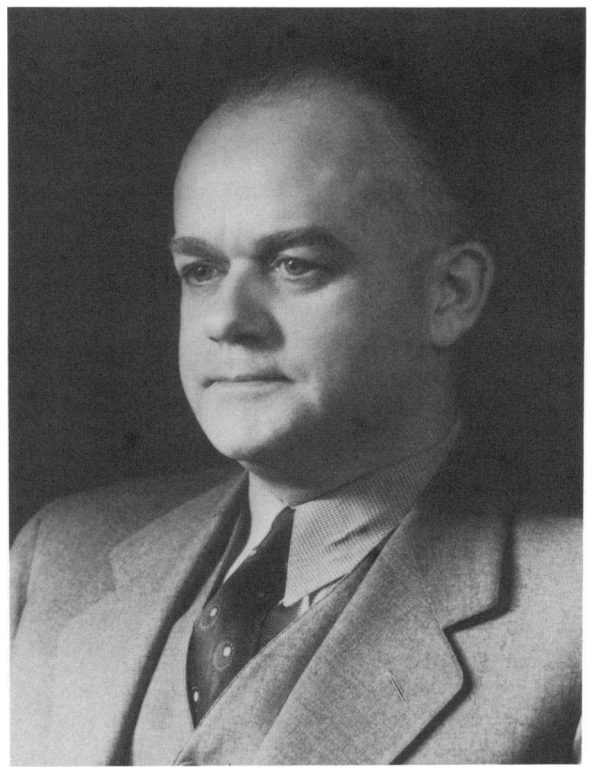

Laurence Hasbrouck Snyder, circa 1942

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Laurence Hasbrouck Snyder: Pioneer in Human Genetics

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Laurence H. Snyder died at his home in Honolulu, Hawaii, on October 8th, 1986. He was a pioneer student of human genetics whom Lear (1956) called "the father of human genetics" in this country. He was one of the founders of the American Society of Human Genetics, served as its president in 1950, and edited volume 7 (1955) of *The American Journal of Human Genetics*.

I will try to describe some facets of his life so that those who did not know him personally will gain a sense of this remarkable man.

Snyder was born on July 23, 1901, at Kingston, NY, the second of five children of DeWitt and Gertrude Snyder, who had been Christian missionaries in the Belgian Congo. He attended Curtis High School in New York and, in 1922, was graduated from Rutgers University with a bachelor of science degree. He entered the Graduate School of Harvard University, from which he received a doctor of science degree in 1926.

While he was at Rutgers, Snyder met and fell in love with a pretty young Norwegian girl, Guldborg Herland. They were married on Christmas Day in 1923 and, in due course, had two daughters, Clara and Margaret. Guldborg was his steadfast companion until his death. (I obtained this information about Snyder's early life and family from his mother's informal autobiography, written in 1959.)

During his active career, Snyder held positions in four academic institutions, all state universities. At North Carolina State College, he was a professor of biology from 1924 to 1930, having accepted this position before he had completed his graduate work at Harvard; at the Ohio State University, he was professor of genetics from 1930 to 1947, professor of medicine from 1933 to 1947, and chairman of the Department of Zoology and Entomology from 1942

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to 1947; at the University of Oklahoma, he was dean of the Graduate College and professor of medical genetics in the Medical School from 1947 to 1958; at the University of Hawaii, he was president from 1958 to 1963 and senior professor of genetics from 1963 until his retirement in 1966. He and Guldborg continued to live in Honolulu for the next 20 years.

Snyder's active career, over a span of 40 years, embraced many more activities than I can mention in this article. He wrote three books, authored more than 150 scientific and professional papers, delivered more than 1,000 lectures while visiting every state in the United States and most of the countries around the Pacific basin, was awarded three honorary degrees, served on numerous scientific committees, and was president of the Genetics Society of America and of the American Association for the Advancement of Science as well as of the American Society for Human Genetics. I will try to impart the essential features of his life and personality by describing his research work, his life as a writer and educator, his life as a lecturer, some aspects of his life as an administrator, and finally some of his personal traits, abilities, and hobbies. Much more information is available in an oral history tape interview (Opitz 1981).

I came to know Larry (as he was called by all who knew him) in the spring of 1941, when he interviewed me for a faculty position at the Ohio State University. He hired me to help him and David Rife teach the elementary course in genetics. We each taught advanced courses as well. He was my "boss" or "chief" for the next 6 years, even though for 3 of those years I was on military leave of absence.

