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Reflections

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Osvald T. Avery and the Nobel Prize in Medicine

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In 1944 the *Journal of Experimental Medicine* published a paper by Osvald T. Avery and collaborators (1) entitled "Studies on the Chemical Nature of the Substance-inducing Transformation of Pneumococcal Types. Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from *Pneumococcus* type III." Avery reported the results of more than 15 years of systematic attempts to identify the chemical nature of the substance that changes a heritable property of a bacterium. He demonstrated that DNA is the chemical equivalent of the then purely formal concept of genes. Considering the scientific developments during the remaining 20th century this was arguably the most important discovery in physiology or medicine of the century. Avery lived until 1955 but was never even in the vicinity of a Nobel Prize in physiology or medicine. Why?

The scientific community was not very interested in nucleic acids in 1944. Only a few scientists were active in this field. One of them was Einar Hammarsten, Professor of Chemistry at the Karolinska Institute in Stockholm. In 1924 he had published a thesis (2) about the preparation and properties of DNA or thymonucleic acid as it was called at that time. In the ensuing 20 years he worked with both DNA and RNA. Only a few students joined his endeavor. Most notable among them was Torbjörn Caspersson who by 1944 already was Professor and head of a Nobel Institute at the Karolinska Institute. Caspersson was surrounded by a large group of young enthusiastic collaborators. Some of them were graduate students; others had already established themselves in medical specialties such as microbiology, virology, and pathology. Caspersson headed one of the most active research centers at the Karolinska Institute. He had developed a new ultraviolet microscope to study nucleic acid and protein metabolism (3), and he and his collaborators applied the new methodology to many different biological systems.

I have described elsewhere (4) my intent in 1945 to start my graduate studies with Caspersson and how, instead, I turned to Hammarsten and became his student. I stayed in his laboratory until his retirement in 1957 and (in particular during the early years) listened to many of his monologues both on nucleic acid research and on Nobel prizes. Later on, as Professor at the Karolinska Institute after 1964, I became rather heavily involved in the work of the Nobel committee during a 20-year period and had the opportunity to learn about deliberations of earlier committees. As described below, I became introduced to Avery's work already as a young graduate student but only later in life began to ask myself questions about why he never received a Nobel Prize. Here, I make an attempt to give my answer. I will first briefly describe the organization of the Karolinska Institute's Nobel activity in the middle of the previous century. I will then in more detail discuss the research carried out by the groups of Hammarsten and Caspersson, their concepts about the biological function of nucleic acids, and how this may have affected their attitude to Avery's work.

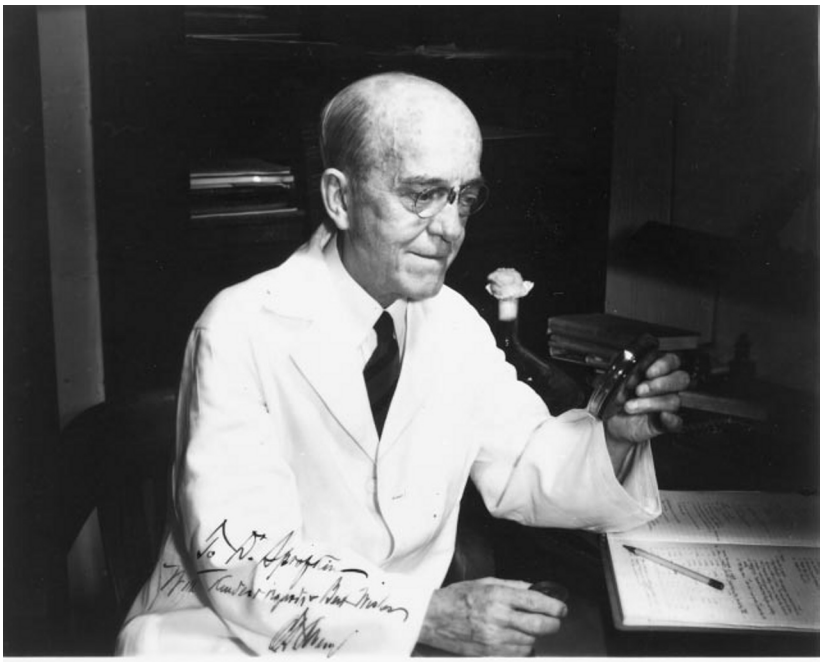

FIG. 1. **Oswald T. Avery (1877–1955).** Courtesy of The Rockefeller University Archives.

