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From human to sea urchin development

An interview with Professor Giovanni Giudice

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Giovanni Giudice´s career started with a degree in Medicine and initially a specialization in Pediatrics. He then moved to the field of Developmental Biology and already by 1961 was able to reconstitute entire embryos from dissociated cells, which represented the first instance of embryo reconstruction from isolated cells in developmental biological history. This opened a new research area in sea urchin developmental biology. Mainly for this he was awarded the Feltrinelli prize of the National Accademia dei Lincei in 1996. He was among the pioneers of molecular biology especially applied to embryology. Among his more recent fields of scientific interest are the heat shock proteins in sea urchin development. He dedicated part of his time to Italian politics, becoming first a Senator of the Italian Republic in 1976, and then a member of the Italian Deputy Chamber in 1979. He has also written leading international monographs on sea urchin developmental biology and has played an important role in science divulgation through both novels and articles in the national press.

You had just got a degree in Medicine and Surgery with the highest grades when you decided to give up Medicine and to dedicate yourself to studying an invertebrate like the sea urchin embryo; what was the reason of such a decision?

The reason has deep roots. In 1956 I had just started my specialization in pediatrics and was moved by seeing children suffer, a fact which too many times I could do nothing about. It left me with the impression that the medical field essentially tries to cure rather than to prevent. My interest lay in prevention. That is when I met professor Alberto Monroy, who had been Associate Professor of the Faculty of Medicine and then decided to change to the Faculty of Natural Sciences and to dedicate his time to the study of developmental biology, or more specifically, of the sea urchin embryo. At the time he was a full professor and was known throughout the world as a first rate scientist. He invited me to collaborate with him, offering me a fellowship which came to a grand total of about 12 dollars per month! This meant giving up a prestigious carrier in pediatrics and a wealthy life for the sake of science. I hesitated and asked him if I could complete my specialization first and then make up my mind, possibly even sharing my time between pediatrics and developmental biology. A few days later Monroy called me and said: "It is impossible to do pediatrics and developmental biology at the same time. Therefore I will make the decision for you; come and work with me!" I accepted and left pediatrics for developmental biology; but for the first year I could not understand why I had to waste my time with such a stupid beast as the sea urchin instead of fighting for

Abbreviations used in this paper: BBRC, "Biochemical and Biophysical Research Communications" research journal.

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Fig. 1. Giovanni Giudice and Alberto Monroy at a party at Monroy´s house in 1961.

children's health every day. But little by little I understood that this was due to my ignorance of the system, and started to understand what a unique model system for cellular and developmental biology the sea urchin was, so that later on I used to joke saying that the sea urchin must have evolved from man.

What did you inherit from your mentor and how did you use this inheritance?

There are two aspects in relation to this question. First, the scientific influence he had on me when he was alive and second the scientific inheritance strictly speaking. I believe that my best work derived from a close working relationship with him, which included open communication and a constant exchange of ideas. I believe that I passed this on to my students and therefore at least part of their best work came from this. This led me to believe in the importance of the exchange of ideas within a group in order for there to be progress in the scientific world. Just a few examples of this are the ideas he gave me for sea urchin cell reaggregation, and for heat shock, and those ideas I gave to him for ribosome activation at fertilization, and to my students, now colleagues, for nucleo-mitochondrial interaction and for animal-vegetal axis, in sea urchins.

An important part of the inheritance is a group of young scientists working on sea urchin development, whom I tried to help to continue, when Monroy moved to Naples in 1969. They have now aggregated into the present Department of Cellular and Developmental Biology at the University of Palermo, and into an Institute of Developmental Biology of the Italian National Research Council, both founded by me. Their work is highly esteemed at an international level, which is one of the main prides of my scientific life, especially considering the conditions of the Italian research organization at the time I founded these Institutions, about twenty years ago.

Monroy's idea was that it was important to send young people to the best labs of the world to "open their minds" and get new ideas and techniques. So he did with his students, including myself, and so I did and still do with my students. Some of them remained abroad forever, sometimes in leading positions. Others however, came back to reinforce the Palermo lab.

One thing I wish I inherited more from Monroy is his genuine interest and curiosity for other people's work, both at a national and an international level, so that he was one of the best informed scientists of the world. I try to do my best in that, but I find it difficult to reach his level.

What was the interest in Italy for this kind of research when you started?

The main interest in developmental biology was centered at the Zoological Station of Naples, where Monroy had been head of department for 8 years, and where people like John Runnström and Sven Hörstadius were still working on sea urchin embryos. Monroy then transferred his interest and enthusiasm to Palermo, where we worked together for fifteen years. What he started was the application of the then nascent field of molecular biology to embryology, and I was immediately attracted to this. Also Silvio Ranzi in Milan had understood this importance, but Monroy's group in Palermo was the first in Italy and among the first in the world to work steadily with this approach. For this reason he sent me in 1962 to work on protein synthesis with David Novelli, deriving from Fritz Lipan's group, at the Oak Ridge National Laboratory in Tennessee.

