MELVILLE SAHYUN: A LIFE IN BIOCHEMISTRY

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Stoutness of heart, humility of soul and open-mindedness are the
Keys to human understanding and happiness;
No one endowed with these virtues can be but honest,
Just and tolerant to his neighbor and himself.
—Melville Sahyun

Abstract

The career of Melville Sahyun comprised three major parts. In the first part he was engaged in diabetes research. In this period his most important contribution was the development of an industrial-scale process for the preparation of a purified insulin solution of standardized potency for clinical application that was based on his studies of insulin crystallization. He then turned to the biochemistry of amino acids and proteins. His major technical contribution in this area was the development of an amino acid supplement solution for intravenous or parenteral administration. In this period he also edited two important monographs on proteins and amino acids. The final phase of his career was devoted to drug discovery. The most noteworthy accomplishment in this period was the invention of the anti-inflammatory molecule tetrahydrozoline, which was formulated for ophthalmic use as Visine™ eye drops.

Introduction

Melville Sahyun (Figure 1) was born in 1895 in Kfarshima, Lebanon, the son of a prominent Beirut physician, Dr. Fares Sahyoun. He graduated (B.A., biology) from the American University of Beirut (AUB), planning to follow in his father's footsteps into a career as a practicing physician. However, he abandoned these career plans in favor of a career in biochemical research. The mantle of medical practice was taken up by his younger brother, Philippe Sahyoun, who ultimately became a distinguished Professor of Pathology at AUB (1). (Note that Melville preferred the Anglophone spelling of his originally Arabic surname, while Philippe opted for the Francophone spelling).

After having served, by his own account (in his personal diary), with British Intelligence in Cairo during World War I, Melville Sahyun emigrated to the United States in 1923. He then began his scientific career, which can be divided into three parts or phases:

1) Diabetes research. This subject had great personal significance for Sahyun, as *diabetes mellitus* (Type 2) was endemic in his family.

2) Proteins and amino acids in nutrition. He was drawn into this area of research by the exigencies of World War II, and became a world recognized expert.

3) Drug discovery. He directed the final phase of his career as the head of his own private research organization, Sahyun Laboratories, in Santa Barbara, California.

This purpose of this article is to review his accomplishments in each of these phases of his career, in turn, and place them in the context of the science of the day.

Figure 1. *Melville Sahyun in the 1930s, at the time he was particularly active in diabetes research. (Author's collection)*

Diabetes Research

Diabetes research in the 1920s and 1930s focused primarily on the chemistry of insulin, following its isolation and the discovery of its therapeutic value by Frederick Banting and Charles Best in the laboratory of Prof. J. J. R. Macleod in Toronto (2). Sahyun's first position in which he could carry out diabetes research was at the Potter Metabolic Clinic of Santa Barbara Cottage Hospital, then headed by Dr. William D. Sansum. This institution subsequently evolved into the Sansum Diabetes Research Institute, as has been documented by Tompkins (3). There Sahyun had the good fortune to collaborate with Dr. Norman R. Blatherwick, Sansum's chief chemist (3).

At the time, insulin was obtained by laborious extraction from the pancreases of slaughtered mammals, usually cattle or hogs, without controls on potency. The response of the blood glucose level in rabbits to a given preparation was used as a method to standardize the dosage of insulin. The problem with this method was that different rabbits responded differently. Sahyun and Blatherwick (4) proposed a method of "calibrating" rabbits used for this standardization by measuring the individual rabbit's response to a reference insulin preparation. In the course of this work they observed that rabbits repeatedly dosed with insulin developed insulin resistance. Their data showed, though the significance of the correlation was not noted at the time, that development of insulin resistance was also associated with weight gain. In this experiment the same rabbits were repeatedly dosed with insulin over a nine-month period, each time with a dose of insulin, *I* (arb. units), just insufficient to produce convulsions. Insulin resistance was demonstrated by the monotonically progressive increase in the required dose; the increase in dosage was reflected in the concomitant weight gain of the rabbits up to a maximum. Their data for two representative rabbits are shown as a semi-logarithmic plot in Figure 2. This observation seems to have anticipated the contemporary understanding of the relationship between weight gain and insulin resistance in humans (5).

A subsequent series of papers (6) continued characterization of the physiological response of rabbits to insulin and established the rabbit as the animal model of choice for pre-clinical evaluation of diabetes therapies. In this work they showed that intraperitoneal, subcutaneous and intravenous administration of insulin were all effective in producing hypoglycemia. Insulin, being a protein. is degraded in the alimentary canal prior to absorption and therefore could not be administered orally, according to the thinking of the day. Although there was the suggestion of an orally active "insulin" even in Dr. Sansum's day (7), an "oral insulin" still remains an elusive target for the pharmaceutical industry.

