

# **EU-PROJECT XENOTRANSPLANTATION: LEGAL PROBLEMS**

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## **Introduction**

Xenotransplantation, that is the transplantation of animal cells, tissues and organs into humans, appears as a new, promising alternative to the established practice of allotransplantation: Xenotransplantation may alleviate the global shortage of human tissues and organs and it may also offer the prospect of being a treatment for diseases with no other effective therapeutic intervention, such as refractory Parkinson's disease or Huntington's disease.

Xenotransplantation, on the other hand, could have adverse consequences such as the cross-species transmission of animal infectious diseases to human xenograft recipients, their contacts and the wider human population. These diseases, called zoonoses, would expand zoonoses (infections transmitted from animals to humans under natural conditions) to include infections not currently recognized as transmitted *via* animals or those in which xenotransplantation alters pathogenicity. In that sense xenotransplantation is a public health issue which must be dealt with at both the national and international level.

Besides the ethical, social and economic assessment of the new method, the legal dimension of this new chapter of human experimentation must be thoroughly examined, since experimentation with animal transplants opens a new chapter in the process concerning experimentation with human beings, a field characterized by moral pluralism and societal fears. At the same time the on-going needs for transplants create a new vast market, where rules defining the margins of human interference are badly needed.

The formulation of principles guiding the legislative action concerning xenotransplantation is hoped to contribute to the clearing-up of the legal landscape and to the definition of guidelines, indispensable in this field, where human rights consideration, societal concerns, economic interests, research optimism and medical options have to be carefully balanced.

There is no specific legal frame for xenotransplantation in Greece. Following rules, concerning medical experimentation with humans and allotransplantation have to be taken into consideration and, if necessary, to be adapted in order to meet the special needs in the field of xenotransplantation.

## **I. International Law**

Article 28 para. 1 of the Greek Constitution of 1975/1986 lays down the principle of the openness of the Greek legal order to international law<sup>1</sup>; for the purpose of this study following European Conventions are of importance:

1. The European Convention of Human Rights of 1950. Its provisions are considered as an integral part of national law and prevail over any contrary national regulation<sup>2</sup>.
2. Greece has also signed the Convention for the Protection of Human Rights and Dignity of the Human being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine on April the 4<sup>th</sup>, 1997 at Oviedo and has ratified it by Law 2619/15.6.1998. The Convention has entered into force on December the 1<sup>st</sup>, 1999 after its ratification by five members of the Council of Europe (Article 33 para. 3 of the Convention). Greece had participated actively at the *travaux préparatoires* and had substantially contributed to the formulation of many of its regulations.

Following principles and regulations enshrined in the Convention are of particular importance in the field of xenotransplantation:

- The protection of dignity, identity and integrity of all human beings with regard to the application of biology and medicine (art. 19).
- The primacy of the human being. As art. 2 sets out, the interests and welfare of the human being shall prevail over the sole interest of society or science.
- The rules regulating the terms for undertaking research, which foresee, among other criteria, that there is no comparable effectiveness to research on humans and that the risks that may be incurred by the patient should not be disproportionate to the potential benefits of the research (art. 16 alinea i and ii).

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<sup>1</sup> Art. 28 para 1 of the Constitution states: “The generally recognised rules of international law, as well as international conventions as of the time they are sanctioned by statute and become operative according to their respective conditions, shall be an integral part of domestic Greek law and shall prevail over any contrary provision of law. The rules of international law and of international conventions shall be applicable to aliens only under the condition of reciprocity”.

<sup>2</sup> The Convention has been ratified by decree 53/ 1974

These regulations can be interpreted as not allowing research with xenografts , if the benefits for the individual patient do not outweigh potential risks. The enrichment of medical knowledge cannot be achieved by infringing upon the a.m. principles.

Art. 3 of the Convention stipulates, further, that the state should take appropriate measures in order to provide equal access to health care of appropriate quality. If medical treatment *via* xenotransplantation should become a current one, then there should be no discriminatory treatment of the patients on financial grounds.

The rules about professional standards (art. 4) and about consent (art. 5 - 7) should be also applied in the field of xenotransplantation.

## **II. Constitutional provisions**

### **1. Human Dignity and Genetic Identity**

1.1. *Human dignity* is guaranteed in Article 2 para. 1 of the Constitution: «Respect and protection of human dignity constitute the primary obligation of the State». This article is exempted from revision, given that it encompasses the quintessence of the anthropocentric character of the Constitution. The prohibition of torture in Article 7 para. 2 is a special manifestation of this basic right.