The bulk of Snyder's own research work is reported in a series of 35 papers, over the period from 1926 to 1949, entitled "Studies in Human Inheritance." These are short papers, in general; a few have coauthors. They range over a wide variety of subjects: blood groups, polydactylism, hemophilia, taste deficiency, koilosternia, baldness, sex ratios, linkage, pyloric stenosis, telangiectasia, feeble-mindedness, and Rh incompatibility. Other papers dealt with various aspects of genetic theory. Probably his most significant research contributions were on the inheritance of blood groups and of phenylthiocarbamide (PTC) taste deficiency.

His first paper on blood groups appeared in 1924 (Snyder 1924). At that time, the hypothesis of two loci, each with two alleles (allelomorphs as they were then called), was regarded as most plausible for explaining the O, A, B, and AB groups. Shortly after that, Bernstein (1925) proposed the one-locus/three-allele hypothesis. Snyder set about collecting family data in North Carolina, giving special attention to the matings of O $\times$ AB, to discriminate between the two-loci and the one-locus hypotheses. His data supported the one-locus concept (Snyder 1926*a*). This idea required a clear exposition and a vigorous defense. There were, of course, several apparent exceptions to the hypothesis that had to be explained away by invoking the possibilities of errors in technique, illegitimate pregnancies, or undeclared adoptions.

Sometime in 1926 or 1927, an event of considerable significance for the birth of medical genetics in this country took place in North Carolina when William Allan sought out Laurence Snyder for help in analyzing family pedigrees of

migraine that Allan had collected. Allan, for whom the William Allan Memorial Award is named, was an internist who had been developing an interest in hereditary diseases for more than a decade. Snyder was the ideal person to help him with the migraine pedigrees. Allan, in turn, helped Snyder with further blood collections (Herndon 1983).

In the mid-1920s, as now, there were some misconceptions about genetic phenomena. Some authors interpreted association between traits as implying genetic linkage. This led Snyder (1926*b*) to write: "The purpose of the present paper is to protest against the hasty conclusions drawn by some authors that there is linkage between blood groups and some pathological, anatomical, or physiological condition. In every case, the conclusions are based on insufficient or absolutely irrelevant data."

In a major paper, Snyder (1927) discussed the applications of blood grouping to blood transfusions, disputed paternity, and serological race classifications. This gave him a chance to stress the value, for characterizing populations, of gene (allele) frequencies p, q, and r over phenotype frequencies for O, A, B, and AB and over various ratios of phenotype frequencies.

The outcome of these endeavors was an invitation to prepare a book on blood grouping. *Blood Grouping in Relation to Clinical and Legal Medicine* (Snyder 1929) was a standard reference for the next 2 decades.

Meanwhile, another investigator had proposed the idea that two linked loci could also explain the frequencies of the blood groups. Snyder pointed out the implausibility of this idea in his 1929 book. But then, in 1930, two eminent authors, W. E. Castle in the United States and R. R. Gates in England, published books in which they each appeared to give credence to the two-linked-loci hypothesis. Snyder's (1931) rejoinder is a strong polemic against the two-loci (even if linked) hypothesis and in support of the one-locus/three-allele hypothesis. This paper, even today, seems to have wisps of steam coming off the pages. It is the only sample of Snyder's extensive writings known to me that reveals a man provoked by the recalcitrance of his distinguished colleagues.

In 1931 it was accidentally discovered that human beings differ in their ability to taste certain substances, such as PTC. That the taste/nontaste trait was inherited was soon inferred. Then Snyder set out to collect sufficient family data to confirm the hypothesis of recessive taste deficiency. He got information on 800 families with 2,843 children, representing taste × taste, taste × nontaste, and nontaste × nontaste marriages. In the paper giving these results, Snyder (1932) makes the first mention and use of generalized population-segregation proportions. In the case of one locus, two alleles, and dominance, the proportions of recessive offspring in the three kinds of matings (dominant × dominant, dominant × recessive, and recessive × recessive) of a random breeding population will be $S_n = [q/(1 + q)]^n$, where $n = 0$, 1, or 2 counts the number of parents with the dominant phenotype and where q is the relative frequency of the recessive allele.