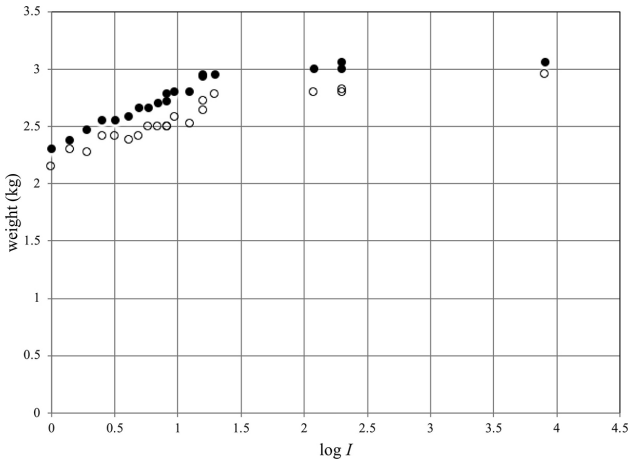
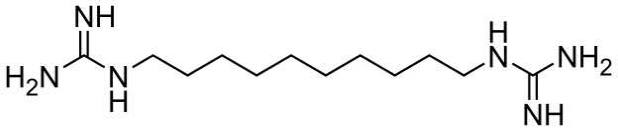


Figure 2. *Weight gain of two rabbits (kg) with increasing insulin resistance, as log I (4).*

Blatherwick and co-workers (8) proposed a standard method for the preparation, isolation and purification of insulin. The potency of their preparation was over twice that reported by Best in Toronto (9). The comparison of methods is offered by H. F. Jensen in his monograph from 1938 (10). By studying the response of their usual preparation to various reagents, Blatherwick et al. concluded that the hormone insulin comprised only a fraction of the material despite its high potency, i.e., despite rigorous purification the best insulin of the day was grossly impure.

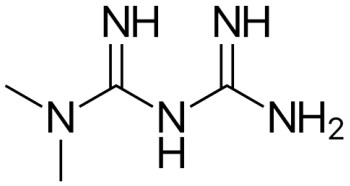
This, of course, is no longer the case, as high potency, high purity insulin (human insulin analog) is now prepared biosynthetically. This biosynthetic insulin, available since 1982, is manufactured using a microbial process based on recombinant DNA technology, in which *E. coli* bacteria have been modified to synthesize insulin identical to the human hormone. As of 2013 this process accounts for the entire US production (11). Some insulin continues to be manufactured abroad by the Sahyun process (see below) or a variant thereof.

Blatherwick, Bischoff, Sahyun, and Hill compared the action of "synthalin" (I) to that of insulin (12, 13). Synthalin was one of the first oral anti-diabetic drugs to be commercialized.



I

Discovered in 1926 synthalin was marketed in Europe by Schering AG of Berlin as "… a synthetic drug with insulin-like properties that could be taken orally" [Author's translation] (14). It was based on the discovery that a guanidine derivative was responsible for the hypoglycemic activity of extracts of French lilac, used since medieval times to treat *diabetes mellitus* (15). Synthalin was never clinically successful owing to its extreme side effects, reviewed by Bischoff, Sahyun and Long (16). The now commonly used drug for treatment of Type 2 diabetes, Metformin (II), is the lineal descendant of this this line of investigation, as described below (17).



II

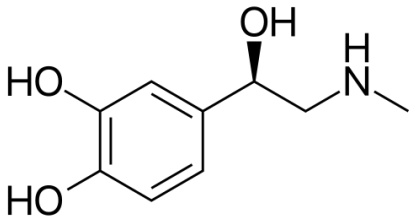
Blatherwick et al. (12, 13) concluded that, in part, the activity of synthalin involved interference with gluconeogenesis (also termed "glycogenolysis," i.e., hydrolysis of glycogen) in the liver. That hydrolysis of glycogen in the liver is a principal source of blood sugar, and thus intimately connected to the etiology of diabetes, had been known since 1857 (18, 19). This understanding laid the basis for the subsequent use of biguanides (now known as AMPK activators (20)), e.g., Metformin, in the treatment of Type 2 diabetes, characterized by excess production of glucose by the liver. Recent research has provided data to support investigation of biguanides for antineoplastic activity (cancer therapy) (21).

The understanding of the mechanism of action of biguanides likewise implied the ineffectiveness of AMPK activators for treatment of Type 1 diabetes, characterized by insufficient insulin production in the pancreas. The distinction between Type 1 and Type 2 was, of course, unrecognized in the 1920s, not being established until 1959 (22). As early as the 1920s, h owever, two separate theories had been advanced to explain the symptoms of *diabetes mellitus*: (1) loss of the capacity of peripheral tissue to metabolize glucose; and (2) overproduction of glucose by glycogenolysis (10). These theories, of course, correspond more-or-less to Type 1 and Type 2 diabetes. Glycogenolysis was later to become the focus for Sahyun's Ph.D. work.