This article is influenced by the theory conceived by Dürig, the commentator of the German Federal Basic Law. Dürig, going back to Kantian philosophy, developed the doctrine that human dignity is violated if the specific individual is degraded to the status of a “mere object”, if he/she is treated as an instrument, a “substituable dimension”. A human person, therefore, should never be treated as a means but always as an end. In protecting human dignity the State has to take all necessary measures to guarantee the autonomous right of self – determination of the individual. The term “human dignity” becomes more concrete in the context of reviewing threats and violations thereof.

The protection of human dignity is supplemented by everyone’s right to develop freely one’s personality and participate in the social, economic and political life of the country, insofar as one does not infringe upon the rights of others or violate the Constitution and moral values (Article 5 para. 1). It is also manifested in everyone’s right within the Greek territory to enjoy full protection of one’s life, honour and freedom, irrespective of nationality, race and language and irrespective of religious or political beliefs (Article 5 para. 2).

Article 7 para. 2 refers to the protection of the personal integrity, the latter being understood as an expression of human dignity: “Torture, any bodily maltreatment, impairment of health or the use of psychological violence, as well as any other offence against human dignity are prohibited and punished as provided by law”.

1.2. The Constitution was again under revision, completed on April 17, 2001<sup>3</sup>. A new article setting out the protection of *genetic identity* is added thereto (as art.5 para.5), upon initiative of the Minister of Culture and Professor of Constitutional Law Evangelos Venizelos. The amendment was unanimously supported by all political parties represented in the Greek Parliament<sup>4</sup>. The new article reads as follows : “All persons shall enjoy full protection of their health and genetic identity. All persons shall be protected with regard to biomedical interventions as provided by law”.

The genetic identity is to be understood as the genetic constitution of the individual, the inherited genetic pattern. The constitutional protection of genetic identity has the following consequences

- a. The protection of genetic identity in conjunction with the principle of equality forbids any form of discrimination, based on the genetic characteristics of the individual. The principle of non- discrimination is expressly foreseen in article 11 of the Oviedo Convention.
- b. The genetic identity is to be protected against any intervention, aiming to limit the individual autonomy. The new provision safeguards genetic unicity and genetic integrity.

*Genetic unicity* refers to the possibilities to be opened by cloning, whereby an individual may be endowed with a given genetic pattern and his/her characteristics may be predetermined in a way stripping him/her beforehand of the freedom they would otherwise enjoy. “Producing a host of theoretically identical beings constitutes an attack on the identity, the nonrepeatable nature and the genetic integrity of the individuals thus born, given that their genetic integrity has also been manipulated or at the very least selected”<sup>5</sup>.

*Genetic integrity* refers to the need to protect the human genome against any intervention aiming to pre-determine and/or to modify it for reasons other than preventive, diagnostic or therapeutic ones and thereby limit the individual autonomy.

Interventions in the *somatic cells* are allowed, if they are dictated by preventive, diagnostic or therapeutic purposes.

At the *germ line therapy* genetic changes in the reproductive cells or in the embryo could be passed on to future generations. The genetic constitution of the individual is to be protected against unlawful interventions seeking to modify the germ line (i.e. interventions to the germ cells (ova and sperm), to the gonads (ovaries and testicles) and to the embryo at the first stages of its developments).

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<sup>3</sup> See the amended constitutional provisions in: Government Gazette A` No. 84 / 2001-4-17

<sup>4</sup> See Z` Revisional Parliament, Report of the Revision Committee, Report by E. Venizelos, pp. 7, 10, 24; Reports by representatives of the political parties of the opposition see I. Varvitsiotis (New Democracy) pp. 85 (97); A. Skyllakos (Communist Party) pp. 129 (135); F. Kouvelis (Coalition of the Left and Progress) pp. 139(146).