What did you work on there?

There were no sea urchins in Tennessee, so I worked on rat liver. There I provided, by inhibiting mRNA synthesis with actinomycin D and enzymatically detecting its product many hours later, the first indirect evidence for the possibility that in eucaryotes, mRNA might have a long half life, as published in BBRC in 1963. Remember that at that time the idea people had of mRNA was of a fugacious molecule, very short lived, as it is in bacteria. The idea of the possibility of storing mRNAs had immediate implications for developmental biology, where in the same year Gross and Cousineu, with a similar approach to that used by me in rat liver, but independently, showed that sea urchin eggs contain stored mRNA to be used later in development. I also demonstrated for the first time, with my friend Piero Cammarano, the binding of aminoacyl-transfer RNA to polysomes, also published in BBRC, and I must say that I had found after Rich's discovery of polysomes in reticulocytes that also the ribosomal population in rat liver was mostly in the form of polysomes, but this was not published because of a hesitation on behalf of Novelli, who suspected this was a technical mistake of mine, and therefore Wettstein and Noll published it first. Young people should appre-

ciate that at that time ribosomes were known only as monoribosomes and the existence of polyribosomes had just been reported only for those synthesizing hemoglobin.

Which work of yours do you consider the most important?

I think the most important is that on dissociation of sea urchins into single cells, followed by their reaggregation with restitution of entire embryos, published in "Developmental Biology" in 1962. This was carried out in Palermo, before my first visit to USA. This represented the first instance of reconstitution of entire embryos of any kind from dissociated cells.

How did this happen?

As it often happens, partly because of an intuition of mine, partly because of luck, and partly because of a suggestion of my mentor. Here is how it went: I was working in 1961 on protein synthesis in isolated mitochondria in sea urchin embryos, and therefore I had to homogenize sea urchin embryos in a medium which would not damage mitochondria, which contained isotonic sucrose, a citrate buffer and a calcium chelator, EDTA (at that time called "Versene"). I observed that after a few strokes of the Potter hand homogenizer, before I got cell breakage, I obtained free sea urchin cells which looked very lively, and were actively moving. I then decided to study their ability to synthesize proteins and therefore started looking for the best incubation medium for that, by changing the various ions one by one. Finally, I realized that the best medium for them was just plain seawater! Up to that point my merit; now the other two ingredients: luck and my mentor's suggestion. Monroy said: "They look well, why don't you try to aggregate them?". I put them into a beaker in seawater with a rotating propeller and went to sleep. The next morning I looked at them and at first I thought I had gone crazy: instead of isolated cells, I found blastulae, which were lively swimming around! These blastulae then made an intestine, a skeleton which was typically elongating in a pluteus-type manner, and finally differentiated into pluteus-like embryos. A new "era" had started: that of sea urchin embryo dissociation-reaggregation studies. The new plutei were not perfect, but, as I used to say, "To me, as their father, they look rather cute". And here Monroy gave me a fundamental lesson which I have never forgotten: he refused to put his name on the paper, "because", he said, "you are still too young and people would believe that I did the work". Consequently I have never put my name on work which belongs fundamentally to my students.

What research derived from this work?

First, I asked myself many questions such as that of the species-specificity of reaggregation. Then, I began to wonder about the way the new embryo was made. Was it through a dedifferentiation and redifferentiation process according to the new place occupied by each cell in the aggregate, or rather through a sorting out? The first answer I gave in 1963 to this second question was that the cells maintained their animal or vegetal destiny at least after Zn or Li treatment of the eggs. An important question was that of the need of cell interactions for a metabolic change to occur at a programmed time during development. This question, asked first by myself in 1967, was then asked by several authors with respect to a variety of activities such as the turning on of specific genes. Another similar question, was that of the need of cell interaction for DNA synthesis during development, to which answers were provided by myself in collaboration with my colleague Letizia Vittorelli. For example it was found that the arrest of DNA synthesis due to the experimental lack of cell interactions could be reverted by a mild treatment with trypsin.

Many other people became interested in the problem of cell dissociation and reaggregation in sea urchin embryos, among which were Melvin and Evelyn Spiegel early on and then Dave McClay, who is presently carrying out probably the most important work in the field of cell interactions in sea urchin embryos. A special case is that of Hans Noll, who after reading my paper on cell reaggregation, came to spend some years in my lab in Palermo starting in 1977. He set out to discover the molecules which keep the cells together in the embryo and permit reaggregation and differentiation. He, in collaboration with a group of coworkers of mine, which included Letizia Vittorelli and Valeria Matranga, used an approach developed in other embryos by Hausman and Moscona, which consisted of the treatment of embryos with diluted butanol. This extracted a surface particle from the sea urchin embryos, which Noll called toposome. Following this treatment, the embryos disaggregated into cells which were no longer able to reaggregate, but if the butanol extract was dialyzed and added back to the cells, they reaggregated again and differentiated into pluteus-like structures. A theory was then proposed by the author that toposome contains positional information which places each cell in the right place in the embryo. This theory has not yet been proved, but is consistent with the data which have been produced so far.