Bischoff, Sahyun and Long (16) further compared the hypoglycemic activity of a variety of guanidine derivatives. These authors concluded that guanylpiperidine, though not clinically useful itself, provided a promising direction for future drug development. The focus on correlating chemical structure with physiological activity in this work presaged Sahyun's future interest in drug discovery and development. More recently, derivatives of guanylpiperidine have shown promise as peptidomimetics for the prevention and treatment of thrombosis (23).

In 1928 Prof. John Macleod, in whose laboratory Banting and Best had first prepared insulin, visited the Potter Clinic and encouraged Sahyun to pursue a Ph.D. in biochemistry rather than the M.D., which had been his

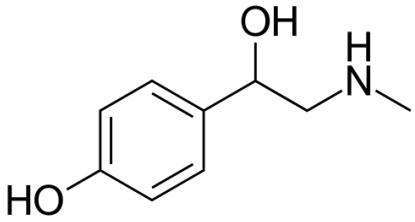
original career goal, and which, according to Tompkins he was still considering (3). Sahyun accordingly applied to and enrolled at Stanford University. In his M.A. thesis work under the direction of Prof. Luck in the Department of Food Science, Sahyun studied the effect of epinephrine (adrenalin, III) on the biochemistry of glycogen in rabbits (24).



III

This work was actually begun at the Potter Metabolic Clinic in Santa Barbara (25). From these studies the authors inferred that epinephrine promotes hepatic glycogenolysis, leading to elevated blood glucose levels. Insulin, on the contrary, was seen as an inhibitor of hepatic glycogenolysis, as well as a promoter of the utilization of glucose by muscle cells.

In one publication on epinephrine from this period, work that was a continuation of his M.A. thesis work, Sahyun and Webster (26) cited the vasodilator properties of epinephrine and related it to other catechol derivatives, e.g., synephrine (IV), studied concurrently by Tainter (27).



IV

In another paper in this series (28) Sahyun noted the effect of epinephrine-like substances on amino acid metabolism, the work of one of his fellow Stanford graduate students, S. W. Morse (29). Morse and Luck, in turn, acknowledged Sahyun's collaboration in their work. This interest appears to have presaged Sahyun's future interest in amino acid metabolism and set the stage for Sahyun's Ph.D. thesis work, under supervision of Prof. Carl Alsberg, on hydrolysis of glycogen, in which he showed *inter alia* that the acid catalyzed hydrolysis is kinetically a first-order reaction (30).

Before leaving Stanford University, Sahyun applied for a patent on a dental preparation which anticipated most modern toothpastes by incorporating a buffer along with the usual surfactants, abrasives, etc. (31). This interesting example of his problem solving creativity had nothing to do with the diabetes research. The patent was cited as prior art in numerous later patent applications on various dental preparations by companies such as Lever Bros. (32) and Colgate Palmolive (33). It has continued to be cited as recently as 2007 (34). Products incorporating Sahyun's technology were not commercialized, however, until after expiration of the original patent, so he derived no financial benefit from the invention.

Sahyun continued his work on insulin when he moved to the laboratories of the pharmaceutical company, Frederick Stearns and Company, in Detroit, Michigan. The company was interested in becoming a supplier of clinically useful insulin, Eli Lilly and Co. being their principal competitor in this market. For their commercialization, Stearns required an insulin that was stable, pure and of reproducible potency. Sahyun focused on exploiting crystalline insulin. (He is sometimes credited with "inventing" crystalline insulin, but this, of course, is not the case). Insulin was first obtained in crystalline form by Abel, reported in 1926 (35).

Sahyun (36) chose to exploit the observations of Scott (37) that crystalline insulin contains zinc, and that if the concentration of zinc is less than "0.04%" (ca. 40 ppm by wt.), the insulin cannot be crystallized. To this end Sahyun and Feldkamp first worked out a method for determining zinc in biological materials (36). Using this method, Sahyun and co-workers were able to show that zinc (ca. 0.02 wt. %) is essential to the stability of insulin preparations (38). This result led to the commercialization by Stearns of crystalline insulin as the zinc derivative in 1938 (39). The actual role of zinc in enabling crystallization was not understood until much later when it was shown that zinc ions assist the assembly of insulin monomers into hexamers (Figure 3) which subsequently crystallize (40).[40] The hexamer is also the form in which insulin is produced and stored in the body; it is converted *in vivo* to the active monomeric form (41).