<sup>5</sup> So the formulation by Carlos M. Romeo Casabona (1998): Legal limitations on research and its results? The cloning paradigm in: Fujiki/Macer (Eds.): Bioethics in Asia, pp. 41 – 50 (46); also I. Kriari – Catranis (2000): Die verfassungsmässige Problematik des Klonens in Griechenland, in: *Revue Hellenique de Droit International*, pp. 591 – 612, *passim*

These interventions could be a threat to human autonomy, if they were to be practised for the purpose of *genetic enhancement*, i.e. in order to endow the individual with desired characteristics at the pre-conceptual or early post-conceptual stage<sup>6</sup>. Given that these interventions are at an experimental stage, they should not be allowed, even if practiced for medical reasons.. Their strict prohibition *expressis verbis* is foreseen in article 13 of the Oviedo Convention.

In the case of xenotransplantation the boundaries between the species will be transgressed. Yet the goal thereof is to offer a therapeutic alternative to the patient, without endangering his health. Therefore this procedure does not entail a threat to the dignity of the individual, if his/her autonomy and his/her decisionmaking authority are respected, (i.e. by giving his/her consent as prescribed by law), if the experiment will not endanger his/her physical/ mental health and if the willingness of the patient to submit to research is not connected to financial gains. If the intervention *via xenotransplantation* into the genetic identity serves therapeutic goals, then it should be allowed, in the frame to be defined by law.

## 2. Freedom of scientific/medical research

The freedom of scientific inquiry is considered as a basic value of our societies and as a condition of their adaptability to the changing world environment . Research, taken generally, encompasses all activities and procedures designed to generate new knowledge; scientific research is a subset that focuses on specific techniques of deriving particular kinds of knowledge<sup>7</sup>. A distinction can be made between the freedom to choose the end or topic of research and the freedom to choose the method for pursuing that end <sup>8</sup> The freedom of research also comprises the freedom of scientific communication and the freedom of publishing the results of research.

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<sup>6</sup> Germ line therapy and experimentation is for the moment banned in many countries, such as Switzerland (Constitutional article 119 para. 2 section 1), Germany (article 5 para. 1 of the Embryo Protection Law), Austria (article 9 para. 2 of the Austrian Reproductive Medicine Law of 1992), Norway (Law 68/87, chapter 1 article 3 and section 7 –1 of the Law on Biotechnology of 1994), Sweden (Law 115/1991). See Ism. Kriari – Catranis (1997): Embryo Research and Human Rights- An Overview of Developments in Europe in *European Journal of Health Law*, pp.43 – 67, (53-54)

<sup>7</sup> In the UNESCO Recommendation on the Status of Scientific Researchers the following definition of science is stipulated:

«The word «science» signifies the enterprise whereby mankind, acting, individually or in small or large groups, makes an organized attempt, by means of the objective study of observed phenomena, to discover and master the chain of casualties; brings together in a coordinated form the resultant subsystems of knowledge by means of systematic reflection and conceptualization, often largely expressed in the symbols of mathematics; and thereby furnishes itself with the opportunity of using, to its own advantage, understanding of the processes and phenomena occurring in the nature and society»; whereby «research» is indirectly considered as the pre-requisite of «science».

<sup>8</sup> See P.D. Dagtoglou, *Constitutional Law - Human Rights* (vol. A. Athens 1991) 665 et seq. At 671 (in Greek); J.A. Robertson. The scientist's right to research: a constitutional analysis, *Southern California Law Review* 51 : 1023-1279 (1978) at 1206-1207.

The freedom of research is safeguarded in article 16 para. 1 of the Greek Constitution of 1975/1986<sup>9</sup>. The respective article reads as follows :<sup>10</sup>

«Art and science, research and teaching are free; their development and promotion are state obligations. Academic freedom and freedom of teaching shall not exempt anyone from his duty of allegiance to the constitution»

The right of research is guaranteed with no restriction; this means that the scientist is generally free from governmental direction or intervention in choosing topics of research or in selecting means to carry out research. Further the article lays down the principle that the State is obliged to take all necessary measures in order to facilitate the conditions of research.

The scientist is not, however, entitled to experiment, if she/he may cause direct, substantial harm to the cognizable rights or interests of others, without their consent, or when his/her activity conflicts with other sufficiently weighty interests<sup>11</sup>. This limitation refers both to basic and applied research, which should not be conducted in a way to cause harm to the rights to life and to health, to impinge on foreign property or to infringe upon human dignity. Therefore, general regulations may be introduced with an aim to protect the rights of persons, that may be violated by unrestricted selection of research methods; the state may intervene, in order to protect human life, health, individual autonomy or property<sup>12</sup>.