The Karolinska Institute and Its Nobel Activities at the Mid-20th Century

The Karolinska Institute was and is the medical school of Stockholm. In 1944 the faculty consisted of ~25 full professors, each representing a clinical or preclinical specialty. Hammarsten's chair was in chemistry, a name that dated back to the days of its first occupant, the famous Jöns Jacob Berzelius, and was a matter of no small pride. Hammarsten had a complete medical education, as had all his colleagues in the faculty, but was rather disdainful of that fact. Only a very limited number of the institute's professors carried out research. The state did not provide money for this purpose until some years after the war, and research depended largely on a few private sources. In this respect, the Rockefeller Foundation played a large role, with Hammarsten and his collaborators being major recipients of support for many years. With Warren Weaver at the helm the Foundation supported mainly biochemical and biophysical research for which Weaver coined the name molecular biology, probably the first use of this term. In Hammarsten's case, the Rockefeller Foundation provided not only the major part of the yearly research budget but also postdoctoral fellowships for young Swedish scientists to allow them to work for some time in an American laboratory. As one of the recipients I can testify to their importance for widening the horizon of a young researcher brought up in a small and closed scientific community.

Once a year the 25 professors of the Institute decided on the winners of the Nobel Prize in Physiology or Medicine and announced their names. A Nobel committee of three members, appointed for a 3-year period, had discussed the competing candidates and made a proposal for the prize. Each year the committee temporarily adjoined several additional professors to its discussion. As only a few professors were active scientists the number of knowledgeable committee members was quite limited. Hammarsten had not a very high opinion of most of his colleagues and delighted in telling the story of how Otto Warburg, Nobel laureate in 1931, had expressed his surprise that "so ein obskurer Aeropag" was given the task to select Nobel Prize winners. Because of his scientific qualifications and seniority Hammarsten participated continuously in the deliberations for the prize during the period of 1946–1955. He had considerable influence on the choice of laureates and would in all probability have been able to make Avery a winner had he set his mind to it. Other knowledgeable faculty members who could have come out for Avery were Caspersson and Berndt Malmgren. The latter was Professor of Bacteriology and originally a close collaborator of Caspersson. Finally, there was Hugo Theorell who was Chairman of Biochemistry at the medical Nobel Institute. In his case, a major complication was that he himself was a serious candidate for the prize and indeed received it in 1955. Caspersson also was a candidate during that period. One can imagine that under those circumstances neither Theorell nor Caspersson would strongly favor Avery for a Nobel Prize.

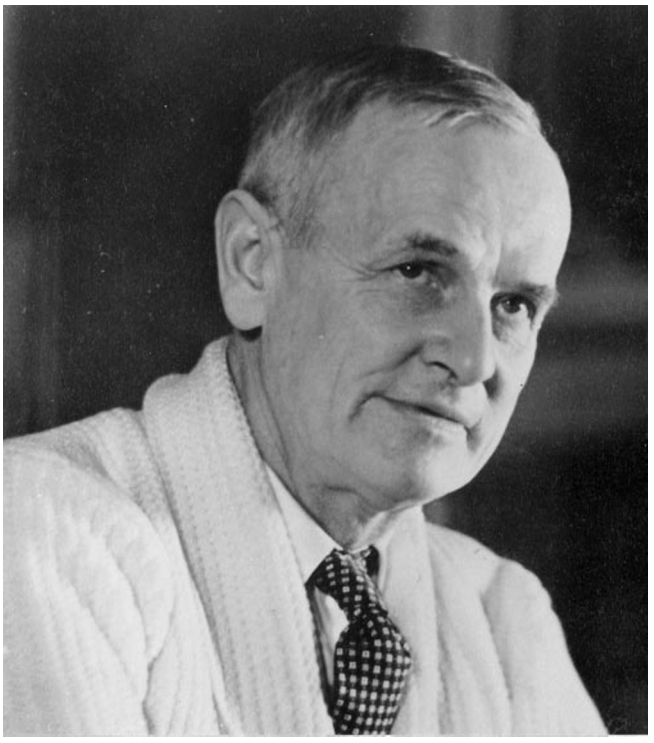

FIG. 2. **Einar Hammarsten (1889–1958).** Professor of Chemistry at the Karolinska Institute, 1928–1957. Courtesy of Professor Ulf Lagerkvist.

