Annals of Academy of Romanian Scientists
Online edition *Series: Medical Sciences*
ISSN 2285-4150 *Volume 3, Number 2/2012*

Personal View

THE HEURISTIC VALUE OF INTERDISCIPLINARITY IN SCIENTIFIC MEDICAL RESEARCH

Nicolae CONSTANTINESCU

Honor Member of Academy of Romanian Scientists
Professor of Department of Clinical Anatomy and Surgical Techniques,
University of Medicine and Pharmacy "C. Davila", Bucharest, Romania

Author for correspondence:
Nicolae Constantinescu,
Mb: 0732.931.754,
E-mail: nae_constantinescu@yahoo.com

Abstract

Interdisciplinarity is characterized by the horizontal transfer of knowledge from one discipline (field) to another, which involves conceptual or methodological exchanges. The border area where the fields intersect is the most fertile to discovery.

Fifty years ago, as a junior doctor at the Sanatorium of Osteoarticular Surgery in Eforie Sud headed by dr. Victor Climescu, I was surprised to notice the superiority of rib transplant over tibia transplant in the treatment of pseudo-arthrosis and bone substance losses. The legitimate question I asked myself: "which is the cause of the rib graft superiority?" could not find an answer in the field of orthopedic surgery, therefore I have turned to another field, the experimental surgery, and I have imagined a study model for tissue transplants combining the advantages of a *window chamber*, of a *diffusion chamber* and of a *tissue culture*. I chose the anterior chamber of the adult rabbit eye as site for heterotopic transplantation of periosteum, cortical bone, cancellous bone and red bone marrow. The experimental model showed me that the red bone marrow has an important contingent of stem cells, which demonstrate a potential to proliferate and differentiate into multiple cell lines: bone cells, endothelial cells, hematopoietic cells. I was able to draw these conclusions after I got familiar with a third field of research - the red bone marrow histology and cytology - so after I entered the territory of hematology. *I elaborated the model of the complex polyvalent genome of the marrow stem cell capable of differentiation on several cell lines, and I thought the sequence bone-sinusoid capillary-red bone marrow as fundamental in sustaining the theory of the keyboard of the phenotypic expression of the polyvalent complex genome of the marrow stem cell in adult*.

In 1980 I published a book about the biological value of bone transplant, which I have sent to some prestigious orthopedists and hematologists from all over the world. Each and all asked me to English translation of the book but neither in Romania nor

abroad this translation wasn't possible. If the English translation had been done, the angiogenesis initiated by the stem cells would have been operational for over 20 years.

Key-words: *interdisciplinarity, bone marrow stem cell, angiogenesis*

Rezumat

Interdisciplinaritatea se caracterizează prin transferul orizontal de cunoştinţe de la o disciplină la alta, pentru un progres ştiinţific conceptual şi metodologic. Limitele acestor domenii în parte se intersectează pentru a deveni mai fertile şi mai atractive pentru cunoaştere. În urmă cu 5 ani, tânărul medic de la Sanatoriul de chirurgie osteoarticulară din Eforie Sud, Victor Climescu a remarcat superioritatea transplantului de coastă faţă de cel de tibie, în tratamentul pseudoartrozelor şi al lizelor osoase.

Întrebarea legitimă care se pune este: autografa poate fi superioară? aspect nou în chirurgia ortopedică. Pornind de la această situaţie, am realizat un model de studiu pentru ţesuturi transplantate, în culturi tisulare. S-a observat că în camera anterioară a ochiului de iepure, sunt situsuri pentru transplant heterotopic de periost din corticala osoasă, osteocite şi pentru măduvă roşie osoasă. Acest model experimental arată că măduva roşie osoasă poate fi un important contingent de celule stem, cu potenţial proliferativ şi de diferenţiere în multiple linii celulare osoase, endoteliale sau hematopoetice. Am remarcat acest aspect, după cercetarea în parte a histologiei măduvei roşii osoase folosită în teritoriul hematologic. Am elaborat un model genomic complex polivalent al celulelor stem medulare, capabil de diferenţiere în câteva linii celulare: secvenţa capilare sinusoide osoase-celule roşii medulare osoase este fundamentul substanţial al teoriei expresiei fenotipice al complexului genomic polivalent al celulelor stem medulare la adult. În 1980, am publicat o carte despre valoarea biologică a transplantului osos în care am menţionat contribuţia unor hematologi şi ortopezi din lume in domeniul celulelor stem.

Cuvinte-cheie: *celule stem medulare osoase, interdisciplinaritate, angiogeneză.*

*
* *

I think it was in 1956 or 1957, when I heard that a series of conferences on general biology topics in correlation with other sciences will be held by Victor Săhleanu and Emil Repciuc in one of the lecture halls of the University in Bucharest. At one of these conferences, I heard Victor Săhleanu who drew three secant circles, each of them representing a field of biological or non-biological sciences, and who spoke about the paramount importance of the intersection area for promoting knowledge (*figure* 1).

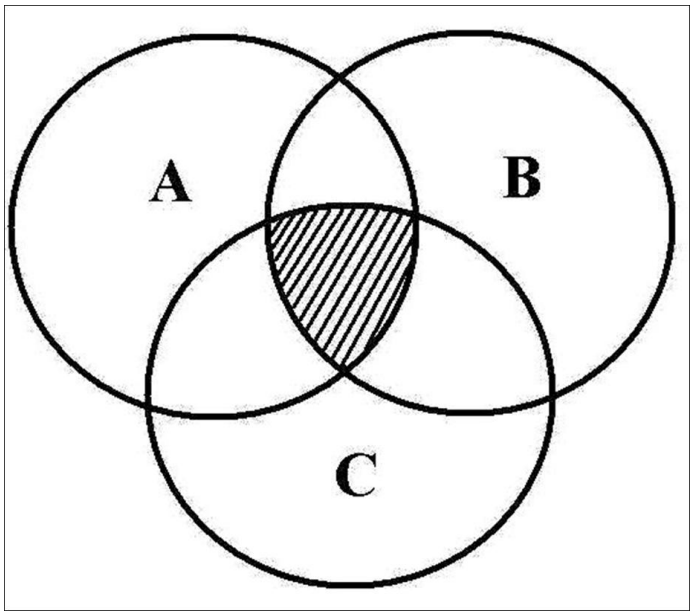


Figure 1: Three secant circles, each of them representing a biological /non-biological field

So, for him, the border area where the three circles meet is the most fertile for discovery, for the progress of science.

