphorylase. Schmidt was familiar with several purification techniques, some of which he had used in 1928 for the fractionation of muscle adenylic deaminase; the deaminase was used for the determination of adenylic acid. (The adenylic acid used for the work in the Cori laboratory was a gift from Pawel Ostern, the Polish researcher, shortly before his death during the Nazi attack on Poland in 1939.) The role of muscle adenylic acid (5′ AMP) in the phosphorolytic splitting of glycogen remained a puzzling problem, however, because it was not consumed in the enzyme-catalyzed phosphorolysis.

In 1939 Walter Kiessling, one of Meyerhof's former as-

sociates who had remained in Heidelberg, briefly reported that glucose-1-phosphate added to a crude yeast enzyme fraction was converted to glycogen. The Coris and Schmidt were puzzled that their muscle enzyme fraction, which was incubated with glucose-1-phosphate (and the other ingredients needed for the phosphorylase), did not catalyze any detectable amounts of glycogen. Among Schmidt's incubates was one that he had absentmindedly left at room temperature overnight. It was included among those being studied for glycogen, and it was found that only this sample gave an iodine color for the presence of polysaccharides—and it was blue-red. To Schmidt and the Coris, this was exciting news indeed, not merely because they had finally succeeded but because of the aberrant way in which the polysaccharide biosynthesis ensued. In addition, Carl Cori strongly suspected that primer formation was at work as a precursor step before the polysaccharide biosynthesis could take place, an idea that was instrumental in the success of their later work. It was an exciting year!

Despite these successes, Gerhard Schmidt was still in search of a permanent scientific home, and in the spring of 1940 he found one at the Tufts University Medical Center. S. J. Thannhauser, head of the Boston Dispensary of the Tufts Medical School, asked Schmidt to set up a section on basic biochemical research. Thannhauser had been a well-known clinician in internal medicine in Freiburg, specializing in the diagnosis and treatment of metabolic disorders. In 1939, a few months before the outbreak of World War II, he escaped from Germany and arrived in Boston. The director of the university hospital medical center, Joseph Pratt, had invited several German-Jewish refugee scholars involved in medical research or in internal medicine to the medical center. Thannhauser was among them; interested in securing a

first-rate researcher in biochemistry for his unit, he in turn approached Schmidt, who agreed to come to Tufts.

Considering Thannhauser's policies as laboratory chief, he was indeed fortunate to persuade Gerhard Schmidt to join his staff. Every publication from the laboratory carried Thannhauser's name, although he was listed as primary author only if he was actively engaged in the lab work as well. Schmidt agreed to this dictum, and for eighteen years the Thannhauser name appeared on every Schmidt publication.[3] Schmidt may not have been particularly pleased with the persistence of this policy, but he was too busy with research and teaching to spend any time challenging the rule.

Be that as it may, Thannhauser brought Schmidt to the Tufts Medical Center and helped him get started on his research, probably with several grants-in-aid. It is also likely that Thannhauser introduced Schmidt to the field of lipid biochemistry, or at the least encouraged experimental work by Schmidt in this field.

During his almost forty years of research at the Tufts Medical Center, Gerhard Schmidt chiefly explored two broad biochemical fields, both dealing with phosphorus compounds: nucleic acids and phospholipids. He addressed himself to both disciplines during his early years at Tufts, as well as during his later years. The succeeding paragraphs will deal first with his work on nucleic acids, a field he had already cultivated when he arrived in this hemisphere.

[3] This author may occasionally have guessed who led in programming the diverse pieces of research. I am assuming that a few publications that carried Thannhauser's name first must have been initiated and largely carried out by him; since the bibliographies in these memoirs do not make that clear, however, I will try to indicate this in the text. In any case, Schmidt was in his late fifties and well into his more embracing and distinguished tenure as a full professor before he had the opportunity to publish and present his name in a style that clearly indicated who was in charge of the research program. Although his colleagues knew, the next generation of scholars may need some orientation.