Sahyun's contribution to the introduction of crystalline insulin to the marketplace may be summarized as developing the findings of Abel, Scott and others into

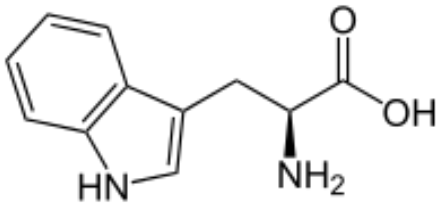
Figure 3*. Insulin hexamer (41b).*

a commercially feasible process. His process patent was issued in 1939 (42). The clinical superiority of this insulin, with respect to both rate of absorption and duration of effect, had already been demonstrated (43). The crystallization, albeit under conditions slightly different to the industrial process, of zinc-insulin by Sahyun's method led to beautiful rhombohedral crystals suitable for crystallographic characterization, which Sahyun provided to the US Food and Drug Administration (44). The actual x-ray structure was not determined until the 1960s by Nobel Laureate Dorothy Crowfoot Hodgkin and co-workers, when techniques for solving such complex structures had finally been developed (45). The structure determination was carried out on rhombohedral crystals, apparently similar to those provided to the FDA by Sahyun, but grown in Hodgkin's own laboratory. According to Vijayan (46) she credited the growth procedure to Scott (37) insofar as she used the citrate buffer preferred by that group rather than the phosphate buffer preferred by Sahyun (42).

Proteins and Amino Acids

With the advent of World War II, research at Frederick Stearns and Company turned to supplements which could facilitate rebuilding tissues of patients with severe wounds and burns, i.e., war injuries, as well as facilitating the recovery of victims of malnutrition due to inhumane imprisonment, e.g., prisoners of war and Holocaust survivors. In the latter case the patients had subsisted on a diet deficient in protein. Such a formulation would also supplement the loss of physiological nitrogen accompanying trauma (47). It would have to be formulated in such a way as to be suitable for use in military field hospitals. It was envisioned that the product in solution form would be administered parenterally or intravenously. In the course of his background research for this ambitious project, Sahyun published a comprehensive review article with over 500 references on the nature of protein deficiency in humans (48).

The scientific context for this work was two-fold. First of all, prior to the 1930s there had been a debate as to whether or not a mixture of pure amino acids could replace dietary proteins in meeting the nitrogen requirements of a growing animal. Willock and Hopkins (49) had identified tryptophan (V) as an essential amino acid, which however tended to be destroyed during acidic hydrolysis of proteins.



V

This specific hydrolysis method had been used to produce amino acid mixtures that failed to provide a dietary replacement for protein, leading to the controversy. It was understood then as now that all ingested protein is hydrolyzed to its constituent amino acids in the alimentary tract, and that it is the component amino acids themselves which are absorbed via the small intestine, i.e., there is no absorption of undigested protein. As noted above, this is the principal problem confronting development of an orally administrable form of the protein insulin.

Secondly, in parallel with this work, was the evolution of the concept of essential amino acids. Essential amino acids are defined as those amino acids that cannot be synthesized by the organism and thus must be supplied from the diet, generally in the form of animal protein. For humans these are now known to be histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine (50). Arginine may be essential in other species, e.g., rats (50).

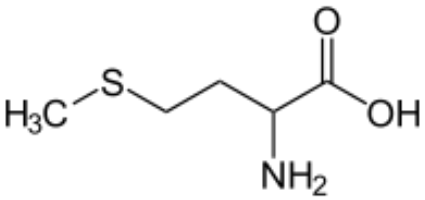
The product developed by Sahyun and his coworkers comprised a solution of amino acids obtained by a combination of acidic and alkaline hydrolysis of a source protein, e.g., casein. Three objectives had to be

met to achieve the goal of a nutritional supplement that could be administered parenterally. First was the need to provide a solution of the amino acids at neutral pH, free from ionic impurities (51). The ultimate process of preparing such a solution involved dividing the protein raw material into two portions, one subjected to acid hydrolysis with H_2SO_4, the other portion subjected to alkaline hydrolysis with $Ba(OH)_2$. These two portions were then combined and purified to yield the neutral solution. The ionic byproduct, insoluble $BaSO_4$, was removed by filtration (52).

Preliminary work, which was not, however, published until 1947, had to address three questions (53):

> (1) Does racemization of amino acids by hydrolysis of a protein occur in such amounts as to reduce the biological utilization of the resulting mixture?
>
> (2) Does the catalytic action of acids on proteins at boiling or at elevated temperature destroy partially or *in toto* any indispensable amino acid or unknown factor other than tryptophane [*sic*]?
>
> (3) Do any appreciable losses of essential amino acids occur during the removal of insoluble inorganic salts and subsequent purification of the hydrolysate?

Secondly, the final solution was likely to be deficient in tryptophan; Sahyun had already published results which showed improved utilization of the amino acids in animal models if the protein hydrolysate was supplemented with tryptophan (54). Tryptophan had to be replaced in an amount sufficient to enable establishment of nitrogen balance (51). A process therefore had to be developed for the isolation and concentration of this amino acid, in this case by adsorption onto activated charcoal from a protein hydrolysate solution (55). Tryptophan could then be added to the protein hydrolysate mixture to fortify the solution in this essential amino acid. The preliminary work (53) had also shown the desirability of supplementing the mixture with methionine (VI) and glycine; casein is deficient in the sulfur-containing amino acids and methionine supplementation is needed to meet nutritional requirements (56). This additional fortification was not, however, disclosed in the final patents (57).