Today we talk about interdisciplinarity, transdisciplinarity, pluridisciplinarity or multidisciplinarity.

In Romania, the interdisciplinary research was initiated, since 1925, by Dimitrie Gusti to study life in villages, the interdisciplinary techniques were established by Henri Stahl, and Stefan Milcu was the one who organized the first group of interdisciplinary research in the Romanian Academy.

Interdisciplinarity is characterized by the horizontal transfer of knowledge from one discipline (field) to another which involves conceptual or methodological exchanges.

In 1964, the National Science Teachers Association (NSTA) in the USA developed a list of common scientific concepts to facilitate interdisciplinary transfer of knowledge.

According to Basarab Nicolescu, the interdisciplinary transfer is based on:

- the structural unit of different scientific disciplines (scientific fact, scientific concept, scientific judgment, scientific reasoning, scientific law, scientific method, scientific theory);
- the relative interdependence of theories in relation to the facts.

There is an *interdisciplinarity of neighboring disciplines* in which case concepts and methods of a discipline can be used by another discipline, and an *interdisciplinarity of problems* that exceed the borders of a discipline and require

working with other disciplines. Some mention interdisciplinary methods or interdisciplinary concepts.

In fact, as noted by Ph. Hughes, the argument which pleads for interdisciplinarity is our incapacity to have a deep and surface overview of a phenomenon, a being or an object when we use a single discipline, hence when we use an isolated approach. When many sciences articulate, they become integrated sciences and bring us closer to the holistic image or the desired answer.

I will try to demonstrate the heuristic value of interdisciplinarity which allowed me to obtain an answer to a fact based on clinical observations.

Fifty years ago, as a junior doctor at the Sanatorium of Osteoarticular Surgery in Eforie Sud headed by Dr. Victor Climescu, I was surprised to notice the superiority of rib transplant over tibia transplant in the treatment of pseudo-arthrosis and bone substance losses.

Here is a demonstrative case (*figure* 2):

- pseudo-arthrosis of tibia after the failure of a bone graft, harvested from the opposite tibia and fused only to the proximal end of the tibia shaft;
- *inlay* rib grafts across the site of pseudo-arthrosis;
- an amazing tibia shaft reconstruction observed on a follow – up radiography at 30 months.

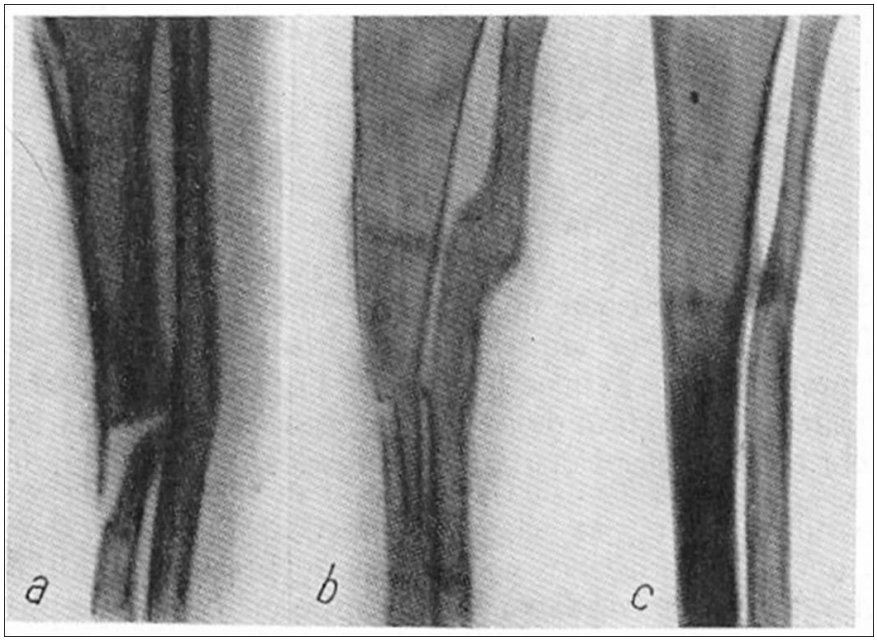


Figure 2: a) Pseudo-arthrosis of tibia;
b) Inlay rib grafts across the site of pseudo-arthrosis; c) Tibia shaft reconstruction

The legitimate question I asked myself, "*which is the cause of the rib graft superiority?* ", could not find an answer in the circle of orthopedic surgery (*figure* 3), therefore I have turned to experimental surgery and I have imagined a study model for tissue transplants combining the advantages of a "window" chamber, of a "diffusion chamber" and of a tissue culture.

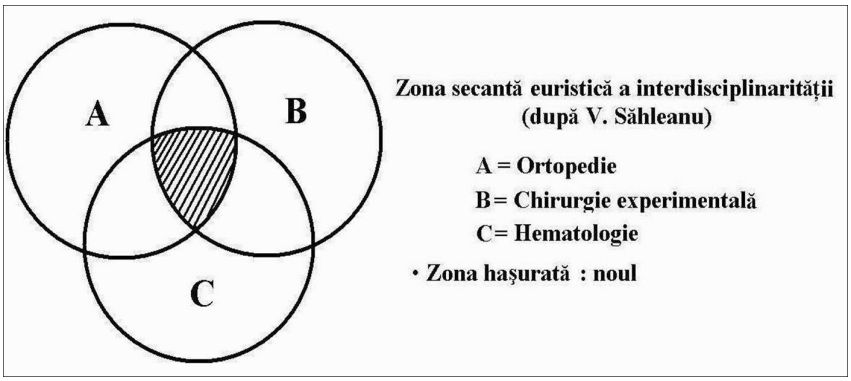


Figure 3: The heuristic secant field of interdisciplinarity (after V. Săhleanu): **a) Orthopedics; b) Experimental surgery; c) Haematology. The shaded area represents the "new".**