Gerhard Schmidt had an unusual ability to develop sturdy analytical methods for quantitative determinations of some of the main constituents of the cell, especially the phosphorus compounds. By 1945 the need for quantitative methods of investigating the nucleic acids had intensified to a point that called for skilled action. Schmidt's familiarity with pentose color reactions from his work on purine nucleotides was not of help for the new task; as he himself emphasized, pyrimidine nucleotides are too acid resistant—in terms of releasing pentose—and deoxyribose is destroyed during the protracted acid hydrolysis needed for release. Schmidt therefore designed a new method for nucleic acid analysis around the determination of phosphorus. The use of dilute alkali brought about the most useful resolution. If tissue extracts (as tissue powder free of lipids) are dissolved in dilute KOH-(1 N) and incubated at 37°C for 20 to 24 hours, a clear solution is usually obtained. A small aliquot of this solution can be used to determine total phosphorus. On the addition of excess trichloroacetic acid (TCA), fortified with 0.2 volume of 6 N HCl, precipitation of the DNA occurs. DNA that lacks the hydroxyl group in the "2" position possesses alkaline-stable diester bonds and remains in the macromolecular, acid-insoluble state; whereas RNA containing hydroxyl groups in the "2" as well as the "3" position is alkaline labile and hydrolyzes to soluble ribonucleotides.

The characteristics of this alkali lability and the mode of action of various nucleases were later explored by Schmidt and others. Schmidt's strategy for the analyses was as follows. The clear filtrate (by now, acid) contained a mixture of inorganic phosphate from the alkaline-labile phosphoserine ester bonds, and purine and pyrimidine nucleotides. The latter were determined as total P (ashing procedure). The total macromolecular phosphorus in the precipitate that appeared following acidification of the alkaline digest represents DNA.

Schmidt described these important methods once more in Colowick and Kaplan's *Methods in Enzymology* (vol. III), which also contains several of Schmidt's enzymatic methods.

During 1946 and 1947, Schmidt returned to one of his favorite fields: the use of specific enzymes to explore nucleotide and especially polynucleotide structure. As mentioned earlier, the tetranucleotide concept was not based on sturdy analyses, yet nobody had produced convincing evidence against the tetranucleotide model. The use of ribonuclease was very much on Schmidt's mind, especially since the Kunitz crystalline ribonuclease had become available. In masterly symposium articles published in 1947 and 1951, Schmidt summarized his experience with the enzymatic degradation of yeast ribonucleic acid and the characterization of its products and pointed out the few options available to obtain new insight. Earlier investigators had used crystalline ribonuclease together with various phosphatase preparations in excess, but they were unable to characterize the products. Schmidt and his coworkers decided on a somewhat different strategy. Yeast ribonucleic acid was first treated with crystalline ribonuclease, which they prepared themselves; but this procedure did not release any inorganic phosphate. Subsequently, a powerful "acid phosphatase" prepared from human prostates (delivered from the Department of Surgery of Massachusetts General Hospital) was successfully employed. Schmidt, however, warned against using an excess of the crude prostate phosphatase because it contained traces of ribonuclease activity. Addition of dilute prostate phosphatase preparations brought about a release of approximately 25 percent of the organic phosphate of the ribonucleate preparation.

But what type of 2′ or 3′ nucleotides released by ribonuclease corresponded to the 25 percent fraction that was so readily dephosphorylated through the action of prostate

phosphatase? Acid hydrolysis in 1 N sulfuric acid at 100°C revealed that they were not the acid-labile type of purine-2′ or -3′ nucleotides; the fraction released by ribonuclease showed an acid hydrolysis curve characteristic of pyrimidine nucleotides. Apparently, ribonuclease had released a mixture of pyrimidine mononucleotides, and the remaining polynucleotides contained all the purines. In addition, other investigators—especially H. S. Loring—had arrived at similar conclusions using different techniques. These results spelled the end of the era of the tetranucleotide hypothesis and paved the way for concepts that could be emancipated from the earlier symmetry model.

Also in 1946, Schmidt and coworkers studying phosphate uptake in bakers yeast and the accumulation of phosphoric esters found an acid-hydrolyzable fraction that was precipitable with barium acetate. (This fraction was particularly conspicuous if the yeast cells had been starved for phosphate prior to its addition.) The accumulated phosphoric ester was identified as metaphosphate in a paper Schmidt et al. prepared reporting their work. Independently, Wiame in Belgium observed metachromatic staining in yeast cells that were subjected to the same physiological conditions (see the review of this research by Gerhard Schmidt in 1951). Schmidt and his coworkers soon found that the uptake of phosphate into yeast (previously starved for phosphorus) and its subsequent accumulation as metaphosphate require the presence of potassium ions. In addition, they discovered that potassium and magnesium ions are cotransported in preference to any other cations (see Schmidt, Hecht, and Thannhauser, 1949). The accumulation as well as the turnover of the metaphosphate fraction were also found to be enhanced by the addition of nitrogen sources to the medium, a response reminiscent of that of RNA-P.