VI

Thirdly, the extreme conditions under which the product might be used in a military theatre of operations and the extended shelf life required for overseas shipment required that the amino acid solution be stabilized against crystallization. To this end Sahyun added a "protective colloid," e.g., pectin (57). The final product was sold under the trade name Parenamine™, and was described in a *Journal of the American Medical Association* editorial as a "…physiologic short cut sparing the need for digestion and absorption in the gastrointestinal tract" (58). The date of this editorial, which accompanied an article disclosing the use of Parenamine in clinical practice (59), indicates that the product, development of which had started as early as 1939, had been made available to the military medical community by 1943.

In the post-War era, Parenamine continued to be marketed. Parenteral amino acids were recommended preoperatively and postoperatively for patients with gastrointestinal disease and/or obstruction (54), and were described as having "…the advantage of producing complete gastrointestinal rest, equal if not superior to that induced by morphine" (47). Much of the above material was used by the Stearns Company to promote the product (60). To the present author's knowledge, Parenamine or its equivalent is still available in the marketplace.

In the course of this work Sahyun became well connected in the community of protein and amino acid researchers and established a strong network among the technical staffs of the suppliers of raw material (e.g., casein, pectin, etc.) as well as in the military medical community, initially US Army Drs. Samuel Altschuler and Helene Schneider. Altshuler had previously been involved in the clinical evaluation of crystalline insulin and was one of the founding officers of the American Diabetes Association (61). This network would prove useful to him in the next phase of his career. Among these colleagues were also Drs. J. D. Fagin and Elaine Pagel at the US Marine Hospital in Detroit. They collaborated on a study that showed that Parenamine therapy in patients with cirrhosis of the liver and chronic alcoholism increased the protein content of their livers, and suggested protective action of protein stores against hepatotoxic agents (62, 63). Branched-chain amino acid supplementation has now specifically been proposed for cirrhosis patients (64).

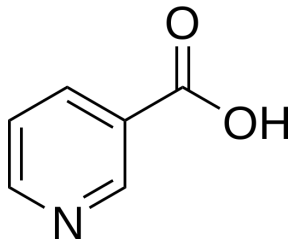
Sahyun was sufficiently highly regarded by his colleagues to be invited to edit a monograph titled *Outline of the Amino Acids and Proteins* (49), which was published in 1944. This book incorporated chapters by academic, industrial and government scientists who

were established authorities in their areas of expertise. In this effort he was strongly encouraged by Prof. Carl Schmidt of the University of California, Berkeley and San Francisco campuses, who wrote the Foreword to the volume. Schmidt had already edited a monograph on this topic (65).

After three generations of family management at Frederick Stearns and Company, in 1946 the Stearns family relinquished management of the firm and sold its businesses to the Sterling Drug Company. Sahyun declined a management position with Sterling, for which he seemed eminently qualified on the basis of his leadership of the Parenamine program, and he chose to re-invent himself as a "Chemist Consultant." He remained in this status for three years, 1946-1949. During this time he maintained an affiliation with the University of Texas Medical Branch in Galveston, Texas.

Sahyun had already arranged in 1945 with his friend and colleague Carl Schmidt to co-edit a more extensive monograph on proteins and amino acids with an emphasis on nutrition. Schmidt, however, passed away in 1946, and Sahyun undertook the editorship of the new volume on his own, he and Schmidt having already agreed on the topics and contributors to be invited. The new book was titled *Proteins and Amino Acids in Nutrition* (66) and comprised 15 chapters. Sahyun's own chapter was entitled "Plasma Proteins and their Relation to Nutrition." The book remains available in facsimile or replica editions (67).

During this time Sahyun chose to enhance his scientific reputation and promote his expertise as a consultant in the field of amino acid and protein chemistry by publishing three definitive review articles. The first (68) dealt with the metabolism and nutritive importance of tryptophan (V). In this paper he summarized the evidence supporting the concept that tryptophan is the precursor of niacin (VII) in *in vivo* biosynthesis and endorsed this theory, even though the biochemistry had not yet been elucidated. This concept is, of course, now well established in the biochemical and popular literature (69). It was not understood at the time, however, that tryptophan is also the precursor of serotonin (VIII) and melatonin (IX). The relationship between tryptophan and serotonin might have been obvious to biochemists from inspection of their chemical structural formulae; serotonin was not isolated and structurally characterized until after 1948, however (70). It was thought at the time that epinephrine (III) was derived in vivo from tryptophan (71).



