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# Early mammalian embryo: my love

## An interview with Andrzej K. Tarkowski

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The scientific interests of professor Andrzej K. Tarkowski have always revolved around experimental mammalian embryology. In 1959, he described the development of normal fertile mice from a single blastomere isolated from a 2-blastomere embryo; this was the first ever, successful experiment in the mouse reported in the literature. Later he proposed that during cleavage, the fate of blastomeres is labile and their further contribution to the inner cell mass or trophectoderm depends on their position in the morula (the so called "inside – outside hypothesis"). In 1961, Tarkowski reported the birth of chimaeric mice produced experimentally by the aggregation of two early embryos. This study again confirmed the great developmental flexibility of early mammalian embryos. He also devised a special technique for studying chromosomes in oocytes and early mammalian embryos, initiated studies on experimental parthenogenesis in the mouse, and studied developmental effects of induced chromosome aberrations such as triploidy, tetraploidy and diploid/tetraploid mosaicism. Tarkowski's group also studied oocyte maturation, fertilization and nucleo-cytoplasmic interactions in germ cells and early embryos, including remodelling of somatic nuclei transplanted to egg-cells. Some of the observations made in the latter studies have contributed to the development of techniques of mammalian cloning. Tarkowski was a head of the Department of Embryology from 1964 to 2003, and director of the Institute of Zoology at the Faculty of Biology in Warsaw University (1972-81 and 1987-2003). In 2003 he retired, but nontheless continues his research.

**A very standard opening question: when did your interest in natural science begin, and why did you decide to study developmental biology, which at that time was called embryology?**

As I recall I undertook the decision to study biology about two years before completion of the secondary school. This decision was made under the influence of books and articles, and was reinforced by excellent lessons of biology taught by Dr Wanda Karpowicz. I was interested in laboratory biology rather than in natural science, I have never been a naturalist. The book that impressed me most was the academic textbook of Embryology by Emil Godlewski Jr (see article by Sliwa in this issue). This was the first volume (General Embryology), which dealt with reproduction, gametogenesis, cleavage and gastrulation. I was fascinated by the earliest stages of embryogenesis, by the variety of patterns of cleavage, and by movements of cells and cell layers during gastrulation. Right from the beginning, embryonic development fascinated me (and appealed to me) because of its dynamism: each developing embryo is an exciting movie. The dynamic changes of one cell – the zygote – into progressively more complex embryo, larva and adult organism have always remained for me one of the greatest miracles of Nature. The second book, which channelled my interest in embryology, was a thin book popularising experimental embryology: works of Driesch, Roux and of Hans Spemann and his colleagues on embryonic induction. In those days this kind of studies was called 'mechanics of development' and this was the title of the book. The author was Stanislaw Smreczynski, the student of Emil Godlewski,Jr., who himself was involved in this field of research before World War II, but after the war, as a head of Department of Zoology at the Jagiellonian University had directed the research of his team toward gametogenesis and early embrygenesis of insects (see article by Jaglarz in this issue).

When I became a student of Biology my interest in embryology continued but it was purely theoretical because there were no animal embryologists at our Faculty who could help in 'materializing' my fascination.

**How did you, in mid 50', come up with the idea to study the regulative potential of mammalian embryo? As far as I know at that time nobody at Warsaw University was studying this particular subject. Did you want to extrapolate experimental approach of Driesch, Horstadius and Spe-**

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**Fig. 1. Andrzej Tarkowski (right) with Christopher Graham** *in his laboratory in the Department of Zoology at Oxford University (January 1985).*