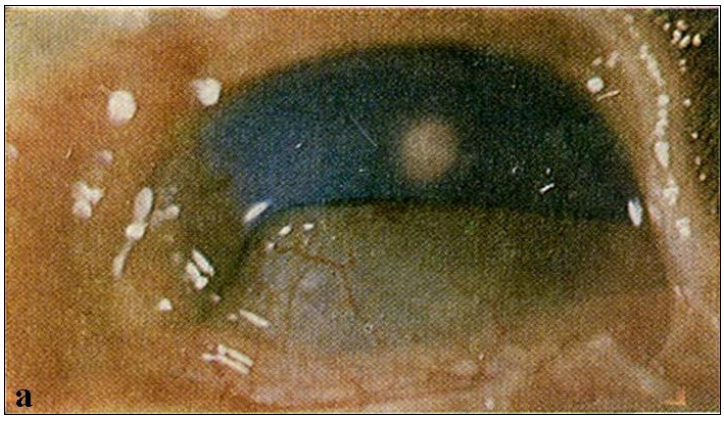
I chose the anterior chamber of the adult rabbit eye as site for heterotopic of periosteum, cortical bone, cancellous bone, red bone marrow, and I observed their development using visual, histological and cytological methods including the biochemical analysis of the aqueous humour. The anterior chamber of the eye works as a *window chamber* that allows visual observation of the inserted fragment, as a *diffusion chamber* because the blood-retinal barrier does not allow passage of cells into the aqueous humour demonstrating the intrinsic transformations of the inserted fragment, and as a *tissue culture* due to the similar composition of the aqueous humour to the extracellular fluid.

That way I solved the problem of costs – prohibitive at that time – of purchase of a miniature camera or of cell cultures production.

In a statistically significant number of cases, the experimental model showed me that the red bone marrow has an important contingent of stem cells (at that time they were called bone marrow primitive reticular cells) which demonstrates, under the circumstances, a potential to proliferate and differentiate into multiple cell lines.

I was able to draw these conclusions after I got familiar with the red bone marrow histology, so, after I entered the territory of hematology – the third circle (*figure* 3). Obviously, besides my determination to find out the superiority of the rib bone grafts employed to restore bone continuity, there were also many favourable factors involved - people or places - that allowed me to conduct these studies: Dr. Lauren□iu Chiosa, dr. Florian Hălălău, dr. Vlad Apăteanu, dr. Lucia Munteanu.

What I found:



Here is the red bone marrow fragment 3 days after being inserted into the anterior chamber of the rabbit eye (*figure* 4).

Figure 4a) Red bone marrow after 3 days;

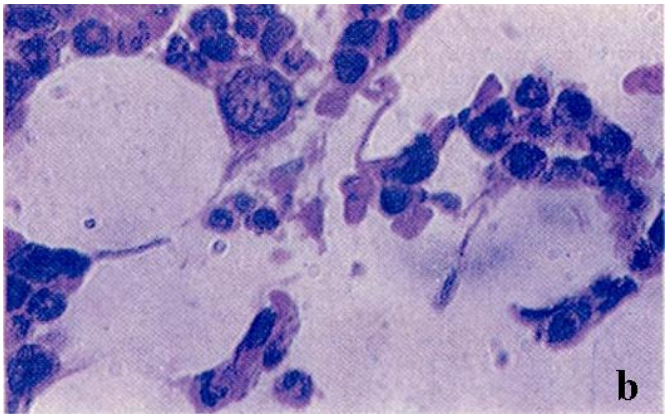


Figure 4b) Primitive reticular cell (stem cell) in the wall of a sinusoid (normal appearance);

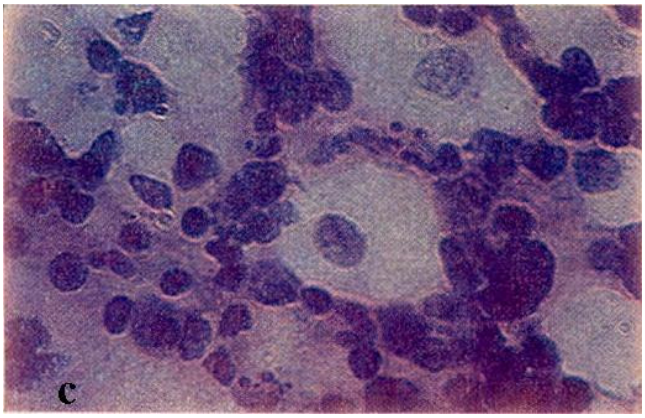


Figure 4c) Stem cells mobilized into the sinusoidal lumen.

This image of the rabbit red marrow shows the stem cell in the wall of a sinusoid. After the first 24 hours, this cell mobilizes and appears in the sinusoidal lumen. At 7 days, histological examination revealed the presence of primitive bone (*figure* 5) which was macroscopically evident after 3 weeks, having the appearance of a whitish, pearly bone plate. After the first 7 days, I also noticed the presence of a sinusoidal network (*figure* 6) and, at 14 days, the anastomosis between the sinusoids and iridial capillaries could be objectified by filling them with a dye injected through the homolateral common carotid artery. At 4 weeks, the new ossicle shows bone structure at the periphery and stroma with few cells in the centre. This ossicle increases in size so that, at 20 weeks, it occupies all the pupillary space (*figure* 7), and bone lamellae with underdeveloped bone marrow are histologically evident.

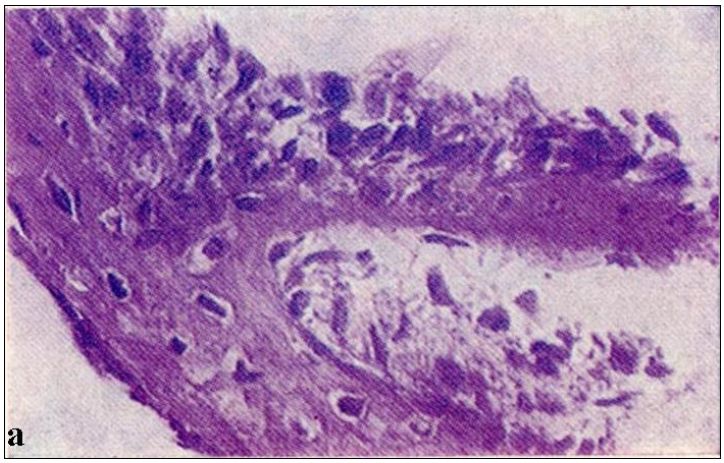


Figure 5a) Primitive bone after 6 days of red bone marrow fragment development;