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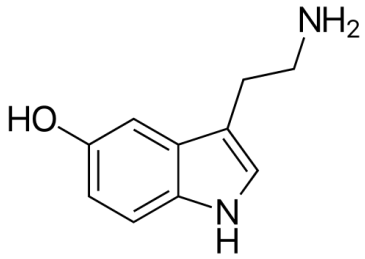

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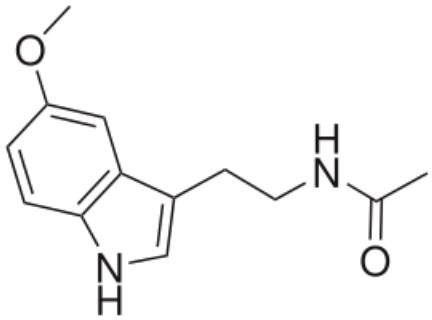


IX

Sahyun went on to write a comprehensive review article on the biochemistry of methionine, another of the essential amino acids (72). In this review Sahyun observes that in the course of the work on amino acid supplementation of cirrhosis patients (above) it had been proposed that methionine metabolism might play a role. Subsequently the role of methionine in cirrhosis was confirmed; impaired methionine metabolism is characteristic of the disease (73). More recent research has shown that methionine may have clinically relevant toxicity, depending on the level provided by the supplement (74).

The final review dealt with the relationship of amino acids to the nutritive value of proteins (75). The main point he emphasized in this article was the importance of the simultaneous availability of all the amino acids for protein biosynthesis, an "all-or-none" situation as he termed it. This point had already been made strongly by Sahyun's colleagues, Madelyn Womack and Charles

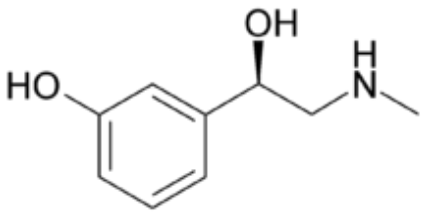
Kade in the earlier monograph he had edited (76). It is now understood that the essential amino acids need to be available not only simultaneously, but in ratios corresponding to the body's requirements (50, 74).

Drug Discovery

In 1949 Melville Sahyun's career took a new direction. He established an independent research organization, Sahyun Laboratories, back in Santa Barbara, California. He was motivated both by his expressed frustration with the bureaucracy of large industrial organizations, and also by the strong desire on the part of his wife, Geraldine, to live in her home state of California. The focus of his new laboratory was to be drug discovery. To this end he put together a team of synthetic organic chemists, including John Faust, Martin Synerholm, and Leonard Jules, to turn his biochemical intuitions into molecular reality. The facility had the shortcomings of not having any capability for animal research, as well as no ongoing collaboration for clinical testing.

Drug discovery at that time was a much more intuitive, hit-or-miss process than now. The arsenal of current drug discovery techniques, including computational modeling, bioinformatics, "brute force" high-throughput screening, and now artificial intelligence (neural network) methods (77) were, of course, not available 65 years ago, nor would a small independent laboratory have had the resources to implement these capital intensive research strategies had they been available. Although there is no documentation of Sahyun having been involved directly in drug discovery prior to the establishment of Sahyun Laboratories, by his own account (personal communictaion) he had been involved in development work on neosynephrine (phenylephrine, X) marketed as a nasal decongestant by Frederick Stearns and Co. This claim on his part appears to be undocumented; in fact the literature indicates that much of that development work had been carried out prior to Sahyun's arrival at Stearns (78).

The laboratory's first successful molecule was biphenamine (2-diethylaminoethyl-3-phenylsalicylate mandelate, XI), for which mild antihistaminic, fungicidal, antibacterial, and anesthetic properties were claimed (79). Structurally it may be viewed as a rather elaborate aspirin (XII) analog.



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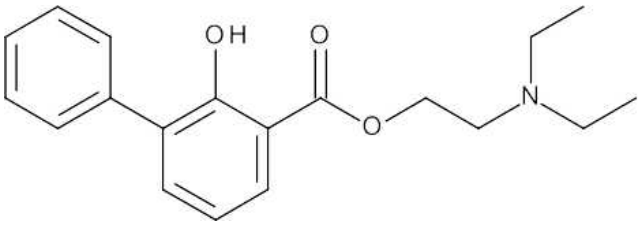
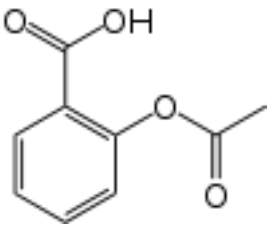


XI



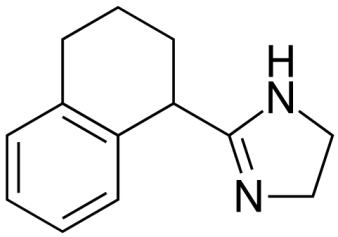
XII

Application of the compound in solution as a urinary bactericidal agent was also proposed. Sahyun went on to formulate it as a topical analgesic-antibacterial preparation for "first aid" application, much as Neosporin™ is used today. Without the backing of a large pharmaceutical manufacturer, the clinical trial data to obtain FDA approval for over-the-counter marketing were not accessible, and Sahyun could only obtain approval for marketing the formulation as an "experimental," prescription-only medication. He tried marketing the product himself under the trade name Melsaphine™ for a short period of time without significant market penetration (79). It turned out to be popular for veterinary applications, however.

