Int. J. Dev. Biol. 39: 671-673 (1995)

The two Hammarstens and nucleic acids

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When DNA was discovered in 1869 by an unknown young physician from Switzerland, Friedrich Miescher, working as a postdoc in the well-known laboratory of Felix Hoppe-Seyler in Tübingen, the scientific community could not have cared less. In fact, when Miescher sent the paper describing his discovery to Hoppe-Seyler, even his old mentor found it difficult to believe the data and he checked them himself before he finally accepted the paper for publication in his journal.

Miescher's difficulties to get this pioneering paper published can be said to set the pattern for how his colleagues would receive the great discovery. It took a long time before the importance of nuclein, as DNA was called in those days, was realized by the biochemists. Instead it was the cell biologists who in the 1880s began to link nuclein to heredity, based on their observations of the fascinating behavior of chromatin in the dividing cell. One might have thought that a role for nuclein in heredity would have been good news indeed for Friedrich Miescher, but not at all. It was the ability to stain chromatin with the new synthetic dyes produced by the booming chemical industry that had provided cell biologists with the necessary tools for their experiments. Miescher therefore contemptuously called them "a guild of dyers", against whom he felt he must defend himself and his discovery. Until his premature death in 1895 he continued to deny vehemently that his nuclein had anything to do with heredity. In the beginning of the twentieth century the theory of nuclein as the basis of heredity fell into disrepute and this was ironically to some extent a consequence of the progress made in the elucidation of nucleic acid structure.

Miescher had shown that nuclein had a much higher content of phosphorus than proteins and this was the main reason why he considered it to represent a new class of substances. When Miescher retired from the nucleic acid field already in 1874, Albrecht Kossel, another pupil of Hoppe-Seyler's, took over and together with the Swedish biochemist, Olof Hammarsten (Fig. 1), he laid the foundations for our knowledge of the constituents that make up nucleic acids. They chose to work with nucleic acid from yeast, what we now call RNA, that had originally been discovered by Hoppe-Seyler in his attempts to follow up and confirm Miescher's results.

RNA proved to be made up of heterocyclic molecules, that were either purines or pyrimidines (often somewhat misleadingly referred to as "bases"), phosphoric acid and a sugar. This was shown by Kossel to be a 5-carbon sugar, a pentose, and later one of the leading nucleic acid chemists of this century, Phoebus A. Levene, identified it as ribose. In the meantime, the towering figure in organic chemistry at the turn of the century, Emil Fischer, had clarified the structure of the purines found in both RNA and DNA – adenine and guanine. The Kossel group and Phoebus Levene determined the structure of the pyrimidines uracil, cytosine and thymine, and it was found that RNA contained uracil and cytosine, but not thymine, while DNA contained thymine and cytosine, but not uracil.

We owe much of our knowledge of how the building blocks of nucleic acids, the nucleotides, are built up from their components – base, sugar and phosphate – to Levene, who also showed that the sugar in DNA is deoxyribose. One of his major contributions to nucleic acid chemistry came in 1935 when he proposed that DNA was made up of nucleotides that were linked to each other by phosphodiester-bridges. Unfortunately, Levene had earlier on become firmly convinced that nucleic acids are tetranucleotides, or at the very most, a couple of times repetitions of this structural motif

His tetranucleotide hypothesis, that was widely accepted during the first half of this century, thus underestimated in a grotesque way the gigantic size of these macromolecules. At the same time it did a lot of harm in the sense that it diverted people

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0214-6282/95/$03.00

Fig. 1. Olof Hammarsten (1841-1932).

from the old and perfectly correct idea of the late nineteenth century, that nucleic acids are carriers of genetic information. Levene's tetranucleotide-DNA, a comparatively small and structurally monotonous molecule, could not possibly be the genetic material! Proteins, with their complicated structures and giant size, seemed much more likely candidates.

I first became acquainted with Einar Hammarsten (Fig. 2) in the late 1940s and I vividly remember that to the young medical student he seemed incredibly old. It is something of a shock to realize that he was ten years younger than I am today. He was a man of short stature with sharp grey eyes in a very pale face. The nose had something hawklike about it and he was always chewing on his pipe, even when he talked to his young collaborators. This made conversation with Einar somewhat demanding, but of course in the long run you learned to decode the garbled message. He was not much of a thesis advisor judged by modern standards. One of his favourite maxims regarding graduate students was: "I give them an impossible problem and then I come back after a year to see if they are still there." At the same time, his ability to influence you and fill you with enthusiasm was remarkable – anyone who came in contact with him could testify to that. He had the knack of infecting young people with his own uncompromising, almost religious devotion to science. Einar was a catcher of souls in an almost biblical sense; he left an indelible mark on all his pupils who would carry it with them for the rest of their lives.

He had been courageous, not to say reckless, in his choice of research field. After all, his uncle was Olof Hammarsten, the leading figure in Swedish biochemistry, who had made important contributions to nucleic acid chemistry (Hammarsten, O., 1894). In addition, the dominant uncle had many other strings to his scientific bow than just nucleic acids and his act must have been a tough one for Einar to follow. Pictures of Olof (Fig. 1) show him as a venerable old man – he lived to be 91 and continued to edit his famous *Textbook of Biochemistry* until he was 85 – with a high forehead under thick white hair and a beard that made him look like the very image of a god-fearing, upright Victorian statesman. To his other achievements should be added that of having been President of Uppsala University. Undeniably a figure that could seem a bit overwhelming to his poor nephew.