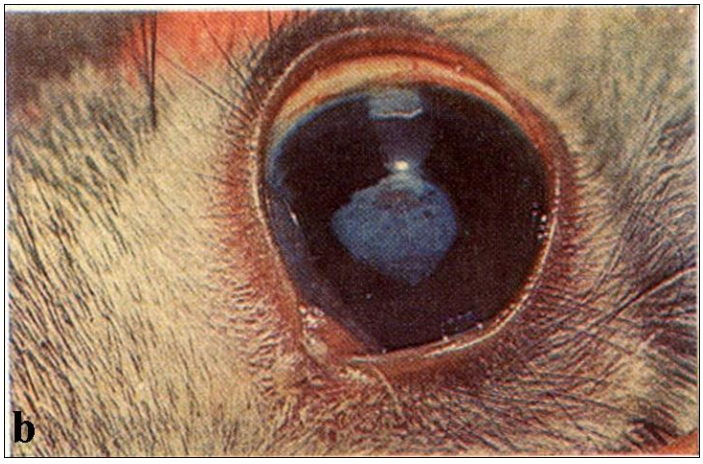


Figure 5b) Bone plate at 3 weeks.

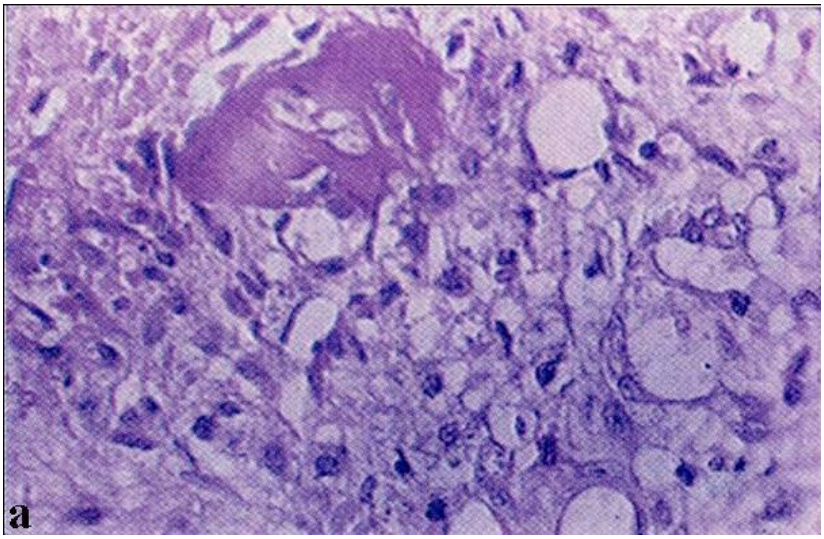


Figure 6a) Sinusoids appearance after 7 days of red marrow fragment development;

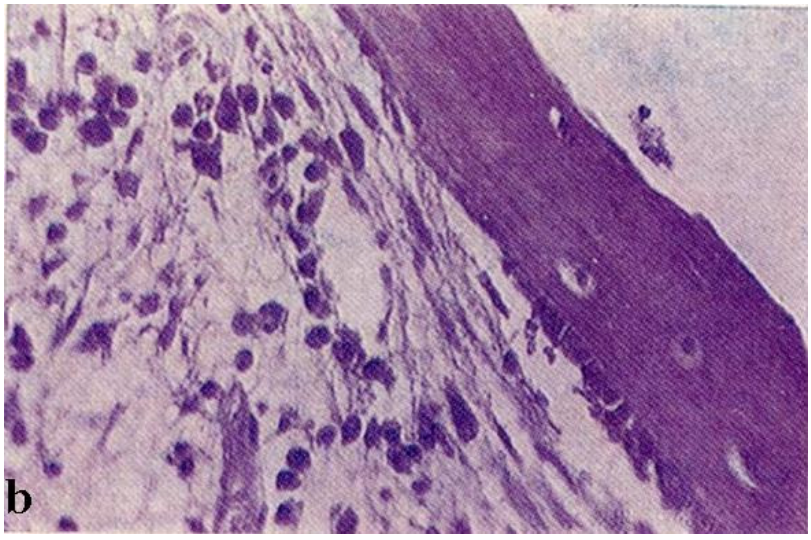


Figure 6b) Bone lamella and vascular structures after 4 weeks of development;

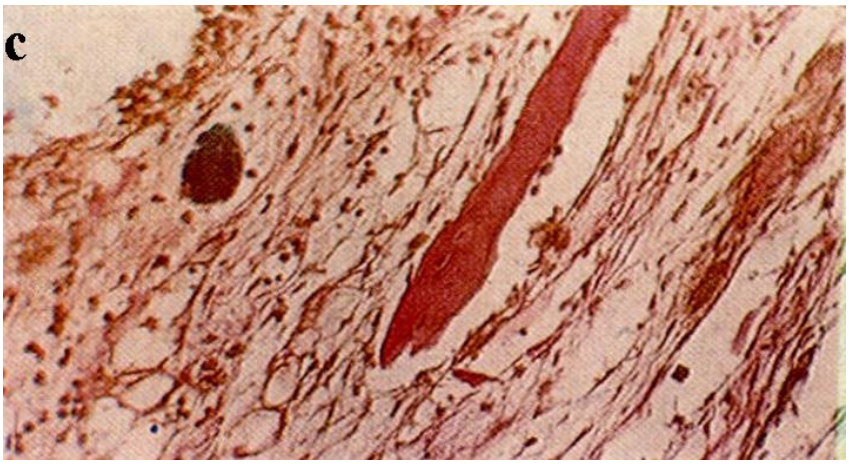


Figure 6c) The anastomosis between the transplant vessels and iridial vessels objectified by the dye present in the capillaries.