What are the other works of yours which you consider especially important?

One tends to consider all of one's own work especially important, but if I have to choose, I will mention a new line of research on heat shock proteins or "hsps" in sea urchin embryos, which

From left to right: **Eizo Nakano, Nino Oliva and Giovanni Giudice in the Department of Cellular and Developmental Biology at the University of Palermo in 1977, on the occasion of a visit of Dr. Nakano to the Palermo lab.**

Giovanni Giudice in his function as Vice-Rector of the University of Palermo, in the Rectorate building (the "Steri", built in 1300). From left to right: **the Dean of the Faculty of Science, Francesco Raimondo, Giovanni Giudice and Giovanni Fierotti.**

once again originated from a suggestion of Monroy, and has been carried out since 1979 essentially with the collaboration of Mariela Roccheri and yourself. We demonstrated for the first time (except for a similar experiment in *Drosophila*) that the ability to respond to heat shock with the synthesis of heat shock proteins only arises at a certain developmental stage, namely blastula in Paracentrotus. We proposed for the first time a protective role for the hsps against heat shock, because if you subject the embryos to heat shock at a stage at which they are not yet able to synthesize hsps, they die, but if you heat them at a stage when they are able to synthesize hsps, they undergo a wave of such a synthesis, then revert to a normal pattern of protein synthesis and survive. Since then, genes for hsps from sea urchins have been isolated by you yourself and mechanisms for the regulation of such a synthesis have been proposed by our group. Another important line I think was that in which in 1966, coworkers and I demonstrated that in sea urchins, ribosomal RNA synthesis which is active during oogenesis, is resumed at a high level following hatching, referred not only to each embryo, but also to each embryonic nucleus (although this last point has been debated); we also demonstrated that this new synthesis is due mostly to the intestine plus mesenchymal cells. In 1966 we predicted the existence of a precursor of ribosomal RNA, which at that time had been found only in mammalian cells. Then in 1970, we demonstrated its presence and described the steps of its maturation, after having developed a method for preparation of oocytes, of their germinal vesicles and of their nucleoli. Also in 1966 we gave the first demonstration of the presence of species-specificity and of the lack of organ specificity of ribosomal proteins, for which there was no information yet at that time. Another interesting point, starting in 1971, was the demonstration beyond any doubt that a heterogeneous RNA, of similar size to the nuclear one, exists also in the cytoplasm of the sea urchin embryo.

Did you get ideas or propose theories which were developed and shown to be true only years later, maybe by others?

I believe that one example of what you asked was an idea of mine which I often discussed with Monroy in the early seventies. It concerned the explanation of the experiments of Hörstadius in 1928 in which he demonstrated that the unfertilized sea urchin egg is already polarized, being able to originate only animal structures from one side and vegetal ones from the other side. I held that this might have been due to the fact that during oogenesis, different mRNAs might have been synthesized from the ovary and stratified in an orderly way in the egg, where some cytoskeletal structure anchored them so as to form a gradient of proteins. I therefore argued that when people would have been able to demonstrate the presence of specific mRNAs and proteins in different parts of the egg, the problem of the egg axes would receive an important help toward its solution. This was shown to be true about twenty years later for other embryos, such as e.g. *Drosophila*. Furthermore, in 1994 a former student of mine, Marta Di Carlo, with young coworkers addressed it in sea urchins and came up with the discovery of some RNAs and proteins localized exclusively in the animal side of the unfertilized egg, which probably have a role in the animal development, since antibodies against them cause exogastrulation. She has now found other maternal RNAs located only in the vegetal side of the egg. On this occasion, following an idea of mine, we found a new way of orienting the sea urchin egg along its animal-vegetal axis, since we demonstrated by microsurgery, carried out in collaboration with my friend and colleague Giuseppina Ortolani, that the egg pronucleus always lies in the animal side.

Has any work been done by the Palermo group to which you gave a fundamental contribution, with initial suggestions and/or encouragement?