Each year the Nobel committee invites scientists all over the world to propose the names of candidates. Some of the nominations are then further evaluated in a written report, often but not always by a committee member, and the committee then orders the candidates into one of three groups: 1) not worthy of the prize; 2) at present not worthy of the prize; or 3) worthy of the prize. The final discussion involves only the last group, which always contains several names. To win the prize, strong candidates must as a rule be nominated and their work evaluated for several years.

Avery as a Candidate, 1932–1946

The first prerequisite to win a Nobel Prize thus is to be nominated. Starting in the early 1930s Avery (Fig. 1) was nominated almost yearly for the Nobel prize for his and Michael Heidelberger's discovery that the antigenic specificity of type III pneumococci depends on their polysaccharide coat and not (as was generally believed) on a surface protein. Their work thus demonstrated the biological specificity of polysaccharides. Many scientists were critical of this conclusion and suggested that the antigenic properties depended on protein contamination. Further work by Avery's group soon dispelled this objection. Before 1946 his work was evaluated in four written reports, one of them by Hammarsten. In all cases the work was not considered worthy of a Nobel Prize.

Starting in 1946 the nominations also began to cite Avery's work on bacterial transformation by DNA. Each year the committee received several nominations, some of them by outstanding scientists including former and future Nobel Prize winners. It is striking, however, that for a long time most nominations included Heidelberger's name and concerned the antigenic specificity of polysaccharides and not transformation by DNA. The latter work was discussed for the first time in 1946 in a brief evaluation by Hammarsten, who was critical and believed that Avery's DNA was contaminated with protein and that protein (and not DNA) was the transforming agent. History had repeated itself.

Einar Hammarsten

Let us now consider the scientific work of the Swedish groups. Einar Hammarsten (Fig. 2) was a remarkable person. His father was the predicant of the royal family and known for his brilliant sermons in the cathedral. His uncle Olof identified pentose in nucleic acids when he was Professor of Physiological Chemistry in Uppsala and later became President of the University. Einar excused the profession of his father by saying that the family of his grandfather was poor and that there was no money to support the younger son, his father, who therefore instead of studying medicine as his older brother had to accept a fellowship at the

theological faculty. For his uncle, who gave up research to become President of the University, he had no excuse. Einar was completely dedicated to research and up to an advanced age worked long days at the bench in the laboratory. He spoke unkindly of his colleagues in the faculty who preferred to spend their time earning money in private practice.

In his thesis (2) Einar had applied a new, gentle method for the preparation of DNA from thymus, avoiding the then common treatment with strong alkali. His DNA differed in many ways from that prepared by the older methods. It was highly viscous, had a low osmotic pressure, and gave fibers on precipitation with alcohol. During the following years he and his collaborators studied this preparation with several of the then available methods of physical chemistry including ultracentrifugation in The Svedberg's newly developed machine and concluded that DNA had a very high molecular weight, possibly about one million (5–8). This clearly did not agree with the then prevalent hypothesis introduced by Phoebus Levene at the Rockefeller Institute that both DNA and RNA were simple tetranucleotides consisting of one of each of the common nucleotides (9). Obviously such a simple structure could not be the genetic material. In a different line of research Einar's student Erik Jorpes demonstrated that RNA from pancreas contained an excess of guanine and thus could not be a tetranucleotide (10, 11). Such results flew in the face of the tetranucleotide idea but were not appropriately recognized in comparison with the chemical work of Levene. One contributing factor was that Einar Hammarsten was not a great communicator. He published very sparsely, and his papers were not always easy to understand.