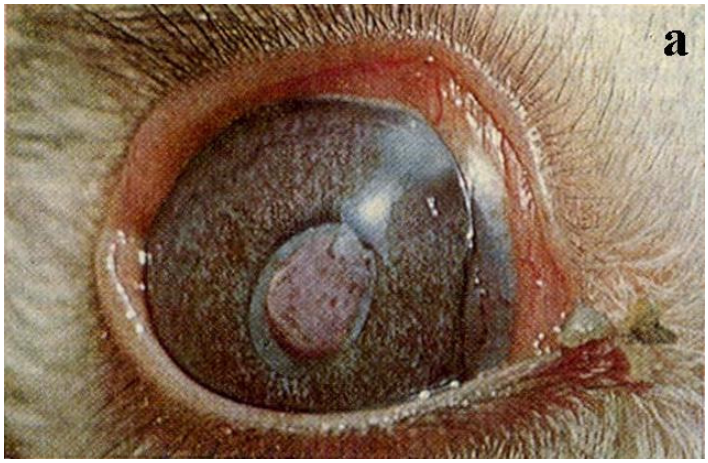


Figure 7a) Bone with red marrow in the center after 20 weeks of development;

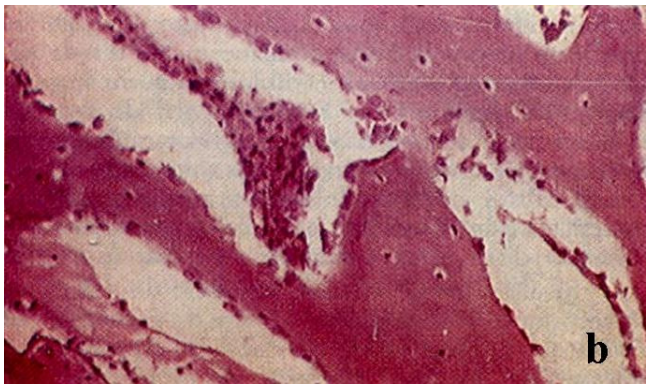


Figure 7b) Bone lamellae and connective tissue in the interlamellae space after 15 weeks of development.

In another series of experiments I proposed a cytological study that I could demonstrate the dynamic changes of bone marrow stem cell. This cell gradually increases its size at 3 and 4 days (*figure* 8), enters heteroplastic mitotic divison on day 5 and, consequently, two osteoblasts secreting ground substance appear on day 6 (*figure* 9).

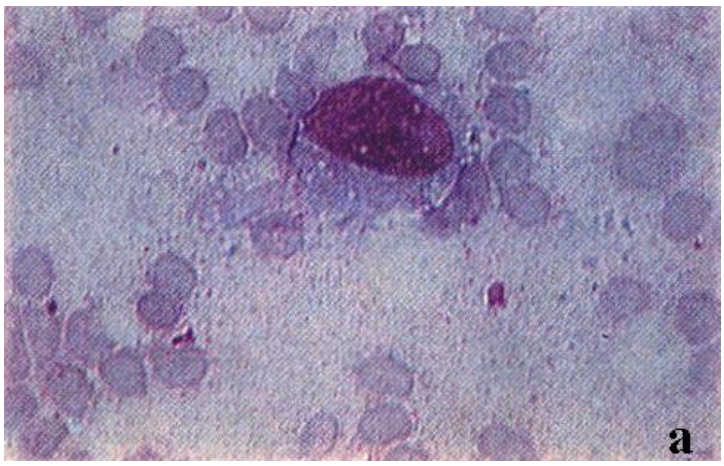


Figure 8a) Reticular cell (stem cell) on day 3;

Figure 8b) Enlarged reticular cell on day 4;

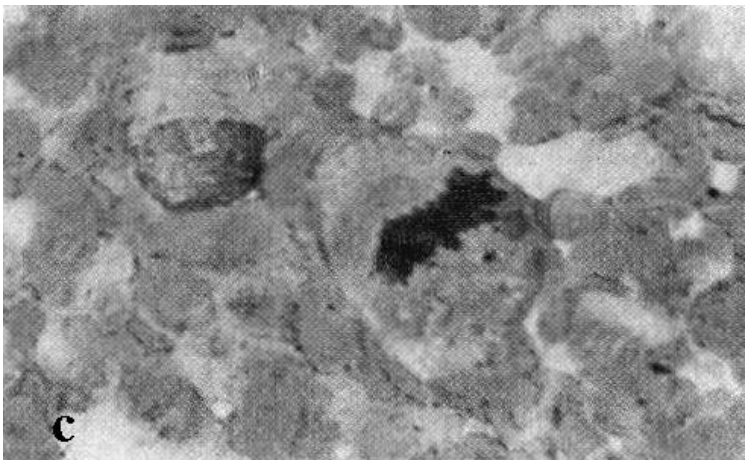


Figure 8c) Reticular cell during mitosis on day 5.

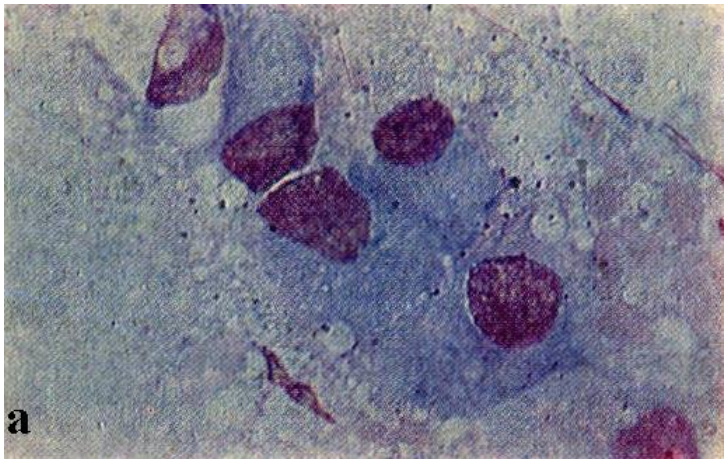


Figure 9a) Osteoblasts from first division on day 6;

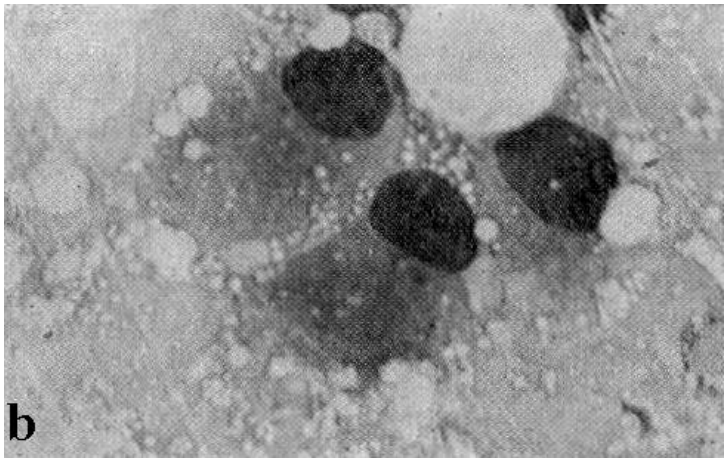


Figure 9b) Secretion of ground substance;