In other research, published by Schmidt and coworkers

in 1951, periodate oxidation was used as a tool for stepwise degradation of ribonucleic acids and oligonucleotides released after digestion of RNA with pancreas ribonuclease. J. M. Gulland and W. E. Cohn had shown that certain nucleases can release 5′ adenylic acid from RNA digests. The labilization of the 5′ phosphoric ester bond of ribonucleotides by periodate oxidation of the 2′ and 3′ hydroxyl groups (to aldehyde groups) was used. In the process, the amine forms a complex with the oxidized oligonucleotide. Schmidt emphasized that the conditions used are relatively mild; yet prolonged exposure to pH 9 for 90 minutes at 45°C—the step needed to release the base—may gradually bring about alterations in the macromolecule. He therefore recommended that this preliminary method rather be used on oligonucleotides not exceeding 8 to 10 units.

It appears that this early edition of purine-pyrimidine sequencing was not further pursued by Schmidt. The "revolution" in nucleic acid biochemistry had begun, and Schmidt followed these developments with admiration. They became an important part of his teaching, however, rather than his research. When he returned later to the nucleic acid field, he revived his early interest in thymus nucleohistone.

In a 1972 study of the amount of binding of divalent ions —Ca^{++} and Mg^{++}—to the phosphoric ester groups of thymus nucleohistones, Schmidt et al. identified the following features. Thymus nucleohistone (ThyNuHi) binds Mg^{++} in up to 50 percent of its phosphoric (P) groups. This corresponds to the capacity to bind toluidine blue. Accordingly, only half of the DNA phosphoric groups of ThyNuHi can be bound to the cation groups of its histone components. ThyNuHi is hydrolyzed slowly by crystalline pancreas DNAase (deoxyribonuclease I), which is much slower than DNA. The remaining macromolecular residue containing the histone does not bind Mg^{++}, and DNAase is unable to

catalyze further splitting. The molecular weight of the resistant residues was determined by Clark and Felsenfeld (1971) and found to be approximately 100,000. Clark and Felsenfeld, as well as Schmidt et al., suggested that the DNA-bound histone might occur as discrete clusters (of similar chain length), alternating with histone-free segments along the DNA chain; only the histone-free segments can bind divalent ions and are susceptible to DNAase, releasing acid-soluble oligonucleotides.

Schmidt, however, found it wise to express some caution concerning interpretations of their findings. He emphasized that the amount of DNA digested was to some extent a function of the amount of DNAase used; large excesses of DNAase after longtime incubation will split nearly 100 percent of the nucleohistone. This reservation, however, was not meant to belittle the potential importance of their findings and those of Clark and Felsenfeld. Because the opus by Schmidt et al. contained fragments that were to be used in a Ph.D. thesis, Schmidt felt that self-criticism was well justified.

The other broad biochemical field of particular interest to Schmidt was phospholipids. Schmidt's interest in lipid research was undoubtedly influenced by Thannhauser; together they produced a number of papers describing observations that in turn stimulated other researchers in the field. Much of their work was done before the introduction of modern chromatographic procedures. To circumvent this limitation, Schmidt tried to devise a scheme by which the partition of lipid phosphorus would provide separate determinations of the sphingomyelin, plasmalogen phosphoglycerides, and diacyl phosphoglycerides in tissue samples of moderate sizes. The total lipid extract was saponified under mild alkaline conditions that deacylated phosphoglycerides. The phosphorus of the aqueous extract represented diacyl glycerophosphatides (containing nitrogenous constituents

like choline, ethanolamine, or serine). Schmidt found it noteworthy that the plasmalogens remained in the nonsaponifiable fraction. He, however, was able to obtain water-soluble phosphorus by a brief treatment with mercuric chloride. He soon realized that saponification as well as hydrolysis of this product with $HgCl_2$ were needed to obtain water-soluble plasmalogen phosphorus.

Schmidt therefore proposed that native plasmalogen contained an additional lipid chain that was removed by saponification. This structural problem was solved several years later by Maurice Rapport. Rapport discovered the existence of an ($\alpha\beta$)-unsaturated ether that on acid hydrolysis gave rise to an aldehyde, thus showing that the acetal structure originally proposed by Feulgen is not the native structure. It is probably needless to state that Schmidt followed Rapport's elegant work with delight.

As a result of these investigations, some structural work, mainly led by Thannhauser, had to be revised, such as the report that the sulfate in cerebroside sulfate was attached to the C_6 of the galactose moiety. Later work by T. Yamakawa established that the sulfate was actually attached to the C_3 carbon.