When I came to his laboratory he had for many years unsuccessfully tried to obtain "native" DNA free of protein. He, better than anybody else, could appreciate the difficulties that Avery faced in trying to remove protein from DNA. Furthermore, Einar believed that the destruction of the transforming principle by deoxyribonuclease was due to proteolytic contaminants in the impure enzyme preparation. This enzyme had been partially purified from pancreas by Avery's collaborator, Maclyn McCarty (12). It was at this point that I came into the picture. I was now a graduate student of Einar and was looking for a thesis project. He suggested that I should crystallize pancreatic deoxyribonuclease and study its properties. To this purpose he provided me with two reprints; one was McCarty's paper, and the other was a paper by Moise Kunitz (13) describing the crystallization of ribonuclease. Einar himself had no experience with enzyme purification, and I was completely left to my own non-existing resources. This was rather typical of him; obstacles were there to be overcome. Noticing my hesitation he admonished me with one of his often used wisdom words: "Rädda pojkar får inte ligga med vackra flickor" (easily frightened boys don't sleep with beautiful girls). I was unsuccessful and had to give up. Kunitz, the great master, crystallized deoxyribonuclease within a few years (14).

At that time Einar had already started a completely new and highly ambitious project. George Hevesy had come from Copenhagen to Stockholm in connection with the Jewish exodus from Denmark in 1943. In 1944 he received the Nobel Prize in chemistry for his work on "the use of isotopes as tracers in the study of chemical processes." Einar realized the enormous potential of the tracer technique for biological experiments and investigated together with Hevesy the incorporation of ^{32}P-labeled phosphate into RNA and DNA in rats (15). The isotope was rapidly incorporated into RNA but not into DNA, reflecting the metabolic stability of DNA. A major impetus for this experiment was provided from the work of Caspersson who from ultraviolet microscopy of cells had suggested that RNA synthesis was required for the synthesis of proteins in the cytoplasm (see below).

Einar wanted to use isotope experiments to investigate this question himself. Schoenheimer's group at Columbia University in New York had at that time already published much of their pioneering work with deuterium and ^{15}N on the synthesis of lipids and proteins that led them to the concept that proteins are continuously renewed in cells (16). Einar decided that this was the way to go: to study nucleic acid synthesis and its relation to protein synthesis with stable isotopes. This required a mass spectrometer, but there was no such machine in the whole of Sweden. So let's build one. Considering that the government provided no money for research and Einar completely lacked the required expertise it was indeed a daunting task. However, obstacles are there to be overcome. After several years and with the aid of two American scientists, Richard Abrams and David Rittenberg, there was a functioning mass spectrometer in the laboratory in 1946. The machine was a prerequisite for a series of theses that appeared from the laboratory during the following years including my own experiments with ^{15}N-labeled nucleosides that resulted in the discovery of ribonucleotide reduction (4).

FIG. 3. **Thorbjörn Caspersson (1910–1997).** Professor of Cell Research and Genetics at the Karolinska Institute, 1944–1977. Courtesy of Professor Nils Ringertz.

Sadly, the technique was unsuitable to solve Einar's question concerning the relation between nucleic acid and protein synthesis.

Torbjörn Caspersson

Caspersson (Fig. 3) had collaborated with Hammarsten in some of the early experiments characterizing DNA, but soon he demonstrated a great talent to construct optical machinery. In his thesis he described the development of a monochromatic ultraviolet microscope and its use to measure the content of nucleic acids and proteins in individual cells (3). Nucleic acids were quantitated from their absorption at 260 nm. A distinction between RNA and DNA could be made with the Feulgen reagent, which is specific for the deoxyribose component of DNA. Proteins were quantified from their absorption at 280 nm. Both RNA and DNA absorb strongly at 260 nm and could be determined with some confidence. Proteins have a much weaker absorption in the ultraviolet; the absorption depends on the amino acid composition, and it is affected both by the presence of nucleic acids and by unspecific light-scattering effects. Despite these difficulties Caspersson believed that it was possible to use the technique to determine changes in protein content of individual cells and even to distinguish between different classes of proteins.

During most of his ensuing scientific life Caspersson improved the instrumentation in collaboration with highly skilled engineers. Improving the machinery was his greatest joy in the laboratory. Later in life he employed the new microscope and fluorescent technology to chromosome banding (17), a technique that revolutionized medical genetics as it made possible the identification of single human chromosomes.

Already before 1940 Caspersson had discovered that cells engaged in rapid protein synthesis contain much larger amounts of RNA than resting cells (18). Also Jean Brachet in Brussels arrived independently at the same conclusion using a completely different technique (19). Both suggested that RNA had a central role in protein synthesis.