**mann to study the early mammalian development?**

It wasn't an easy and short way to Tipperary[1]. After the third year of my biological studies I had to make a decision about the subject of my M.Sc. thesis. At that time I had been already a 'deputy assistant' in the Department of Zoology. Because many pre-war assistants and lecturers lost life during the war, in the first years after the war students were often employed as part-time instructors. The head of the Department, Professor Zdzislaw Raabe, was a protozoologist, but he accepted my interest in embryology and advised me to contact two people who might help me in choosing the topic of my thesis. The first was Stanislaw Bilewicz who was organizing a new Department of Embryology at our Faculty (see article by Tarkowski *et al.* in this issue). However, I did not like the reproduction of the fruit fly project that Bilewicz had suggested and I contacted August Dehnel, who at that time was a head of the Department of Comparative Anatomy at the University of Maria Curie- Sklodowska in Lublin. August Dehnel was an embryologist by training (see article by Tarkowski *et al.*) but at that time he was organizing the field station in Bialowieza, a place known for the restored herd of the European bison and for the National Park of primeval forest, and he was interested in morphology and biology of wild mammals, especially of a small insectivore, the common shrew (*Sorex araneus*). He asked me whether I would be interested in describing a phenomenon of foetal resorption in this species that he had observed making autopsies of females caught in the wild. I accepted this suggestion, not expecting how difficult this project would be. I have collected dozens of pregnant females, made histological sections of hundreds of ovaries and dozens of resorbed implantation sites. The most confusing were histological pictures of resorbed foetuses and degenerating placentae. Fortunately I 'discovered' an old paper by Hubrecht published in 1894 and devoted to the placentation in the shrew. Incredibly detailed drawings helped me to understand the structure of this one of the most complicated organs and allowed me to prepare a publication. The material that I collected permitted me to write another article devoted to various aspects of reproduction of common shrews in the wild. These two publications had been 'born' in pain, because I worked mainly by myself and could not expect much help from anybody in Poland. As a result of this first 'love affair' with embryology and reproductive biology I came to the following three conclusions: first – I wanted to switch from wild mammals to laboratory mammals, second - I preferred to do experimental work rather than to describe existing phenomena, and third - I was capable of doing research in embryology and I had fallen in love with this discipline.

During my work on the reproduction of the common shrew I came across the name of F.W. Rogers Brambell who, before the war, did similar studies on this species in Great Britain. In one of his papers he described the phenomenon of delayed implantation in lactating mice and discussed its possible mechanisms. One of his hypotheses suggested that the arrest of embryos at the blastocyst stage is caused by unknown factor secreted to the uterine lumen. It occurred to me that the easiest way to verify this hypothesis would be to transplant early cleaving embryos to the uteri of lactating females and to check whether they stopped to cleave. Discovering a hypothetical factor that stops mitotic divisions appeared to me a very attractive task. However, in order to carry out this experiment I had to learn the technique of embryo transfer, and again I had to do it without any help, just on the basis of description of earlier trials by other authors. After trying various approaches I found the technique of oviduct transfer to be the best for my purposes. One day, while conducting these manipulations I observed among normal embryos the presence of a 2-cell embryo with one damaged blastomere. Being curious about how such an embryo would develop, I decided to transplant it and to look at it after a couple of days. I found that it formed a small but normally looking blastocyst, accompanied by traces of the damaged blastomere. I considered this observation interesting enough to be studied further. And this launched my doctorate. People think often that important experiments always begin with thorough analysis of available knowledge, formulating a working hypothesis, and proving it by an experiment. At that time I was of course aware of classic experiments on the development of isolated blastomeres of sea urchin and amphibian embryos and of similar experiments by Nicholas and Hall on the rat and by Seidel on the

[1] *"It's a Long Way to Tipperary"* is the title of one of the most popular anthems sung by soldiers on their way to the Western Front during the early enthusiasm of the Summer of 1914. The song was written by Jack Judge and Harry Williams in 1912. Tipperary is a town in the south west of County Tipperary, Ireland.

rabbit embryos. However, I had not planned to do this experiment until I saw this spontaneously damaged embryo and until I did not find out that I could experimentally inflict the same kind of damage. I also realised how very little was known about the regulative capabilities of early mammalian embryos and that this field was just awaiting for experimentalists. I felt that I found my place in embryology. What I find most thrilling in doing this type of research is to ask embryos difficult questions: show me what you can do in the unusual circumstances? This is my main approach to the study of development, but certainly there are other valuable approaches. As one of my friends said recently: you are interested in what may happen if you interfere with the development, but there are people who are interested how normal development proceeds without any intervention. Perhaps there is a grain of truth in this statement, but I too am interested in learning how the normal development proceeds, but my strategy of obtaining this knowledge relies on experimental interference with the normal course of events.