Yes!, As I said the best things derive from group conversation. In 1972 one of Charlie Metz's students named J. Chamberlain, at the fertilization and gamete physiology training course in the Marine Biological Laboratory of Woods Hole, Massachusetts, was working on the synthesis of mitochondrial RNA in sea urchin eggs, and in order to avoid contamination from nuclear RNA, he had used enucleated egg halves obtained by the centrifugation method of Harvey, to which he added radioactive RNA precursors. I had noticed that he obtained a good incorporation of radioactivity into mitochondrial RNA, while I in similar experiments performed on whole embryos had obtained poor incorporation. I then suspected that removal of the nucleus might have

stimulated the synthesis of mitochondrial RNA. Therefore when back in Palermo, I suggested to Anna Maria Rinaldi that she test such a hypothesis by comparing RNA synthesis in whole eggs versus enucleated halves. She did it and through a series of experiments in collaboration with others of the Palermo group, including my friend and colleague Vincenzo Mutolo, demonstrated that it is the nucleus that prevents mitochondrial replication in the early development of sea urchins and also of amphibians.

From left to right: **Giovanni Giudice, the former Minister Giuliano Vassallo and Rita Levi Montalcini at the accademia dei Lincei in Rome on the ocasion of the award of the Feltrinelli Prize to Giovanni Giudice in 1996**.

Besides your own experimental work, do you think you have contributed to sea urchin developmental biology also by other means?

Yes, by telling the story of sea urchin developmental biology, which I did in a book written in 1973 for Academic Press entitled "Developmental Biology of the Sea Urchin Embryo". This represented the first complete story of sea urchin developmental biology after Harvey's book in 1956 "The American Arbacia and other Sea Urchins". Other aspects of sea urchin embryology were covered at the same time as my book by two other authors, Hörstadius and Stern. After that, I wrote a second book in 1986 for Springer Verlag entitled "The Sea Urchin Embryo. A Developmental Biological System", in which I tried to briefly resume the content of the first book and to tell what had happened thereafter.

Have other books on sea urchin development ever been published since then?

Not to my knowledge, although many review articles on different aspects of sea urchin developmental biology have of course appeared, the most comprehensive of which is that of my coworkers Giovanni Spinelli and Ida Albanese, which appeared in 1990 in the book entitled "Reproductive Biology of Invertebrates" edited by Adiyodi and Adiyody. I myself however have contributed with 3 review articles in the last 6 years on the molecular biology of sea urchin embryos, the last of which appeared in 1999 in "Current Topics in Developmental Biology" with the title "Sea urchin genes and their products". The title itself reflects the difficulty to draw sensible conclusions from the increasing crowd of data in the field; but I think I will try to write similar reviews periodically in the future, always with the hope of being able to draw more conclusions than in the previous edition. I believe, however, that data which are only a list in one edition will become at least more understandable in terms of the solution of problems in the following one, to which on the other hand a new list of new data will be added, which will not yet lead to conclusions, but which will, I hope, serve the purpose of providing the reader with information listed by groups of problems.

Giovanni Giudice with his closest co-workers at the Department of Cellular and Developmental Biology. From left to right: **Mimmo Cascino, Gabriella Sconzo, Giovanni Giudice and Mariela Roccheri in 1999.**

In your opinion, what are the next important steps in developmental biology?

I believe that the next important question to be asked concerns the mechanisms which orient mitotic furrows in development. This question is crucial to understanding what establishes the body plans in early development and the shape of organs later on. Obviously there have already been attempts to address such a question, but we are still at the beginning; as the first break-through is made, however, we will see a rush to the solution of such a fundamental problem.

Has science always taken up most of your attention and time, other than your private life?

Fortunately, I have been able, up to a certain age, to dedicate most of my time to science. Then, for organizational reasons, I had to become involved with structural organization in our University, becoming Dean of the Faculty, Head of the Department, Vice-Rector of the University, and Director of a new Institute of Developmental Biology. For seven years I also became involved in national politics becoming first Senator to the Italian Republic in 1976, and then Deputy in the National Parliament from 1976 to 1983. For local scientific policies I think I made a somewhat positive contribution. As to national politics, I did not expect to do much! What I can say is that I did not do damage to it, which I believe is already something important, and I can say that I personally contributed to two bills presented by myself, which were both approved by the two wings of the Parliament and became national laws. One solved a small problem for University teachers, and the other one prevented an ecological disaster which threatened to destroy all the life in the Adriatic sea. An activity of some importance has been and still is that of science divulgation on the national press and that of writing novels, which always have some scientific content. I believe however that the time I dedicated to para-scientific activities was important mostly for the part involving the foundation of new scientific institutions, especially when one considers the conditions of research in Italy and in particular in the South at that time.

If you had to choose the most important achievement in your scientific and political life, what would it be?

The fact of having fundamentally contributed to the creation of a group of scientists here in Palermo that are working at an international level in developmental biology and related fields, and of having ensured the continuation in Palermo of the tradition of the study of sea urchin developmental biology at a cellular and molecular level. All these scientists actively contribute to that, but it would be unfair not to mention in this context the especially important contribution of my former student and now colleague, Giovanni Spinelli, who has developed an internationally leading group in our Department.

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