We might pause a moment to try to recapture a bit of the thrill that Snyder must have felt when he discovered this neat relationship. He was not particularly adroit with mathematical maneuvers, but he had schooled himself in the

algebra of gene frequencies. In setting out a table of matings and offspring, he discovered that the probability of recessive offspring, $2pq^3$, where $p = 1 - q$, when divided by the probability of dominant × recessive matings, $2p^2q^2 + 4pq^3$, reduced to $q/(1 + q)$ and that the probability of recessive offspring, p^2q^2, when divided by the probability of dominant × dominant matings, $p^4 + 4p^3q + 4p^2q^2$, reduced to $q^2/(1 + q)^2$. Later, Snyder (1934) gave a full exposition of the derivation of the proportions and their probable errors (the statistic then popular).

When Cotterman (1940) undertook his extensive symbolic study of the probability relationships between incompletely specified genotypes, he found that these same proportions frequently recurred. Later, Cotterman (1969) arranged these proportions and their complements in a 2 × 2 form (as determined by the parents having dominant or recessive phenotypes), which he called a Snyderian matrix, and commented that "Dr. Snyder did much to dispel the once commonly held misconception that exact mathematical expectations could not be hoped for in the analysis of human heredity." Li (1955) has referred to these proportions as "Snyder's ratios" and has said that "the student may find it helpful to remember that *S* is the initial of Snyder." Li (1953) has also shown that q of the formula could also be the product of the q's of recessive genes at two or more loci. This means that, if the trait under study is quite rare, one should be wary of claiming single-locus control on the strength of a good fit to Snyder's proportions. Wariness is, however, nothing new to population geneticists.

Snyder's other professional writings (as distinct from research reports) deal with a wide variety of genetic topics: linkage, the nature-nurture controversy, individuality and personality, genetics in medicine, and the elements of population genetics. I will mention some of these below.

All of Snyder's writing is characterized by an easy grace and absolute clarity. Yet, I would not dub him a wordsmith. He did not have to pound words and bend them to new uses. To prepare a research paper or a public lecture, he wrote out his text in long hand, in a large, rotund style that was easy to read. Then, without need for any of the insertions, deletions, translocations, transpositions, and inversions that characterize the drafts of most other writers, he passed his manuscript to a secretary for creation of a typescript.

In addition to the book on blood grouping, already mentioned, Snyder wrote two other books. One of these, *Medical Genetics* (Snyder 1941), is a set of lectures that he gave to medical students. The other, *The Principles of Heredity* (Snyder 1935–57), went through five editions between 1935 and 1957. For the last edition, Paul R. David was a coauthor. The fourth edition was translated into Spanish and German. This was one of the most popular pre-DNA books on genetics. More than 500,000 copies have been printed. The success of this book made Snyder well known throughout the world. It is worth taking a moment to see how it came about.

When Snyder joined the biology faculty at Ohio State University in 1930, he was asked to take over the teaching of genetics. At the start, there was one elementary class per year. Soon there were nearly 1,000 students per year

(Paddock 1969). The growth of enrollment was clearly a reflection of Snyder's infectious enthusiasm for genetics. The book was designed to help with the instruction. He used copious exhibits of familiar living plants and animals—and many examples of human inherited traits. He also had a collection of interesting remarks about such traits as hemophilia in the royal families of Europe and baldness in human beings, both male and female. In connection with baldness, he recited the following:

Lives of bald men all remind us
We must choose our wives with care,
And, departing, leave behind us
Kids who have a little hair.

In addition, Snyder offered a course in advanced genetics in which he explained the techniques of pedigree analysis, the collection and analysis of population data, the computation and utility of gene frequencies, and problems about blood grouping, taste deficiency, or whatever was unresolved at the moment. By this means, he attracted such people as Charles Cotterman to the field of genetics.

Snyder also offered the first required course in medical genetics in this country. In 1933, he was appointed professor of medical genetics in the Department of Medicine and asked to teach a course to the second-year class. The course consisted of 12 1-h lectures fortified by abundant clinical materials (Snyder 1933). He continued to offer the course until his departure in 1947. He also taught such a course in 1941 as a visiting professor at three North Carolina medical schools (Duke, North Carolina, and Wake Forest), as well as in his years at the University of Oklahoma and to practicing physicians in Honolulu while he was at the University of Hawaii (Snyder 1955; S. L. Halperin, personal communication).