It was a long way from the observation of a single embryo with the incidentally destroyed blastomere to Ph.D. thesis describing a "half" embryo step-by-step development into an adult mouse. However, after I had worked out a technique that permitted me to routinely destroy selected blastomeres in 2- and 4-cell embryos (at that time I did not have a micromanipulator), the rest of the project was a piece of cake.

**Apart from the fact that you were a pioneer in your field at your home institution you had to overcome other, much more general obstacles. Poland heavily destroyed during the WWII and being cut off from the West by Iron Curtain certainly was not the best place to do modern biology research. Genetics was banned in Soviet Block and ties with international science were severed, or dramatically reduced. Did you feel any political pressure in the early years of your career? How did you manage to keep up with the current scientific developments?**

From the very beginning of my adventure with embryology I have been a great fan of simple techniques. As long as it is feasible I prefer to operate embryos manually rather than with a micromanipulator. I was able to do my studies cheaply and without sophisticated equipment. It was a very prudent strategy because in communist Poland the modern equipment and specialty chemicals were practically unavailable if one did not have proper "connections". And I have never been good in looking for 'connections' and influential supporters.

In the late 1940s and early 1950s, Polish science was forced to follow Soviet trend of "new Marxist biology' and 'lysenkism', and all genetic studies and lectures were eradicated from the academic curriculum. Fortunately the research at our Faculty had never followed 'new Marxist biology' and 'lysenkism' trend. Besides, the embryology was not considered a treacherous discipline like genetics and I could proceed with my research without any problems. Finally, the recess of lysenkism started in the Soviet Union as early as in 1953, and the political situation in Poland improved considerably after 1956. I received my M.Sc. Degree in 1955 and Ph.D. in 1959, when the worst times were already over. In these complicated times the contacts with the western science were not easy but were never completely cut off. Fortunately the University Library continued to subscribe 'western' scientific journals and I do not remember of having problems with access to papers that were important for my research.

**Your first paper in *Nature*, on development of isolated mouse blastomeres, appeared in 1959. Although at that time the most oppressive Stalinist rule was over, it was extremely unusual for Polish scientist to publish in Western journal. How did you, very young person at that time and without any support from older, recognized mentor, managed to do so?**

After 1956, on the 'wave of thaw' (as we have used to call the period of de-stalinization and limited liberalization of communism) attempts were made to restore pre-war contacts with various international institutions and agencies, including, among others, the American Ford and Rockefeller Foundations. In 1959 one of the representatives of the Rockefeller Foundation visited Poland in search for candidates for fellowships. I was lucky to be one of young scientists interviewed by him and I was offered the fellowship. I think that two other persons had played a role in this positive outcome: Professor Kraczkiewicz (see article by Kloc in this issue) who as Deputy Rector organized this interview, and,

**Fig. 2. With Magda Zernicka-Goetz** *after the ceremony of granting her a Ph.D. diploma at Warsaw University (1993). Zernicka-Goetz was a student and subsequently a collaborator of Tarkowski in the Dept. of Embryology. At present she has a laboratory in Cambridge, U.K., and continues studies on early mouse embryos.*

**Fig. 3. Members of the staff of the Department of Embryology (Warsaw University) in the old premises around 1997/1998.** *Standing, from the left: Malgorzata Waksmundzka, Andrzej K. Tarkowski, Anna Krukowska (Ph.D. student), Waclaw Ozdzenski, Renata Stanislawska and Marek Maleszewski (current head of the Department); sitting, from the left: Ewa Borsuk, Darek Maluchnik, Maria Anna Ciemerych, Teresa Rogulska, Zofia Dubak, Renata Czolowska.*