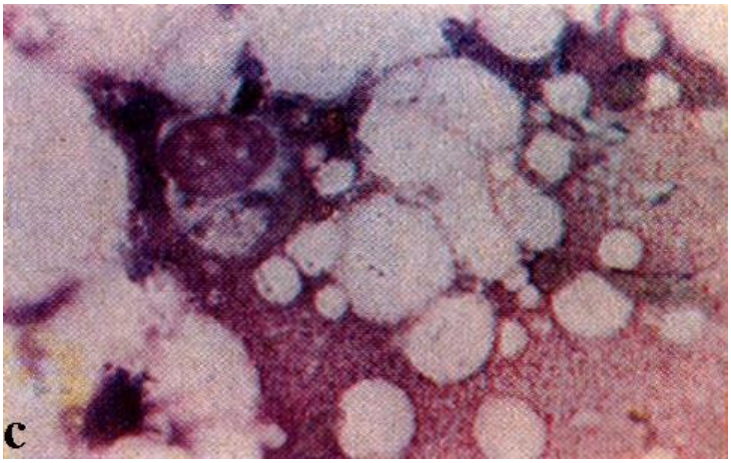


Figure 9c) Ground substance populated with collagen fragments and bone mineral deposits.

This substance is populated with small fragments of collagen that is impregnated with bone mineral so that, on day 7, an osteocyte surrounded by complete mineralized bone substance is formed (**figure 10**). In parallel with osteoformation I noticed the endothelial - like cell differentiation beginning with day 3.

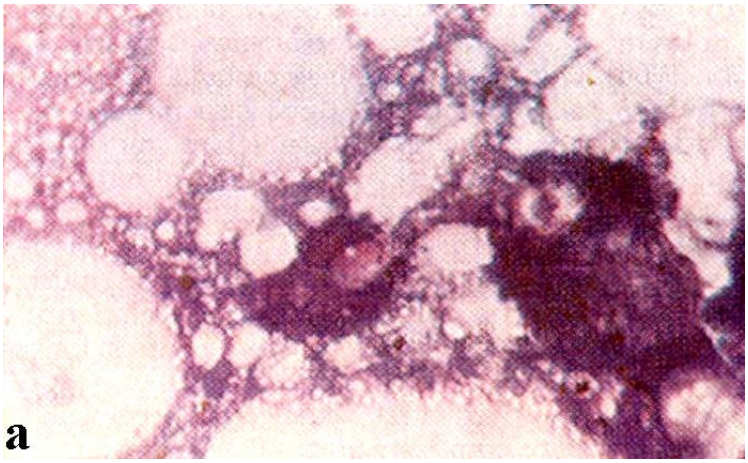


Figure 10a) Osteocyte surrounded by completely mineralized bone substance (day 7);

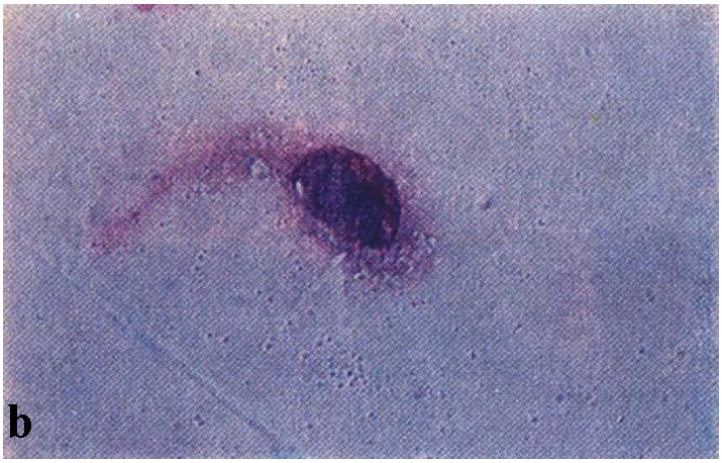


Figure 10b) Endothelial – like cell or angioblast (day 3).

At the end of my research, I elaborated the model of the complex polyvalent genome of the bone marrow stem cell capable of differentiation on several cell lines (*figure* 11), and I thought that the sequence of bone –sinusoids - red bone marrow was fundamental in sustaining *the theory of the keyboard of the phenotypic expression of the complex polyvalent genome of the bone marrow stem cell in adult*, which I elaborated as explanation of the histogenesis of heterotopic bone marrow transplantation. According to this theory the multiple genetic informations are issued in a strict order by the control and suppression mechanisms as when you press the keys of a piano. My theory was consistent to the model of genetic control of Britten and Davidson, in which a single signal reaching the genome may initiate a development program in successive stages.

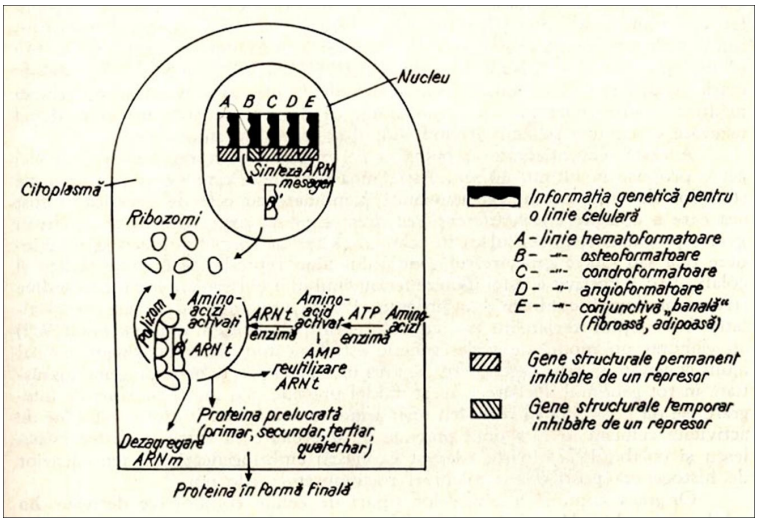


Figure 11: The model of the complex polyvalent genome of the bone marrow stem cell

I presented these results at the 5th International Congress of Hystochemistry and Cytochemistry held in Bucharest in 1976 (*figure* 12, *figure* 13).