One of Sahyun's former Stanford colleagues, Thomas Schulte, MD, who was an equestrian along with being a practicing physician, had noticed in using the product on horses, that biphenamine facilitated debriding of wounds, i.e., cleansing of the wound by removing foreign material and dead tissue, so that the wound would heal without increased risk of infection. After the original patent expired Schulte patented a formulation of biphenamine with aloe vera for this specific application in veterinary medicine (80). Schulte also patented biphenamine, in admixture with dimethyl sulfoxide, as a topical analgesic (81), and as an opthalmological

anti-inflammatory (82). Biphenamine is reportedly the active ingredient in the Sebaclen™ antibacterial shampoo marketed by Carter-Wallace Inc. (83), and is currently manufactured in Germany as a raw material for the pharmaceutical industry (84).

The second important molecule to come out of Sahyun Laboratories was tetrahydrozoline, also known as tetryzoline [2-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydro-1H-imidazole, XIII], synthesized by Synerholm and Jules (85).



XIII

While the basis for Sahyun's conception of biphenamine is not at all transparent, the intellectual process leading to the design of tetrahydrozoline is much more apparent and illustrative of the process of drug discovery in those days. It is obvious that the chemical structure of tetrahydrozoline incorporates the β-phenylethylamine framework, common to vasopressors such as epinephrine (III) and neosynephrine (X), with which Sahyun had previously worked. It had already been established by Barger and Dale that the "…optimum carbon skeleton for sympathomimetic activity consists of a benzene ring with a side-chain of two carbon atoms, the terminal one bearing the amino-group" (86). These authors had also observed enhanced pressor (blood pressure enhancement) activity when this optimum structure was rigidized in the form of β-tetrahydronaphthylamine. Development of tetrahydrozoline was thus a matter of optimization of the pressor response by various molecular modifications of the known, active compounds. Since the structure-activity inferences of Barger and Dale had been based in large part on naturally occurring compounds, this strategy exemplifies the confidence of synthetic organic chemists of the day in their ability to improve upon nature. Surprisingly tetrahydrozoline lacks the aromatic hydroxyl groups, which conventional wisdom held to be essential to sympathomimetic action (87). Hydroxylated analogs of tetrahydrozoline showing strong adrenergic activity were subsequently reported by DeBernardis and co-workers at Abbott Laboratories (88).

Like neosynephrine, the pressor activity of tetrahydrozoline results from a vasoconstrictor (blood vessel contracting) action (89). This suggested to Sahyun its application as a decongestant, like neosynephrine, and as an anti-inflammatory agent. He also patented it as a sedative (90), a usually undesirable side-effect for a decongestant. The decongestant application was developed in collaboration with Chas. Pfizer and Co., and marketed as a nose drop preparation under the trade name Tyzine™. The product is currently manufactured for Kenwood Therapeutics by Denison Pharmaceuticals (91), and available by prescription.

About 1952 it occurred to Sahyun that tetrahydrozoline might have ophthalmic application. This was largely because the present writer, then twelve years old, was experiencing serious eyelid irritation from swimming pool chemicals. With myself as principal clinical test subject, he formulated tetrahydrozoline into a standard lubricant eye drop formulation. He (and my mother) thought the product might be successful in the marketplace because of the high level of eye irritation being experienced by Southern California residents at the time, owing to photochemical smog (92). The concept interested drug manufacturer Chas. Pfizer and Co. with whom he was already working on the Tyzine product, and Pfizer brought the eye drops to market as Visine™, but apparently not before 1954 when the Synerholm patent was applied for. Pfizer continued to market the product until 2009 when its consumer product line (and accompanying trademark portfolio) was sold to Johnson and Johnson Inc. At least three other manufacturers now make an ophthalmic product essentially identical to the original Visine, but not sold under that name, according to the Health Canada database for products approved for over-the-counter sale (93).

Interest in tetrahydrozoline continued. Pfizer scientists also patented it as a central nervous system depressant for veterinary application (94). In this patent tetrahydrozoline is described as adrenolytic (sympathomimetic inhibiting), whereas Sahyun had understood that it was adrenergic, as disclosed in the original patent application (85). The preponderance of evidence on human health effects of tetrahydrozoline collected by the National Library of Medicine (95) supports Sahyun's understanding, contrary to the claim in the Gardocki et al. patent. Scientists at Bayer Cropscience AG later also claimed insecticidal activity for compounds of a general class which included tetrahydrozoline, though based on their patent claims it was not their preferred embodiment (96). Human toxicity of tetrahydrozoline, if ingested, is

now well-documented; it is especially severe in children (95). Tetrahydrozoline has allegedly even been used as a murder weapon (97).

The dihydroimidazoline ring in tetrahydrozoline is, of course, an amidine functionality. It was therefore not surprising that the Sahyun Laboratories group addressed amidine chemistry as a route to other pharmacologically active molecules (98), namely compounds that exhibited sedative and adrenolytic properties, similar to the action claimed surprisingly by Gardocki et al. (94) for tetrahydrozoline itself. Another patent described an antifungal salicylamide compound (99). None of the compounds covered by these later patents appear to have been commercialized.