At about this time Caspersson also reported that the DNA of insect chromosomes was localized in distinct bands (20, 21), reminiscent of the bandlike structure of genes, and suggested that DNA was involved in gene replication. It would have been only a small step to the insight that DNA is the genetic material, but Caspersson never took this step. Instead, he

wrote that only the structure of proteins offered enough variations to function as genes (20) and suggested that DNA during gene reproduction underwent a polymerization of smaller groups into a larger aggregate (21) that could serve as a rack on which extended protein molecules were reproduced. He supported this idea with results from Astbury's x-ray crystallographic work (22) that demonstrated that the spacing of nucleotides in DNA was identical to the spacing of the side chains of a fully extended polypeptide chain. The Caspersson group also had distinct ideas of how RNA participates in protein synthesis (23, 24). From measurements of the 280 nm absorption of cells during protein synthesis it was proposed that basic proteins of the cell nucleus migrate from the heterochromatin to the membrane of the cell nucleus and there induce the synthesis of RNA, resulting in the synthesis of globular proteins in the cytosol. Proteins were thus placed at center stage, with both DNA and RNA performing auxiliary functions.

Avery as a Candidate 1952–1955

My contact with Avery's work had been brief but alerted me to his ideas. His results were not a major theme of discussion in the laboratory, and I had no inkling that Avery could have been in the vicinity of a Nobel Prize. Even though the awarding of the Nobel Prize is and was shrouded in great secrecy, Hammarsten did not hesitate to comment on the committee's discussions, especially when in his opinion it had resulted in a flawed decision, but I never heard Avery's work mentioned in that context. Hammarsten did not believe that genes consisted of DNA. This was obviously not because he viewed DNA as a simple tetranucleotide. He himself had demonstrated the macromolecular nature of DNA, which together with variations in base sequence provided the structural requirements for biological specificity. This concept was reinforced in a memorable seminar by Erwin Chargaff, who visited Stockholm around 1947. His analyses of DNA by paper chromatography demonstrated considerable variations in the base composition of DNA from various organisms. Chargaff was enthusiastic about Avery's results and actually proposed him for the Nobel Prize. For me his seminar was memorable because it illustrated the power of chromatography and induced me to use starch chromatography for the purification of nucleosides in our tracer experiments (4).

Why then did Hammarsten not accept Avery's conclusion? First, there was his own experience that proteins also always contaminated highly purified preparations of DNA, but he was also influenced by Caspersson's model for the metabolic interrelation between proteins and nucleic acids, which gave nucleic acids a secondary role. It was to elaborate on Caspersson's ideas that he had decided to start the construction of a mass spectrometer.

In the meantime the evidence for DNA was mounting. Avery had retired but others continued his work at the Rockefeller Institute. Citrate is a strong inhibitor of deoxyribonuclease, and its inclusion during the purification of the transforming principle greatly increased its yield (25). Most importantly, there appeared reports of other DNA-dependent instances of bacterial transformation. Rollin Hotchkiss (26) transferred penicillin resistance with DNA preparations from appropriate strains of pneumococci, André Boivin in Paris (28) reported that DNA induced directed mutations in *Escherichia coli*, and Hattie Alexander and Grace Leidy (27) reported DNA mediated transformation in *Hemophilus*. A separate line of evidence in favor of DNA came from Boivin and the two Vendrelys (29). They found that all mammalian diploid cells contain the same amount of DNA, twice the amount of haploid cells. This provided a parallel to the halving of the number of genes from somatic to germ cells.

Nevertheless the old paradigm of genes being proteins and DNA only providing a structural support during gene replication did not die easily. As Maclyn McCarty relates in his lovely book (30), Avery himself did not loudly spread the new gospel. He apparently had a quiet and self-effacing personality, presented his work in a low key manner, and was adverse to speculation. His presentations were few, and when invited to speak at larger meetings he usually sent his younger collaborators. I was particularly struck by the description of his refusal in 1946 to travel to England to receive the prestigious Copley Medal from the Royal Society (30). It was, instead, brought to him to the laboratory in New York by the President of the Society, Sir Henry Dale. Avery was a modest man and hardly a prophet for his ideas. Of course he would never have dreamt to come to Stockholm to give a lecture and present his work.