Larry Snyder was a popular lecturer. He was invited to give single lectures or sets of lectures or entire courses at universities or academies or associations all over the country. Many of these were named, endowed lectureships. Since these lectures were to be printed, he often read them from a prepared typescript. He did not, however, have the stultifying delivery often associated with a read lecture. His written and spoken prose were essentially identical.

All of the lectures were about some aspect of genetics. All carried the implicit message that great opportunities lay ahead for the study of human heredity. Here is the way in which Snyder characterized the study of human inheritance in the Tenth Harry Burr Ferris Memorial Lecture at Yale University:

> The principles of heredity so extensively formulated during the first part of the present century were developed as a result of experimental laboratory methods. Under such situations, where selection and inbreeding can be practiced freely, the genotypes in each mating can be controlled and through examination of the resulting Mendelian ratios, the mode of inheritance of a particular variation may be determined. In the study of human inheritance, however, the genotypes are in many cases capable only of incomplete specification, so that even well-classified data will often contain mixtures of different types of matings.

> Under such circumstances, involving large populations breeding more or less at random, there emerges an importance of certain concepts which are relatively unimportant in laboratory genetics. These concepts include the proportions in the population of a gene and of its alleles, and of the genotypes formed by a gene and its alleles. Thus the study of human inheritance is essentially a study of population genetics. (Snyder 1947)

The responses from medical schools were gratifying but not overwhelming. By 1955, in addition to those schools already mentioned, courses—or at least some lectures—in medical genetics were being given at the New York State Psychiatric Institute, the University of Michigan, Bowman-Gray School of Medicine, University of Minnesota, University of Utah, and Tulane University (Snyder 1955; Herndon 1956).

Why was the response not greater? Many of the traits under study in the 1940s and 1950s were of relevance to clinical medicine. But Snyder often dealt with population genetics, mentioning the importance of gene frequencies, mutation rates, selection, and racial differences. It may have been hard for medical educators to see how the study of populations might be relevant to the problems of caring for individual patients.

At every opportunity, Snyder continued his missionary work. After 1955, the situation changed dramatically. Various sexual aberrations were found to be associated with visibly detectable variations in chromosome numbers, and ubiquitous biochemical polymorphisms became accessible to study. With these advances, there is now scarcely a medical school that does not have some deliberate instruction in genetics. As C. N. Herndon (personal communication) has said, "I think that Larry's efforts in getting the medical profession to take genetics seriously was his most important contribution to the field."

In his address as retiring president of the American Association for the Advancement of Science, Snyder said, "The rapid and widespread development of medical genetics at the present time owes its inception to the recently renewed interest of human geneticists in Garrod's demonstration that, through mutation, the dysfunction of a gene-controlled enzyme necessary for normal metabolism is a basic mechanism in the production of genetic disease" (Snyder 1959).

As an administrator, Snyder was the do-it-now type. I was treated to an example of this trait the first day I met him. My wife and I had traveled to Columbus by overnight train and expected to depart the next night the same way. Instead, Snyder asked us to stay overnight with him and his wife at their home in Worthington, just north of Columbus. When we arrived there, Guldborg told Larry that some wall lamps that they had ordered had just arrived. In no time at all, a hand drill and screwdriver appeared. I was holding the lamps while Larry marked the exact points on the wall for screw holes. He drilled the holes. I secured the lamps while he drew the screws tight.

Snyder's eminence as an educator and his obvious capacity for dealing with human problems made it inevitable that he would be sought after for more responsible positions in academic institutions. The right opportunities came from Oklahoma and Hawaii.

At the University of Oklahoma, one of Snyder's first acts, as dean of the Graduate College, was to declare that there would be no more segregation on the basis of race in the graduate programs. This was a courageous stand at the time, but he made it stick (G. L. Cross, personal communication). With the passage of time, Snyder improved the lot of the graduate students so that they were no longer treated as if they were undergraduates, and he improved the lot of the graduate assistants so that they were no longer treated as low-class employees (T. Self, personal communication).

As president of the University of Hawaii, Snyder decided that the emphasis on intercollegiate football was distorting the academic objectives of the university. He decided, therefore, to abolish intercollegiate football. In the laconic words of Richard Kosaki, a former professor of political science and chancellor at the Manoa campus, "This had a positive effect as it temporarily activated the alumni association" (Kosaki 1986). Twenty-five years later that act was still regarded as one of the significant turning points at the university, even though intercollegiate football was eventually restored (Smyser 1986).