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<sup>9</sup> On the Greek constitution see in general Philippos Spyropoulos, *Constitutional Law in Hellas* ( Kluwer/Sakkoulas 1995). On article 16 see A. Manessis, *The Constitutional Protection of Academic Freedom, Constitutional Theory and Praxis* (Thessaloniki 1980) 674 *et seq.* (in Greek).

<sup>10</sup> The need to use science and technology in an anthropocentric way, guaranteeing ample freedom of research for the scientist and at the same time strengthening the moral values which underline our civilization, has been stressed at the parliamentary debates about article 16 of the 1975 Constitution : see Hellenic Parliament, *Parliamentary Minutes of the Subcommittees of the Parliamentary Committee on the Constitution of 1975* (Athens 1975) 436 *et seq.*, especially the speech of Deputy D. Nianias at 453-454: also Hellenic Parliament, *Parliamentary Minutes of the Fifth Revisionary Parliament on the Constitution of 1975* (Athens 1975) 490-491.

<sup>11</sup> Dagtoglou, *sopra*, 675-676: A. Raikos, *Lectures on Constitutional Law* (vol. B. 1, Athens 1986) 199 *et seq.* At 214 (in Greek); I. Kriari-Catranis, *Biomedical Developments and Constitutional Law - Constitutional Issues Related to Assisted Reproduction Methods and Genetics* (Sakkoulas, Thessaloniki 1994) 159 *et seq.* (in Greek).

According to one opinion limitations should be accepted only in public institutions with research activities and in the relation to article 16 para. 1. B referring to the duty of allegiance to the Constitution, see G. Papadimitriou, *Constitution and Freedom of Science*, 3 *To Σύνταγμα* (To Syntagma - ToS) 1992, 515-528 at 522.

<sup>12</sup> See also the opinions expressed by Professors Jean Bernard and Alain Pompidou in *Rogers/Durand de Bonsingen, Bioethics in Europe* (Council of Europe Press, 1995) 64-65:

« Science without safeguards, which could force us to accept its conclusions rather than helping us to rise and take advantage of our own intelligence, could not be ethical, similarly in as much as science is also an issue which concerns society as a whole, the respect shown for the «object of experimentation» also depends on the prominence given to human rights by society».

Scientific publications are exempted from the regulations of article 14 para. 3 of the Constitution, the latter foreseeing that the seizure of newspapers and other publications, by order of the Public Prosecutor, shall be allowed exceptionally after circulation in some cases<sup>13</sup>.

Restrictions of the right to research should be governed by following principles:

- a. It is not the research that is in need of justification, but rather its restriction. The validity of the limitation imposed depends usually on a strong showing of necessity by the state<sup>14</sup>.
- b. The constitutionally recognized principle of proportionality must be safeguarded: The regulation should be carefully tailored to limit the right to the minimum extent only. Legally permissible restrictions should not go further than what is absolutely necessary in order to achieve the given purpose, and they must be commensurate to that purpose<sup>15</sup>.
- c. The principle that no human right should be infringed in its core, i.e. its essential content is not subject to any restriction.
- d. The principle of respect for the dignity of the individual, which is inviolable<sup>16</sup>.

This provision applies also in the case of human experimentation, which should be allowed, if it be accompanied by the free and informed consent of the subject and if the subject does not get any financial reward in order to submit to research<sup>17</sup>. The need for consent stems from the principle of the inviolability of the human body and is an expression of the autonomy and independence of the individual, which presupposes that the human being can freely take decisions concerning his own body.

In the case of xenotransplantation the regulations concerning research should respect all the above principles, which should be read in conjunction with the principles of the European Convention on Human Rights and Biomedicine: i.e. research projects should not endanger the life of the individual, even if the expected benefit is of great importance for the society. The prohibition of research or the elaboration of criteria

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See also Carlos-Maria Romeo-Casabona, Human Rights Issues in Research on Medical Genetics, *Ethics and Human Genetics, 2<sup>nd</sup> Symposium of the Council of Europe on Bioethics* ( Council in Europe Press, 1994) 167-174 at 168.

<sup>13</sup> Dagtoglou, *supra* note 5, 676.

<sup>14</sup> *Ibid.*, 671; Albin Eser, Genetik, Gen-Ethik, Gen-Recht? In Rainer Floehl (ed.), *Genforschung - Fluch oder Segen ?* (1985) 248 *et seq.* at 250; I. Kiriari-Catranis, Embryo Research and Human Rights - An Overview of Developments in Europe, *European Journal of Health Law* 4:43-67 (1997) at 53-54.