Maybe I have exaggerated the hampering influence of his famous uncle on Einar. After all, he was not one that stood in awe of great men or was easily impressed by authorities and the powers that be. To illustrate this let me tell a little story that is very typical of him. The department was in the process of moving to a new campus outside Stockholm. Funds for the equipment of the new premises had been appropriated by a paternalistic government, but Einar kept delaying the actual moving month after month. In the end it appeared that there was no money for equipment – we had spent it all on our research. Einar went up to the Ministry to break the good news and it must have been a black day for the well-behaved government officials in charge. I do not know what he said to them, but knowing Einar it probably was something like: "By all means, put me in jail!" It did not come to that, of course. Instead they gave us new money for equipment, which shows the truth of another of his maxims: "Timid boys never get to sleep with beautiful girls."

Einar Hammarsten's greatest scientific achievement is that he was one of the first to show that DNA is a macromolecule (Hammarsten, E., 1924). Phoebus Levene's tetranucleotide hypothesis rested on two main points – the fortuitous observation of equimolar proportions of the four nucleotides when undefined mixtures of RNA were analyzed and the complete lack of reliable

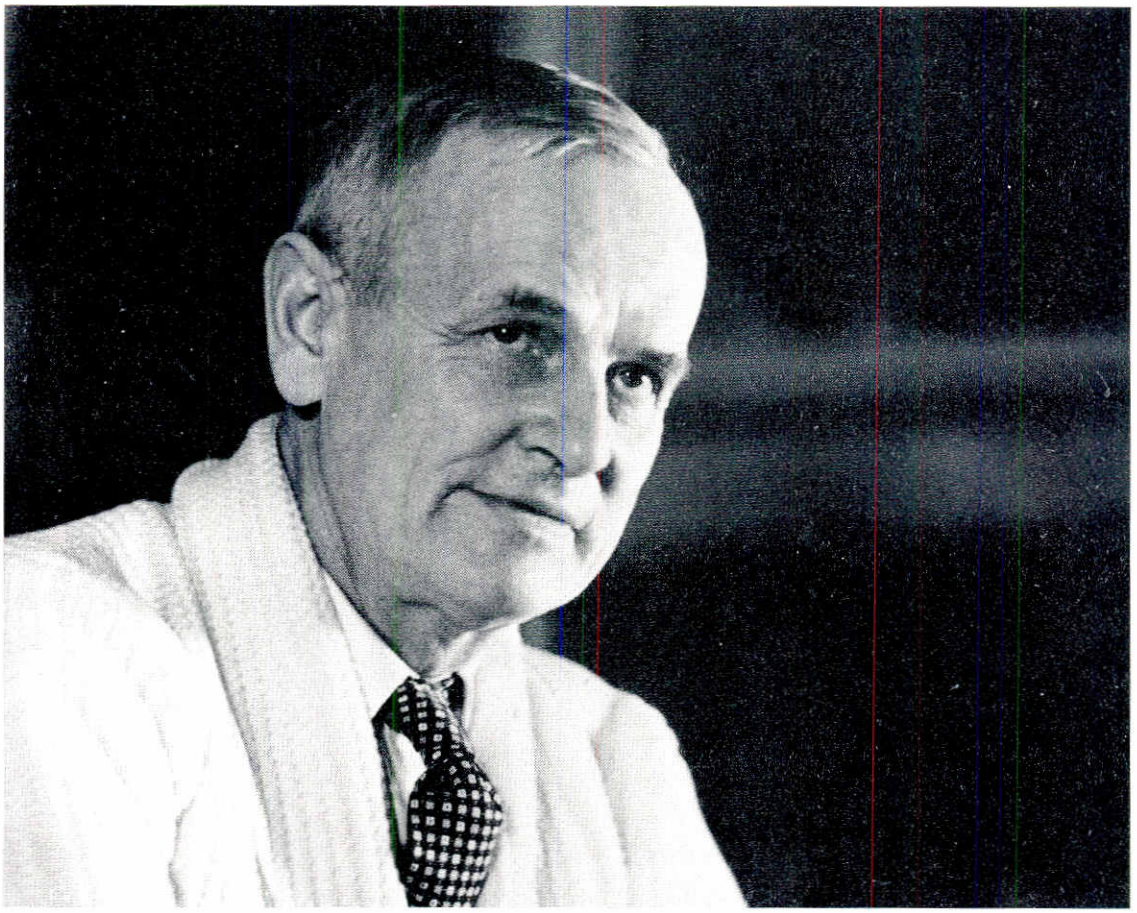

Fig. 2. Einar Hammarsten (1889-1968).

information on the molecular weight of both RNA and DNA. Certainly, Miescher had found that his salmon sperm nuclein did not diffuse through a membrane permeable to smaller molecules, but these early observations were disregarded or put down to aggregation of the ubiquitous tetranucleotides. It was therefore an important step forward when Einar and his collaborators could show in 1938 that carefully prepared DNA from thymus (Hammarsten, E., 1924) behaved as thin, rod-like molecules with an apparent molecular weight approaching a million. These results undermined the tetranucleotide hypothesis and when in 1950 Erwin Chargaff showed that DNA did not contain equimolar proportions of the four standard nucleotides as Levene had maintained, the hypothesis became definitely untenable.

In my humble opinion Einar Hammarsten's contributions to nucleic acid chemistry compare favourably with those of his famous uncle. His most important contribution to science, though, was Einar Hammarsten himself – his enthusiasm and dedication, and his ability to persuade young people that science is something worth devoting your life to.

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