In a 1970 paper, Schmidt, together with E. L. Hogan and K. C. Joseph, described his studies of the composition of cerebral lipids in murine sudanophilic leucodystrophy. The research involved measurement of the cerebrosides and sphingolipids in brains of mice with genetically determined disorders of myelination. In normal myelination during development, sphingolipids and cerebrosides increase by a factor of approximately four; phospholipids increase twofold. "Jimpy mutants," a mouse mutant described by R. Sidman, have defective myelination in the central nervous system. In these mice, cerebrosides are highly defective, and sphingolipids are also lowered; phospholipid composition remains

unaltered. In 30-day-old jimpy mice with seizures, the cerebrosides were almost totally lost (only 5 to 10 percent were left); sphingolipids were below 20 percent; and only phospholipids were preserved.

At the time of development when myelination is most active, the leucodystrophic mice mutants showed increased levels of cerebrosides in the brain. The ensuing relative deficit points against a defect in the biosynthesis of cerebrosides. The quaking mouse mutants, a less fulminant form, showed a more moderate loss of cerebrosides.

In addition to his research responsibilities, Schmidt taught at the Tufts Medical School, and this duty he not only fulfilled but greatly treasured. His lectures for first-year medical school biochemistry students covered structural macromolecules, preferably proteins and nucleic acids. At least, this was the case during the middle 1960s, according to Schmidt's son Milton, who attended his father's lectures at that time. According to Milton Schmidt, the lectures were ". . . exquisitely lucid and logical. Details were present . . . as a way of getting across a point. In spite of logic and clarity, he was never dry or dull. As in his cello-playing, he was truly rhapsodic when he lectured, conveying intense enthusiasm to everyone."

Gerhard's devotion to music was a very important feature of his personality and certainly deserves mention here. His approach to art centered on music, a choice that had probably been influenced by his mother, Isabella Schmidt (née Gombrich), who was a talented pianist and teacher. (When only in her late teens, she went to Berlin and was invited as a pianist to the rehearsals of the preeminent Joachim string ensemble; the late Dr. Ernest Bueding, a colleague of Gerhard's and an active viola player himself, praised Frau Isabella's perceptive and brilliant piano playing in chamber music.)

Gerhard played his cello with gusto, especially in chamber music; the great works of Mozart, Beethoven, and Schubert were perhaps closest to his heart. What inspired him in music was not only beauty but strength and originality. I shall never forget when I received a special gift from him, a record of one of Schubert's most demanding and magnificent string quartets (the great G major), which is only very rarely played in concert halls. Gerhard had told me about its special "texture," exemplifying Schubert's genius at its greatest. He was pleased to know how deeply my wife and I appreciated his gift.

Gerhard enjoyed great popularity among young as well as older colleagues. His warm humor shone through, especially in his happy family circle[4] but also among his friends. He could and often did make fun of his own absentmindedness. In his youth he enjoyed the German humorist Wilhelm Busch, and he could still cite long passages from Busch's work in his later years. He of course found and enjoyed many humorists in this country, even those bordering on slapstick; many of us recall Gerhard's laughter over Laurel and Hardy.

In later years, Gerhard Schmidt remained as active in the lab as in his earlier career. He arrived early and stayed late in the evening, regardless of snowstorms and lack of public transportation. As one of his former students, Dr. Peter Cashions, puts it: "I can't recall a day in five years that he missed, excluding vacations and meetings. I recall once when during a blizzard all traffic was stopped—he apparently nonchalantly walked home to his apartment along the Fenway and Mission Hill—some of the toughest districts of the city. . . . His typical workday had the serene, unhurried ca-

[4] Gerhard Schmidt was married in 1940 to Edith Straus-Horkheimer. They had two sons: Michael, who is a social worker in a psychiatric hospital in New York City, and Milton, a psychiatrist in the Boston area. Schmidt greatly enjoyed his family life, which in later years included two grandchildren.

dence that might be associated with, or more akin to, the pressure of a glacier rather than the frenetic state of agitation, more often linked to high achievers. A particularly good example of this was when he'd go out and buy a 10-pound lobster, dissect out one of the nerves from which he'd extract sphingomyelin. Then he would melt down a pound of butter, boil the rest of the lobster, and everyone would have a feast at about 8 p.m. in the lab."