<sup>15</sup> The principle of proportionality is derived from the general principle of the rule of law; see Raikos, *supra* note 8, 187 *et seq.*

<sup>16</sup> Dagtoglou, *supra* note 5; Raikos *supra*, vol. B. 2, 7 *et seq.*

<sup>17</sup> Dagtoglou, *supra*, 212.

different than the ones applied to clinical trials in general should be justified by the existence of a imminent danger to the individual or to the society.

### **3. The right to health**

The special care for health is expressly determined in the Constitution as an obligation of the State (Art. 21, paras. 2 and 3) and as a human rights (article 5 paragraph 5).. To that obligation corresponds the social right to health. Social rights are not legally enforceable; the State cannot be compelled to render performance. The State is however expected to take all necessary measures in order to protect the health of its citizens, especially of the aged and disabled ones<sup>18</sup>.

If a new method, such as xenotransplantation, promises to offer a solution to the acute shortage of organs, then the state has the duty to endorse all activities aimed thereto, especially the respective research, and to safeguard, at the same time, the health and the wellbeing of the individual patient.

### **4. Privacy**

Privacy in general is safeguarded in article 9 para. 1 of the Constitution:” Every person’s home is a sanctuary. Personal and family life of the individual is inviolable”. The new article 9A safeguards the protection of the individual with regard to the collection, storage and use of their personal data, as prescribed by law.

Royal Decree of 25.06.1955 on *Regulations on the exercise of the medical profession* contains a specification, in part, of the prohibition to intrude one’s privacy as the *principle of confidentiality*. Article 15 of the Royal Decree provides that the doctor must take all steps to prevent the appearance of information in medical records and publications which would infringe the obligation of confidentiality. He may not issue any certificate, report or opinion without expressly stating the purpose of issue and the name of the addressee. However, there are exceptions to medical confidentiality in the face of the need to protect certain rights.

Article 23 of Law 1565/1939 states that doctors and their assistants have a moral and legal duty to keep confidential any information concerning their client disclosed to them by virtue of their profession. The same obligation binds the persons who subsequently obtain relevant information. Article 371 of the Penal Code declares the breach of doctor’s confidentiality a criminal offence, unless it was effected during the performance of a duty or if it was the exclusive means, whereby a legitimate

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<sup>18</sup> See Anthopoulou , X. (1993): The protection of health as a fundamental social right in: The Constitution p. 741 - 783 (in greek); I. Kriari - Catranis (1999): *Genetic Technology and Human Rights*, Athens- Thessaloniki, p. 46 et seq. (in greek).



interest could be served (i.e. at court proceedings or in order to establish self defense or in order to avoid the spread of a disease)<sup>19</sup>.

Law 2472/1997 on the *Protection of individuals with regard to the processing of personal data* qualifies health data as “sensitive ones” and stipulates special guarantees for their collection, storage etc., after obtaining permission of the respective Authority, responsible for the protection of personal data (art. 7).

These regulations about medical data, in general, are applicable in the field of xenotransplantation, too. Given that this intervention is at an early experimental stage and the danger of causing an epidemic cannot be ruled out at the moment, we support the view that relevant data be kept at a separate register, in order to facilitate the monitoring and following up of this process.

## 5. The protection of the environment

The protection of the natural and cultural environment constitutes a duty of the State (Art. 24 para. 1). Other provisions in the same article provide for the protection of forests and for sustainable urban and regional planning. In accordance to these provisions the Statute 1650/1986 has elaborated some principles and procedures for environmental protection.

The principles of environmental protection have been systematized by the 5<sup>th</sup> Section of the Council of State (High Administrative Court)<sup>20</sup>. First among these principles is the fundamental rule of sustainability, meaning that no public policy may threaten or entail reduction or degradation of the natural capital. This principle is supplemented by the procedural principle which requires a comprehensive environmental impact assessment prior to the decision for any public policy affecting the natural environment<sup>21</sup>.

This jurisdiction, which aims at balancing the freedom and rights of the individuals and industry with the need to reduce the risk of adverse effects to the environment and to health is in accordance with the *precautionary principle*, endorsed by the Commission of the European Communities<sup>22</sup>.