I have mentioned these few episodes out of possible thousands to illustrate the point that Laurence Snyder was, along with all his scholarly talents, a strong and dedicated leader. He loved people and was happy to work on their behalf. He enjoyed it.

At Hawaii, his stewardship of the presidency was marked by the construction of 37 new buildings (including one named Snyder Hall), many new academic programs, a doubled enrollment, and the creation of the East-West Center. He was instrumental in moving Hawaii from an enlarged college into the ranks of the full-fledged universities (Kosaki 1986; N. E. Morton, personal communication).

After he retired from the presidency in 1963, Snyder attended a 2-wk "Short Course in Medical Genetics" being given in Bar Harbor, ME, under the joint sponsorship of the Jackson Laboratory and the Johns Hopkins University Medical School. He remarked that his own personal efforts to retool himself by learning about DNA chemistry, protein chemistry, and metabolic pathways after his years in administration had apparently paid off. He felt that he could confidently assume a position as senior professor of genetics at Hawaii. In N. E. Morton's words, "Larry returned to teaching with extraordinary enthusiasm. He was undoubtedly one of the most loved professors at the University of Hawaii. He is remembered with great affection by his former colleagues" (N. E. Morton, personal communication).

No depiction of Snyder's life would be complete without mentioning some of his personal characteristics, of which all who knew him have fond memories. He was average in height but looked shorter because of his rotund body and face. A King Edward cigar, not always lighted, was usually in hand. If at dinner he was served a piece of cake with icing, he would carefully dissect the icing from the cake in order to eat it last. He enjoyed good food and was popular with hostesses because he praised them and their accomplishments. His hosts also received praise if they served bourbon and ginger ale.

Snyder's ability to identify birds was legendary. At North Carolina State

College, Snyder wrote a bird-identification booklet (Snyder 1928). He could identify birds by their shapes and markings, and he was superb at recognizing their calls. When the Snyders moved to Oklahoma, the president, George Cross, drove him into the countryside "where the forest of the east gives way to the grassland of the west." They saw a jackrabbit, a roadrunner, and a pair of scissortail flycatchers. According to G. L. Cross (personal communication), Snyder remarked that the area was a "zoologist's paradise." He loved to sit outside at night and identify the migrating birds flying overhead by their calls (T. Self, personal communication). In turn, when he interviewed prospective members of the graduate faculty, he liked to take them out to see scissortail flycatchers (H. Brown, personal communication). He enjoyed sharing his pleasures.

He is probably most remembered for his piano playing. He was endowed with the ability to "play by ear." At any suitable gathering—at a home, on shipboard, or in a seminar room—if a piano was present, Snyder could be counted on to bring happiness to the throng by playing the piano, usually getting the listeners to join in singing old college favorites.

A. G. Steinberg (personal communication) has told of the time that he and Snyder and some others were on a long automobile trip. To relieve the boredom, Snyder got them all to sing songs of various states. "What did Io*weigh* boys . . . , she weighed a Washing*ton* boys . . ." Larry knew all the verses.

At a meeting of the Ohio Academy of Science, Snyder found himself scheduled last on an already overlong program. As he rose to speak, he appeared to drop a few pages out of his manuscript. Then he threw the rest of the pages about himself. After that he said, "Oh, nuts! Let's have some boogie-woogie." He went to a nearby piano and played boogie-woogie, to the delight and amusement of the audience. That was the end of the session (H. H. Parker, personal communication).

The Snyders' move to Hawaii merely exposed him to a wholly new musical culture, whose many songs he could play on the piano. The move to Hawaii also opened up the possibility of a retirement project. Snyder (1977) collected the seeds of Hawaiian trees and tree-sized legumes. The polished seeds, in various combinations of colors and sizes, he then strung as beads. Female visitors to his home in Hawaii were usually offered a choice of a necklace or a bracelet as a gift (J. B. Graham, personal communication; H. L. Carson, personal communication). A most pleasant remembrance of a pleasant life of a pleasant man.

I am grateful to all of Larry's many friends and former colleagues who supplied me with information about his interests and activities, including those who are not explicitly cited as well as those who are noted herein and in the References.

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