How did all this affect the Nobel committee? In 1952 Malmgren, Professor of Bacteriology and former collaborator of Caspersson (24), prepared the first detailed evaluation of Avery's

work on transformation for the committee. He also discussed Hotchkiss' experiments in support of Avery and now considered it unlikely that protein was involved in transformation. Nevertheless he then concluded that the final evidence for DNA as the transforming principle was missing and that Avery therefore at the present time was not worthy of a Nobel Prize. This also became the conclusion of the committee.

The turning point in the general opinion came with the paper by Alfred Hershey and Martha Chase (31) in 1952 and, in particular, the paper by Jim Watson and Francis Crick (32) in 1953. The first publication demonstrated that ^{32}P-labeled DNA but not ^{35}S-labeled protein entered *E. coli* during infection with bacteriophage T4. Because viruses were recognized as counterparts of genes the experiment strongly supported the ability of DNA alone to show genetic activity. Hershey was a member of the highly influential phage group who had viewed Avery's claims with considerable skepticism. From a recent book (33) commemorating Alfred Hershey it appears that he actually had not expected the outcome of his experiment. Indeed the amount of ^{35}S (= protein) introduced into *E. coli* indicated a much larger contamination by protein than in Avery's experiments, but now time was ripe and Hershey's experiment was generally accepted as transfer of genetic information by DNA. The famous paper by Watson and Crick demonstrating the complementarity of the two strands of the DNA double helix provided a molecular explanation for gene replication and dealt the final blow to the protein paradigm.

In 1954, after the appearance of the two publications, Hammarsten made a third evaluation of Avery's work for the committee. The report was very short. It is somewhat surprising that no mention was made of the new discoveries. Hammarsten now accepted that DNA and not protein is the transforming principle. He pointed out that the discovery was of great importance but concluded that the mechanism for the transformation was completely unknown and that for this reason the discovery at the present time was not worthy of a Nobel Prize. This became again the conclusion of the committee.

Before sitting in judgment on the Nobel committee we should consider some of the elements involved in the committee's yearly deliberations. Nobel's testament stipulates that the prize should go to a discovery that "during the preceding year shall have conferred the greatest benefit on mankind." For the medicine prize this stipulation has never been met. It takes time to verify a discovery and to understand its importance, as is evident from Avery's case. There are several examples in which a prize in medicine was given prematurely for a discovery that later on was faulted, most blatantly in 1926 to Fibiger for his discovery of the "Spiroptera carcinoma," a non-existing disease. Nobel prizes therefore go to well established discoveries, which are recognized by a large majority of the scientific community. A prize to Avery could therefore hardly be considered seriously before 1952–1953. The committee can, however, be faulted for accepting in 1952 and in 1954 the conclusion of its experts that Avery was not worthy of the Nobel Prize.

Avery died in 1955. There was a window of 2 years during which he could have become a Nobel laureate. I believe that this window would have been too narrow, even if the 1952 evaluation had been positive. Nobel committees move rather slowly, and a discovery resulting in a prize is generally in the forefront of the committee's deliberations for several years, in competition with other discoveries. In 1953 the prize went to Krebs (citric acid cycle) and Lipmann (coenzyme A) and in 1954 to Enders, Weller, and Robbins (poliomyelitis virus). Hammarsten had been fighting for the biochemical prize, and the strength of the second group whose work resulted in the development of the polio vaccine is obvious. Both groups had been strong candidates for several years. With hindsight we can blame the committee for having bypassed the greatest biological discovery of the century, but considering the circumstances of that period it is understandable.

Circumstances changed rapidly. Acceptance of DNA came overnight. A few years after Avery's death we find the names of J. Lederberg (1958), A. Kornberg (1959), and F. Crick, J. Watson, and M. Wilkins (1962) among the laureates. The composition of the Nobel committee had changed. The number of professors at the Karolinska Institute increased dramatically and made possible an increase and renewal of the committee that greatly expanded its scientific expertise.

Avery was 65 years old in 1944 when he published his first paper on the transforming ability of DNA. It is a good thought that a great discovery can be made at an advanced age. Considering the increase in longevity in our time, it may now even be possible to live and receive a Nobel Prize for the discovery.

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