perhaps, also Professor C.H. Waddington from University of Edinburgh to whom I presented my experimental data when he came to our Institute during his private visit to Poland. Getting a fellowship was an enormous success, and the question arose what laboratory should I go to. I mentioned earlier the name of Professor F.W. Rogers Brambell, whose hypothesis on the mechanisms of delayed implantation indirectly channelled my involvement in experimental embryology of mammals. One of my mentors, Professor August Dehnel, in whose laboratory in Bialowieza I did all experimental work for my Ph.D. thesis, wrote to Professor Brambell to find out whether he would be willing to accept me to his laboratory as a Rockefeller Foundation Fellow, and whether the highlights from my Ph.D. thesis merit publication in *Nature*. Professor Brambell answered positively to both questions. He edited my manuscript and submitted it to *Nature*. I am sure that this facilitated the publication, and in autumn 1959 I experienced a joy and pride of being the addressee of a flow of reprint requests. At the beginning of January 1960 I arrived in Brambell's laboratory at the University of North Wales in Bangor. The main reason why I did not choose famous Oxford or Cambridge, or any of the American universities, was that neither my mentors nor I knew other mammalian embryologists to whom we could apply. And the choice was perfect.

**Your second *Nature* paper on mouse chimaeras was published in 1961. In my opinion this is your most fascinating paper. There were some earlier indications that blastomeres isolated from the mammalian embryo can develop to term and this type of regulation was previously demonstrated for some invertebrate and vertebrate embryos. But aggregation chimaeras were completely uncharted waters! I guess that it was an enormous thrill, when these famous patched mice were born! There has to be a fascinating story behind this research. But before you tell the story, tell me why this research was done in Wales?**

While the study of the regulative capabilities of a single blastomere of the 2-cell mouse embryo was to some degree stimulated by an incidental observation, the chimaera experiment was deliberate and precisely planned. However, I would lie if I said that I predicted the outcome of these experiments and that I was aware of all consequences of chimaeric constitution for embryonic development. In addition I was not aware of an enormous potential of chimaeric animals in research and agriculture.

First let me answer your last question: why I did this experiment in Wales rather than in Poland? The answer is very simple: few weeks after defending my Ph.D. thesis I left Poland for Rockefeller Foundation fellowship. I thought about doing this experiment while writing my thesis but there was not enough time for new experiments. Besides, I was not ready to do this experiment because of unsolved technical problems. In Bangor, Professor Brambell was full of enthusiasm toward all my experiments (apart from chimaera work I did also an experiment on interspecific transfer of embryos between mouse and rat). I did my 'individual private' project in the laboratory that at that time was nearly totally devoted to the problem of passive transition of immunity from mother to foetuses or young.

There were three technical problems to be solved in order to make chimaeras: first - the zona pellucida had to be removed without injuring embryos, second – the two embryos had to be somehow aggregated together so that they could establish stable contact, and third – the aggregated embryos had to develop up to the blastocyst stage before they could be transplanted to recipient females. It took me about three months to overcome these obstacles, and another three to do the whole experiment. My experiments rarely proceed smoothly and fast, but this one went amazingly smoothly. My fellowship lasted only 15 months, and shortly after I left Bangor, at the very beginning of June 1961, the results were already published in *Nature*. But not all parts of this experiment went well. For unknown reasons a litter of potentially 'patchy' chimaeras died, one young after another, during the first five days *post partum*. So we did not see patchy chimaeric mice. The unquestionable evidence of chimaerism of the newborns was the patchy composition of the outer layer of retina in their eyes.

The true hermaphroditism of some newborns also suggested that they were composed of two populations of cells of the opposite genetic sex. Because the true hermaphrodites were rare and males predominated, I postulated that sex chimaeras (i.e. those composed of XX and XY cells) developed preferentially into phenotypically normal males. This assumption had been later confirmed by karyological studies in our laboratory in Warsaw by Dr. Ewa Mystkowska and myself.