Although Sahyun had published prolifically during the first twenty-five years of his career, he virtually stopped publishing when he redirected his interests to drug discovery. His career in this later phase can only be traced through the patent literature. In summary it appears that though the idea of an independent research organization may have been a dream-come-true for him, his limited scientific contributions during this time, up until his retirement in 1973, made it the least productive period, in terms of publication and significant scientific accomplishment, in his career.

One exception to Sahyun's lack of publication during this period was a tutorial article on "The Discovery of Insulin," which provided a capsule history of diabetes research up to the work of Banting and Best (18). In this paper he emphasizes the role of liver glycogenolysis in the etiology of diabetes. This appears to have been his last published paper. Since Sahyun's mind was still on diabetes, one of the mysteries of this period is that he did not choose to follow up on the lead of guanylpiperidine as an inhibitor of liver glycogenolysis, which he had reported in 1929 (16), and address this target as a route to a diabetes medication. This would have been a high-priority endeavor once the distinction between Type 1 and Type 2 diabetes had been elucidated (21). It is possible, as suggested by one of the reviewers of this paper, that the companies he worked with did not have an interest in entering this market, so were not prepared to support research in this area.

Conclusions

The career of Melville Sahyun comprised three major parts. In the first part he was engaged in diabetes research. In this period his most important contribution was the development of an industrial-scale process for the preparation of a purified insulin solution of standardized potency for clinical application, based on his studies of insulin crystallization. He then turned to the biochemistry of amino acids and proteins. His major technical contribution in this area was the development of an amino acid supplement solution for intravenous or parenteral administration. In this period he also edited two important monographs on proteins and amino acids. The final phase of his career was devoted to drug discovery. The most noteworthy accomplishment in this period was the invention of the anti-inflammatory molecule tetrahydrozoline, which was formulated for ophthalmic use as Visine™ eye drops. Dr. Melville Sahyun died in Santa Barbara, California, in 1977.

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About the Author

M. R. V. (Mel) Sahyun is the son of the subject of this article and figured in at least one of the technological accomplishments described herein. He received his Ph.D. in Chemistry at UCLA under supervision of Nobel Laureate D. J. Cram, and went on to career positions of varying responsibility at the US Public Health Service, 3M Corporate Research, and the University of Wisconsin–Eau Claire. For twelve years he was senior editor of the *Journal of Imaging Science and Technology*, shepherding it from a publication, which emphasized photochemistry, optics and materials science, to one embracing digital technology. Among other awards he is recipient of the Berg Prize of the International Committee for Imaging Science, citing his promotion of international cooperation through science. His most cited paper involves photophysics of TiO_2 analyzed by high-speed laser spectroscopy, work done as a Visiting Scientist at Concordia University, Montréal, in collaboration with Prof. Nick Serpone and his group.

2018 HIST Award to David E. Lewis

The History of Chemistry Division (HIST) of the American Chemical Society (ACS) is pleased to announce that Professor David E. Lewis of the University of Wisconsin-Eau Claire is the winner of the 2018 HIST Award for Outstanding Lifetime Achievement in the History of Chemistry. This international award has been granted since 1956 under sequential sponsorships by the Dexter Chemical Company, the Edelstein Foundation, the Chemical Heritage Foundation, and HIST. A symposium honoring the work of Prof. Lewis, including a lecture by the awardee, was held on August 21, 2018, at the ACS Fall meeting in Boston.

David Lewis was born in the borderline bush area around Adelaide, South Australia. He matriculated from Salisbury High School, and moved on to the University of Adelaide, where he graduated with Honors in Organic Chemistry in 1973. He conducted graduate research in natural products until he was beckoned to the United States and the state of Arkansas in 1977. Professor Lewis earned tenure and the rank of Associate Professor at Baylor University in 1988, then moved to South Dakota State University, where he became a Full Professor in 1993. He was called to The University of Wisconsin- Eau Claire in 1997 as Chair of the Chemistry Department, where he continues a very active program in synthetic organic chemistry. His work was recognized in 2012 with a DSc. Degree from the University of Adelaide, and he was elected a Fellow of the Royal Society of Chemistry in 2015.

Lewis picked up an interest in the history of organic chemistry, joining HIST and starting to publish in its journal (now 15 papers, including two Best Paper Awards in 1997 and 2010). He served as the Chair of the Division from 2003-2005. His focus has been organic chemistry in Russia, especially at Kazan. He is recognized in Russia as the author of "a wonderful series of works devoted to the history of Russian chemistry." His collected works were translated and published in Russian in 2016. His 2012 book, *Early Russian Organic Chemists and their Legacy* has been hailed as the most important contribution to this previously understudied area. More information on Seeman and the award can be found at acshist.scs.illinois.edu/awards/hist_award.php.