In 1980, Medical Publishing in Romania published my book on the biological value of bone transplant (*figure* 14), which I have then sent abroad to some prestigious orthopedists and hematologists from all over the world. Here are some letters of response:

Dr. Blount from the USA the president of the American Society of Orthopaedics wrote me that *he knew no studies so accurate as those that I proved the superiority of the spongeous bone transplant*. Dr. Charnley from England who had launched the world's first total hip prosthesis for which he was ennobled with the title of Sir, asked me for the English translation of the book, as did Burwell who had published the most serious studies about bone transplantation. Professor Yves de la Caffinière asked me for the French translation. *The signaling of the angiogenic capacity of the bone marrow stem cell was considered worthwhile* by Dr. Georges Duhamel, the president of the French Society of Hematology, and Dr. Begemann, professor of hematology in Munich, literally wrote *"the research represents a real discovery"*. In Romania, Ştefan Berceanu, who was at that time the president of the Romanian Society of Hematology, has made a request in writing to Medical Publishing asking for the translation of the book in English and its dissemination abroad. Medical Publishing requested approval from ILEXIM, but the request was denied. I contacted two foreign publishers (Butterworth, Grune & Stratton), but they refused to publish the book in English.

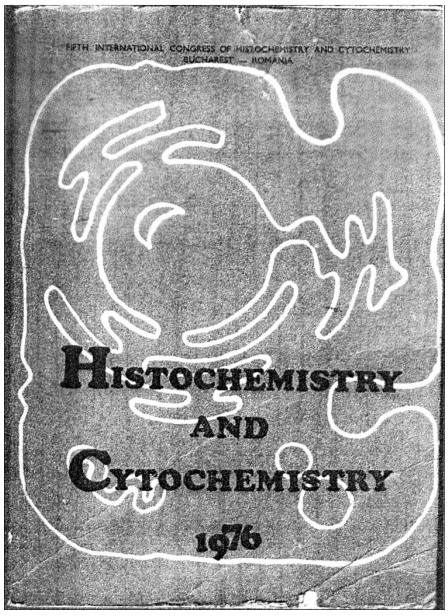
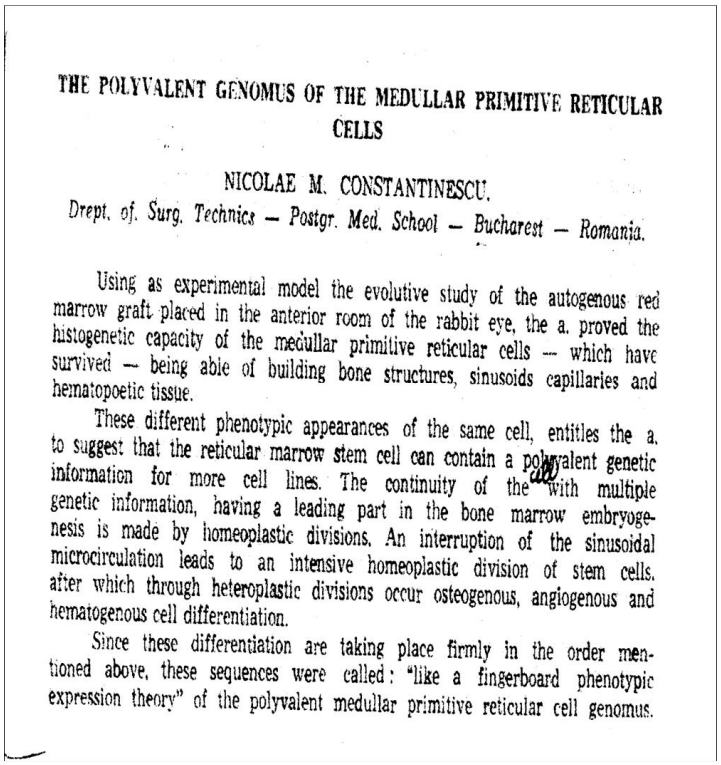


Figure 12: The 5th International Congress of Hystochemistry and Cytochemistry, Bucharest, 1976: Abstract book



THE POLYVALENT GENOMUS OF THE MEDULLAR PRIMITIVE RETICULAR CELLS

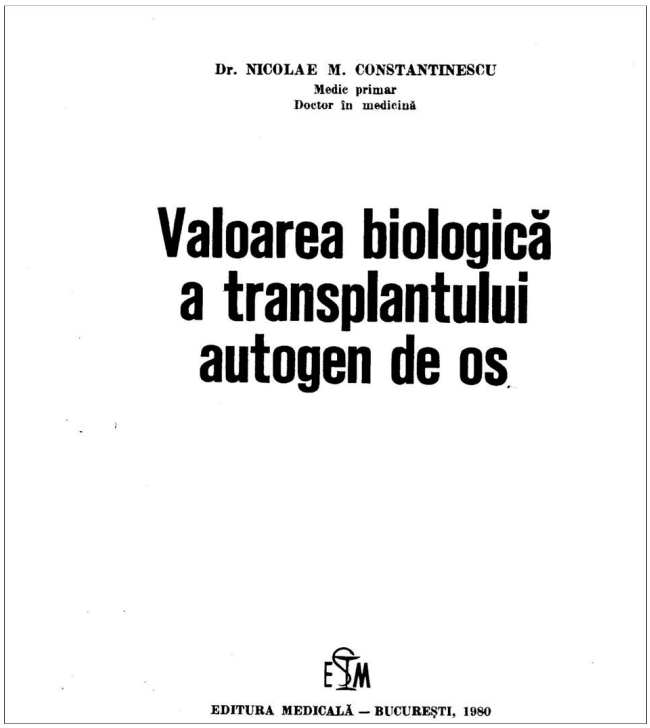
NICOLAE M. CONSTANTINESCU.
Drept. of. Surg. Technics — Postgr. Med. School — Bucharest — Romania.

Using as experimental model the evolutive study of the autogenous red marrow graft placed in the anterior room of the rabbit eye, the a. proved the histogenetic capacity of the medullar primitive reticular cells — which have survived — being able of building bone structures, sinusoids capillaries and hematopoetic tissue.