In mammalian experimental embryology, the chimaera experiment was the first and dramatic example of nearly identical studies carried out at the same time by two independent laboratories. Nowadays, it is very common that similar or identical studies are conducted concurrently and often in perilous race, by two or even more rival laboratories. However, at the beginning of 1960ies, there were very few people working on early mammalian development. At the CIBA Foundation conference devoted to 'Preimplantation stages of pregnancy' in 1965, there were only 26 participants, and not all of them were involved in experimental studies. In 1960, when Beatrice Mintz and myself started to make chimaeric mouse embryos, we certainly knew of our existence, but we were completely unaware of the fact that we were doing the same experiment. Probably – though I can speak for myself only – we both considered the probability of another person having the same experimental idea as being close to zero. My paper was published in June 1961 and the abstract of Beatrice Mintz's work on the same subject appeared one year later. She had just a bad luck. However, she contributed greatly to this field of embryology and later she published a number of fundamental papers on the various aspects of chimaerism.

**Your work on regulative development in mammals brought you an immediate recognition in international scientific world. Many people wanted to work with you, and you enjoyed travelling and collaboration. You met so many scientists from all over the world. Whom do you consider as having the greatest influence on your scientific career, and who was the most interesting or remarkable person you met?**

It is true that my publications in *Nature* and other papers that I published at that time greatly facilitated my scientific contacts with many laboratories and famous embryologists. In late sixties and seventies I travelled and lectured a lot, and this allowed me to witness the progress and acceleration in the field of experimental mammalian embryology. Right from the beginning of my career I was fully aware that my only chance to compete with West European and American laboratories is to have the new ideas and to be at least half a step ahead. At the beginning it was possible, but it could not last because more and more brilliant young people entered the field.

Your last question is somewhat embarrassing for me, and requires a very diplomatic answer. Let me start by saying that I am very rarely satisfied with myself, and I have never been self-confident. Having said that I must confess that I could not think of a person who had great influence on my career or inspired me with great ideas. However, I would like to mention here three Professors, who certainly helped me very much in my career. These were Zdzislaw Raabe and August Dehnel in Poland and F.W. Rogers Brambell in Great Britain. They helped me either by creating optimal laboratory environment for the realization of my research plans, or simply by accepting my projects, which at that time might have looked very wild.

The most interesting and remarkable person I have met? In a scientist I am very impressed by precise, logical thinking and the ability to convey this logical reasoning in a simple and precise way. The first names that come to my mind (of course only in 'my' field of research interests) are John Gurdon (see Smith, 2000), Christopher Graham (see Graham, 2008) and the late Anne McLaren (see Renfree and Short, 2008), and certainly this is not the end of my list. Their 'cold' logic sometimes irritates me, what obviously is irrational. Why does it irritate me? Probably because I am not able to think as logically as they do, and perhaps also because I often function in science more as a semi-educated inventor acting by trial and error rather than by following logically deduced concept that has a great chance of success. Perhaps for these reasons I also greatly appreciate and admire those scientists who ask innovatory questions (it is even better if they also know how to verify them), and for whom scientific explorations remain a kind of a romantic adventure. Very strange and old fashion attitude, no doubt.

**After your early success you did not follow the typical path,**

**Fig. 4. Andrzek Krzysztof Tarkowski in the foyer of the new department (2002).** *In the background, decorating the walls are some of Tarkowski´s own photographs. (Photograph by Tadeusz Pozniak©).*

**taken very often by young ambitious folks from Poland, who lived in the second half of the XX century and wanted to do a real research. It was to leave Poland permanently and to settle abroad, far from problems, frustrations and inconveniences that plagued all of us under communist rule. You decided to stay here and create your group at Warsaw University. Was it a premeditated decision, or it happened rather by chance?**

To stay in Poland and to build a laboratory here did not require from me heroic decisions. Already during my first visit to Britain in 1960/61, I realised that I wouldn't be happy living abroad forever (and at that time refusal to return home could have meant just that). Despite of the vicious political system I felt tied to my country, to Polish culture, tradition and certainly to my family, friends and colleagues at the University. Besides, I knew that if I stayed abroad I would remain forever a foreigner, and that I would never be able to master the language, to learn well history and culture of my new country, and a sense of humour I love would never be fully accessible to me. Simply, I would always feel a half-educated person. For many reasons it was better to stay at home and to create a laboratory that I can now be proud of.