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<sup>19</sup> Th. Koniaris/ A. Karlovassitou – Koniari (1999): *Medical Law in Greece*, Kluwer/ Sakkoulas, p. 116 et seq.; I. Kriari – Catranis (1998) *Biomedical experimentation and human rights in Greece* in *Revue Hellenique de Droit International*, pp.79 – 88 (84); I. Rokas (1994) *Greek National Report in Genome Analysis: Legal Rules – Practical Applications*, reports of the Workshop, 11 –14 june 1992,, pp. 235 – 245, (237).

<sup>20</sup> See Siouti, Glykeria (1993): *Environmental Law - General Part : public Law and Environment*, Athens, p. 41 et seq.

<sup>21</sup> See M. Dekleris (1996) *Manual of Sustainable Development*, Athens, Sakkoulas (in greek), *passim*.

<sup>22</sup> See Communication from the Commission on the precautionary principle, Commission of the European Communities, COM (2000) 1, Brussels, 2.2.2000

The xenotransplantation procedure with genetically modified animals may entail risks not only with regard to the health of the individual but also with regard to the environment (i.e. through the deliberate release into the environment of genetically modified organisms). The assessment of the relevant risks and the adoption of measures should respect the a.m. jurisdiction and the guidelines about the *precautionary principle*.

### III. Legal regulations

#### 1. Legal regulations concerning experimentation with human beings

General regulations related to scientific research are to be found in the Convention on Human Rights and Biomedicine (articles 15 – 18), which forms an integral part of domestic Greek law since December 1999.

Ministerial Decision A67 10983/1/ 1984<sup>23</sup> on *Clinical trials of drugs and the protection of the human being* is the only specific statute on medical research with regard to «human experimentation»; it is based on the World Medical Association's revised Declaration of Helsinki“ (1975/1983),

As «drugs are defined substances and preparations of substances applied to man for preventive, diagnostic and therapeutic purposes, in order to prevent, alleviate or cure a disease or its symptoms or in order to modify physiological functions to the benefit of the patient (art. 2). Animal cells, tissues and organs used in xenotransplantation can be considered as «drugs» for the purpose of this Ministerial Decision and the xenotransplantation can be considered as a modification of the functions of the human body.

«Clinical trials» are systematic studies of drugs on human beings with the purpose to investigate or verify their effects or side-effects as well as studies about the absorption, distribution, metabolism and excretion of drugs.

Clinical trials, which can be classified in four categories, may be carried out under the following conditions, defined in article 3 and 4:

- The risks to the research subject should be medically accepted and they should not be disproportionate to the potential benefit (art.3 para. a).
- The persons undergoing research must receive written information by a doctor as to the potential risks thereof and must give their consent thereto ( art. 3 para. 1b and art. 7 para. 5) The consent may be withdrawn at any stage of the research.

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<sup>23</sup> Government Gazette B 886 of 20 December 1984. See also Ismeni Kriari – Catranis (1998) Biomedical experimentation and human rights in Greece, National report at the XVth Int'l Congress of Comparative Law *Revue Hellenique de Droit International*, 1/1998, 78 – 88 and Penelope Agalopoulou (1998): Conditions regissant la recherche biomédicale et la responsabilité médicale selon le droit hellénique, in the same volume, 71 – 78: L.-A. Sicilianos, Experimentation biomédicale et droits de l'homme – Textes internationaux et pratiques étatiques in: Fondation Marangopoulos pour les Droits de l'homme, *Experimentation Biomedicale et Droits de l'homme* (1988) 217 –300.

- Clinical trials are to be undertaken in medical establishments with proper facilities by doctors with adequate experience
- The drug to be tested has already undergone complete pharmacological and toxicological control.
- Persons undergoing medical research are to be compensated for injury and loss caused by the research.
- Research can not be carried out on persons deprived of their liberty (i.e. prisoners)
- Clinical trials on minors are exceptionally permitted, if the drug aims at the prevention or detection of diseases which affect minors and if reliable results cannot be achieved from similar research on adults.

Article 4 stipulates that clinical trials may be carried out on patients, if it is expected to produce a direct and significant benefit to his (her) health; they may be also carried out on legally incapacitated persons, provided they are able to understand the purpose, aim and risk of the trial and their consent, as well as the consent of their legal representative can be obtained.