These different phenotypic appearances of the same cell, entitles the a. to suggest that the reticular marrow stem cell can contain a polyvalent genetic information for more cell lines. The continuity of the with multiple genetic information, having a leading part in the bone marrow embryogenesis is made by homeoplastic divisions. An interruption of the sinusoidal microcirculation leads to an intensive homeoplastic division of stem cells, after which through heteroplastic divisions occur osteogenous, angiogenous and hematogenous cell differentiation.

Since these differentiation are taking place firmly in the order mentioned above, these sequences were called: "like a fingerboard phenotypic expression theory" of the polyvalent medullar primitive reticular cell genomus.

Figure 13: The 5th International Congress of Hystochemistry and Cytochemistry, Bucharest, 1976: The abstract of my paper.

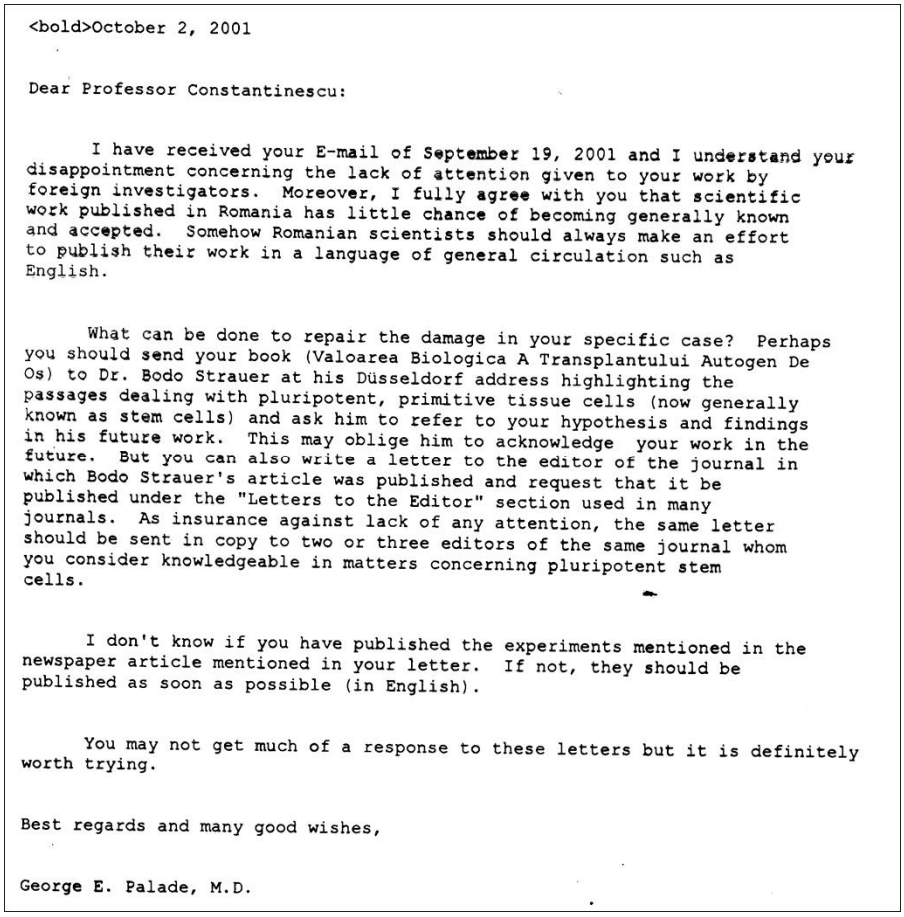


Dr. NICOLAE M. CONSTANTINESCU
Medic primar
Doctor în medicină

Valoarea biologică a transplantului autogen de os

EDITURA MEDICALĂ — BUCUREȘTI, 1980

Figure 14: The cover of my book on the biological value of autologous bone transplant published in Romanian, in 1980.



<bold>October 2, 2001

Dear Professor Constantinescu:

I have received your E-mail of September 19, 2001 and I understand your disappointment concerning the lack of attention given to your work by foreign investigators. Moreover, I fully agree with you that scientific work published in Romania has little chance of becoming generally known and accepted. Somehow Romanian scientists should always make an effort to publish their work in a language of general circulation such as English.

What can be done to repair the damage in your specific case? Perhaps you should send your book (Valoarea Biologica A Transplantului Autogen De Os) to Dr. Bodo Strauer at his Düsseldorf address highlighting the passages dealing with pluripotent, primitive tissue cells (now generally known as stem cells) and ask him to refer to your hypothesis and findings in his future work. This may oblige him to acknowledge your work in the future. But you can also write a letter to the editor of the journal in which Bodo Strauer's article was published and request that it be published under the "Letters to the Editor" section used in many journals. As insurance against lack of any attention, the same letter should be sent in copy to two or three editors of the same journal whom you consider knowledgeable in matters concerning pluripotent stem cells.

I don't know if you have published the experiments mentioned in the newspaper article mentioned in your letter. If not, they should be published as soon as possible (in English).

You may not get much of a response to these letters but it is definitely worth trying.

Best regards and many good wishes,

George E. Palade, M.D.

Figure 15: The letter of response from Professor George Emil Palade, Nobel Prize Winner.

The text I presented above has two overtones:
- the first and the most important is about the heuristic, creative role of the contact area between several fields, which took me to decipher a fundamental biological mechanism due to the multipotent cells remaining as stem cells through adult life in the bone marrow;
- the second refers to the difficulties that we Romanians face when we want to promote our work internationally. Butterworth Publishing said that there were favorable reviews of my book at the highest scientific level, but they refused the translation and publication noting with some malice that my reputation would benefit greatly by publishing the book.

Today I can declare that if the English translation had been done, the angiogenesis initiated by the stem cells would have been operational for over 20 years.

Today it is considered that the bone red marrow contains two types of stem cells: some with hematopoietic differentiation and others with mesenchymal (non-hematopoietic) differentiation, with proven ability to differentiate into bone, cartilage, medullary stroma, cardiomyocytes, astrocytes, hepatocytes, endothelial cells.

On this basis, which proves the exceptional potential of differentiation of the stem cells in adult organisms, we have witnessed in recent years the birth of a new medical field: *regenerative medicine*.

Selective bibliography:

Constantinescu, NM - *Valoarea biologică a transplantului autogen de os*, Editura Medicală, Bucureşti, 1980