**The general conclusion from your research demonstrating strong regulative properties of the early mammalian embryo, is that the mammalian embryo is not pre-patterned, and the earliest developmental decisions depend on the position of the blastomere. You formulated "inside-outside" hypothesis correlating the position of the blastomere with its further developmental fate. Unexpectedly this widely accepted model was recently challenged. This has raised a heated and still unsettled debate among mammalian embryologists. On the both sides of the barricade there are your old colleagues and your former students. However, you seem to distance yourself, at least on more official ground, from this controversy. Would you like to comment on this controversy?**

This is another difficult question. I think that I remain faithful to my old concepts. However, many new observations made in recent years have to be taken into account. Some of these observations are probably irrefutable, but other such as the contribution of the faster and slower dividing blastomere of the 2-cell embryo to the inner cell mass and trophectoderm do not find general support. Probably in some embryos the 'faster' blastomere does contribute more cells to the ICM, and in others it does not. If this is the case, and in my opinion it is likely to be so, the question arises what is the importance of these and also some other recently described events. I can accept that a certain pre-pattern resides in the mouse egg and that it is usually followed by the developing embryo, but what is its significance if it can be easily changed without any visible and deleterious effect for further development? Does this concept really help to understand why (not 'how') the embryo develops into a blastocyst composed of two populations of cells?

The 'outside-inside' hypothesis, in its essence, may continue to be true, but it should be formulated in much more precise terms. What do these 'enigmatic' inside and outside conditions really mean? What are the real factors that switch on and off transcription of the early expressed genes? In my opinion these are the most important questions, and the answers (which we may learn not in a very distant future) to these questions will truly contribute to the understanding of the establishment of the first two cell lineages in the mammalian embryo.

Yes, officially I do distance myself from the controversy that you mentioned. The main reason is that in recent years I have not contributed any new data to the problem under discussion, and I could participate in the controversy armed only with old arguments, and these, as I have just said, need to be updated. I hope, however, that soon I will be able to re-enter the field with new observations.

**I know very well that despite the fact that more than half of the century passed since you have begun your research, you are still fascinated with the early mammalian embryo. In your opinion what is the most intriguing and still unanswered question about the mammalian embryo?**

Other scientists have already answered many questions that have intrigued me. Also my greatest dream, which was to clone a mouse from a somatic cell in our laboratory, was achieved elsewhere.

There are two issues that have puzzled me for years. One is concerned with the establishment of two cell lineages in the early mouse embryo. We have talked about this issue just a while ago. What causes the blastomeres of the 16-cell mouse embryo to make a decision about their final fate, i.e. to become cells of the inner mass or trophectoderm. We know now that cells that have been allocated in the 'inside» or 'outside' of the embryo do not immediately make irreversible decisions, i.e. for some time continue to be developmentally labile. What then is the foundation of the final and irreversible decision?

The second issue we know very little about is of different nature. What is specific and unique in the interaction between the nucleus and the cytoplasm in early mammalian development? You may ask why do I imply the existence of any specificity in this interaction at this particular embryonic stage. In the past we have repeatedly tried to produce hybrid rodent embryos using a variety of approaches. All these attempts failed: the embryos survived one, sometimes two cell cycles and invariably stopped to develop. On the other hand it is known that somatic cells of very remote species can be fused and such hybrids can proliferate for long time. It has been also shown that when in interspecies nuclear transfers the fibroblasts are used as donors of the nuclei, the constructed embryos do not die immediately but often develop at least to the blastocyst stage. Why foreign fibroblast nuclei can function in the egg cytoplasm during several cell cycles (and in mammals even at this early stage a correct transcription is required for normal development to proceed), and a foreign sperm nucleus or blastomere nucleus cannot? Perhaps we have used pairs of species that were taxonomically too distant. But is a pig and a macaque more closely related to a cow, than mouse to a rat or a bank vole? If time permits, I may try to approach this mysterious issue.

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Note: For a representative bibliography of the Tarkowski group, see article entitled "Mammalian and avian embryology at Warsaw

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