The consent must be given to the caring doctor in the presence of one witness. If the patient is not able to consent, then the legal representative alone has to give his consent, after he has been fully informed by a doctor about the foreseeable risks of the trial and its aim.

In case of emergency, if the patient or his legal representative are not in position to give their consent, medical research may be carried out only if it is of utmost importance for the life of the patient or otherwise serious harm is likely to occur to his/her health.

In consequence of the a.m. regulations, which should be applicable in the field of xenotransplantation, if it cannot be assessed that the clinical trial will be advantageous to the research subject/patient or if it is presumed that it will cause the transfer of zoonoses, it should not be allowed.

Article 7 and 8 paras.1 and 2 regulate the research procedure: The research will be conducted in accordance with a clearly defined protocol, which gives information on: Justification and aim of the trial, description thereof, description of the substances and criteria adopted for selecting the patients, number of patients, emergency and safety measures, method of results evaluation, method of documentation of side effects, creation of a register on research subjects/patients (art.8).

Before any research is undertaken the research protocol must be submitted to the Scientific Committee of the Institution, where the research is to take place and then to the Hospital Board ( art. 60 of the Law 2071/1992). Then the Protocol will be forwarded to the National Drug Organization, which is to issue the final permission for the realization of the experiment (Article 13 of the Ministerial Order). Research results should be also sent to the National Drug Organization, in order to be registered and followed up in its Documentation Department. The organization is entitled to propose

modifications of the research or even its termination (article 9 of the Ministerial Order). Further the National Committee of Bioethics and Deontology at the Ministry of Health and Social Security has been assigned to supervise medical research.

These regulations should be followed also in the case of xenotransplantation. At the present stage of scientific knowledge xenotransplantation experiments should not be undertaken on minors or persons unable to form a valid consent, given the seriousness of the problems connected thereto.

Two points should be further precisely regulated.: Consent and registration of the research subjects

a. Consent

Consent should be obtained after the patient has received ample written information about the risks, the problems and the potential benefits of the experimental procedure. Consent usually refers to the estimation of risks *v.* benefits to the individual patient/research subject. In the frame of xenotransplantation, however, the dangers may inflict not only the patient. In the case of zoonoses, they may bring about the spread of epidemics. Seen from that point of view the consent of the individual patient is of particular importance, given that no one can „consent“ to a danger for the society. We suggest, therefore, that in the field of xenotransplantation, special attention should be paid to the formation of consent. For that purpose the opinions of the ethics/deontology committees of the hospitals should become available to the patients. These bodies are in position to evaluate the risks and promises of innovative treatments in a much more accurate way than the frustrated individual patient. The information and assessment contained in these reports should be used to enable the research subject to decide accordingly.

Another issue to be dealt with in the frame of consent is related to the role of the physician during a xenotransplantation treatment: After the highly publicized case *Moore v. The Regents of the University of California et al.*, *Supreme Court of California, In Bank, July 9, 1990* ( *271 California Reporter, 146 et seq.*) special attention is paid as to the disclosure of the research/economic interests of the physician. As stated in the decision (Physician and surgeons): «Physician must disclose personal interests unrelated to patient's health, whether research or economic, in obtaining patient's consent to medical treatment, that may effect physician's professional judgement; physician's failure to disclose such interest may give rise to cause of action for performing medical procedures without informed consent or breach of fiduciary duty». In the majority's opinion this statement is further explained: «...Yet a physician who treats a patient in whom he also has a research interest has potentially conflicting loyalties. This is because medical treatment decisions are made on the basis of proportionality – weighing the benefits *to the patient* against the risks *to the patient*...A physician who adds his own research interests to this balance may be tempted to order a scientifically useful procedure or test that offers marginal, or no, benefits to the patient. The possibility that an interest extraneous to the patient's health has affected the physician's judgement is something that a reasonable patient would want to know in deciding whether to

consent to a proposed course of treatment. It is material to the patient`s decision, and, thus, a prerequisite to informed consent...» (page 151).

Though the legal system in Greece and in the most European countries is radically different from the American one, the opinions expressed in the a.m. decision merit our attention, since xenotransplantation research is bound to be connected with potential financial gains. We share the view, therefore, that the economic interests of the reseacher should be made known to the patient/research subject.

b. Collection of data

Collection and registration of data about xenotransplantation research should be regulated in a way to meet not only research needs but also the general safety. In our opinion data about research subjects, their relatives and the medical staff should be collected and stored nominally, in order to enable quick and direct monitoring of potential risky sideeffects of the experimental intervention.