In the lab, Schmidt insisted on doing practically everything with his own hands, and when his modest dexterity began slipping during his later years, former students recall many an evening loaded with a highly charged atmosphere. He was not always able to convey to his students in the lab his frustrations with his own manual mistakes. Sometimes after a number of attempts at a particular technique, the frowning professor would be breathing heavily; but he might still be unable to convey to a student when the instrument would be available. Arguments with him about lab procedures were spare and laconic, however, since Schmidt, a veteran of many bold lab experiments, did not think that anybody else's advice was warranted.

Some of this tension during Gerhard Schmidt's last years in the lab may have been related to a particularly intense and important project that he discussed with me. This project, which involved a return to the study of thymus nucleohistones, was very close to his heart. And although the study was never completed to his own satisfaction, Schmidt's energy and enthusiasm persisted to the last.

Gerhard Schmidt was a member of several scientific societies including the American Society of Biological Chemists, Canadian Physiological Society, New York Academy of Sciences, American Chemical Society, and American Association for the Advancement of Science. Among the honorary societies that elected him as a member were Sigma Xi, the Amer-

ican Academy of Arts and Sciences, and the National Academy of Sciences. There have also been posthumous honors as well. Volume 100 of Colowick and Kaplan's *Methods in Enzymology* is dedicated to the memory of Gerhard Schmidt as a scholar and artist; it includes a photograph of him playing his beloved cello and a charming little dedication by Sidney Colowick and Nathan Kaplan. In 1981, the president of Tufts University established an annual Gerhard Schmidt lectureship commemorating Schmidt's long and distinguished service to the Tufts University School of Medicine. Four distinguished lectures thus far have been delivered at Tufts University Medical School in Boston.

IN PREPARING this biographical memoir, my thanks are due to many friends of the late Gerhard Schmidt. At the Tufts University Medical School, Drs. R. L. Kisliuk and H. Mautner rendered much help. Regarding Gerhard's terminal year at the University of Frankfurt, the late Dr. Ernest Bueding of Johns Hopkins University provided important information. In trying to formulate the section on lipid research, my thanks are due to Drs. George Hauser, Harvard Medical School; Norman Radin, University of Michigan; and M. M. Rapport, New York State Psychiatric Institute. Concerning such aspects of his life as teaching and lab work with students, I am grateful to Drs. Milton Schmidt of Boston and Peter Cashions of the biology department of the University of New Brunswick. The late Dr. Sidney P. Colowick of Vanderbilt University gave me particularly valuable encouragement, criticism, and stimulation in general in my efforts to formulate the memoir. And finally, special thanks are due Mrs. Edith Schmidt for her help and advice, and for her generous encouragement as well.

ACADEMIC HISTORY

1919–1922	Student of Medicine, University of Tübingen, Germany
1922–1924	Student of Medicine, University of Frankfurt, Frankfurt am Main, Germany (State Board)
1924–1925	Intern in Medicine, Municipal Hospital, Stuttgart, Germany
1925	Intern in Medicine, University Hospital, Frankfurt
1925–1926	Graduate Student in Medicine, University of Frankfurt
1926	M.D. Degree Awarded (Thesis in Biochemistry; Supervisor: Professor G. Embden)
1926–1929	Postgraduate Research Fellow, Department of Biochemistry, University of Frankfurt
1929–1931	Assistant and Director of Biochemical Research Laboratory, Department of Pathology, University of Frankfurt
1931–1933	Instructor (*Privatdozent*) in Pathological Chemistry, Department of Pathology, Faculty of Medicine, University of Frankfurt
1933	Dismissed on April 1 by the Hitler government because of "Jewish race"
1933	Research Biochemist, Marine Biological Laboratories, Naples, Italy; Department of Biochemistry, University of Naples (April through September)
1933–1934	Research Fellow, Department of Biochemistry, University of Stockholm, Sweden
1934–1935	Research Fellow, Department of General Pathology, University of Florence, Italy
1935–1937	Carnegie Foundation Research Fellowship for Displaced German Scholars, Department of Chemistry, Queens University, Kingston, Ontario, Canada
1937–1938	Assistant, Research Laboratory of Chemistry, Rockefeller Institute for Medical Research
1938–1940	Research Fellow, Department of Pharmacology, Washington University School of Medicine, St. Louis, Missouri

1940–1948	Research Associate, Thannhauser Research Laboratory, Boston Dispensary, Tufts University School of Medicine
1948–1955	Research Professor of Biochemistry, Department of Biochemistry, Tufts University School of Medicine
1955–1972	Professor of Biochemistry, Department of Biochemistry, Tufts University School of Medicine
1972–1981	Professor Emeritus of Biochemistry and Research Biochemist, Department of Biochemistry and Pharmacology, Tufts University School of Medicine

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