## **2. Legislation on Epidemic Diseases**

The greatest problem of xenotransplantation is the danger of transfer of infection diseases from animals to humans.

The legislation on epidemic diseases (Legislative Decree 278/1969 and Royal Decree 383/ 1972, ratifying the International Hygienic Regulation) refers to already existing viruses and lays down the principles against the spread of already known diseases, as cholera, typhus, pest, yellow fever etc. Its provisions refer to mandatory declaration of the infectious illness, discovery of the focus of infection, treatment of persons who carry germs, vaccinations, declaration of existence of epidemic state, notification of the WHO, disinfection.

This legislation does not face the problem of the emergence of new diseases, emanating from medical interventions. Its provisions could be analogically applied in the case of xenotransplantation, i.e. the patient should be notified to the competent medical authority ( title II,art. 2), he/she should be put under observation (titleIV, art. 27) etc.

The importance of the early discovery of viruses, suspect to create new diseases, make it imperative, that new regulations be elaborated, related to notification, treatment and monitoring procedures.

### 3. The Law on Allotransplantation

Law 2737 of 27.August 1999<sup>24</sup> on the transpantation of human tissues and organs constitutes the legal frame concerning allotransplantation in Greece<sup>25</sup>. The Law is anticipated to facilitate the organizational difficulties surrounding organ donation from deceased and living donors<sup>26</sup> and to contribute to the arousing of the public sensibility on this topic. The law distiguishes between transplantsations from living donors and transplantsations from dead donors. The main principles enshrined in the law are:

- Organ and tissue transplantsations are carried out in specially organised units in medical establishments. The transplantsation units operate upon permission of the Minister of Health and Care. The permission is granted upon proposal of the National Transplantsation Organization and opinion of the Central Council of Health. The permission is granted initially for a period of three years; after the expiry thereof and the assessment of the unit contribution to the transplantsation needs the permission is followed by a final one (art. 4).
- Tissues banks are founded upon decision of the Minister of Health and Care. Conditions of operation and control mechanisms are specified in decision of the same Minister, issued upon opinion of the National Transplantsation Organization (art. 6).
- The harvesting of tissues and organs from living or dead donors and their transplantsation to another human being may be undertaken only for therapeutic purposes, following the provisions of the law ( Art. 1).

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<sup>24</sup> See M. Kourtis (2002): Transplantsation Law, P.N. Sakkoulas Publications (Law and Economy), Athens, Greece (in Greek); for the previous regulations see: A. Varka – Adamis (1993): Transplantsation Law, Athens, 1993 (in Greek).

<sup>25</sup> The transplantsation units in Greece are: Laiko Hospital (Kidney, Heart, Lung, Liver, Bone Marrow)

Eyangelismos (Kidney, Heart, Lung, Liver and Bone Marrow)

Aretaiio (Kidney, Heart, Lung, Liver)

Onasseio (Heart)

Aghios Savvas (Bone Marrow)

Ygeia (Bone Marrow)

Ippokrateio (Kidney, Heart, Lung, Liver)

Papanikolaou ((Heart, Lungs and Bone Marrow, Cornea)

Ahepa (Heart, Cornea)

University Hospital of Patras (Kidney, Cornea)

State Ophthalmological Clinic (Cornea)

<sup>26</sup> The situation in Greece is characterized by a strange feature worth notice: Only 5,5 cadaveric organs per million opposed to 7,8 organs from a living donor per million (the latter being one of the highest percentages in Europe). This situation is attributed to the close family relations still existing in our country, which produces twofold results:

Readiness, on the one hand, among the population, to donate his/her organ, and

Reluctancy, on the other hand, to consent to the removal of the organ from a dead relative (only 40% of the relatives consent whereas in the rest of Europe this number climbs to 70-80%) (the features are from the Report: Ethical Assessment of the Transplantsations, by the Bioethics Cimmittee of the Holy Synod of the Church of Greece: Rev. N. Chatzinikolaou: The Situation about transplantsation in Greece and Internationally, p. 4- 6, July 1999).

- The harvesting of organs should not give rise to financial gain. Any transaction between donor and recipient is forbidden (art. 2 para. 1).
- For the transplantation from *living donors* following conditions must be met:
  1. There is no possibility to obtain cadaveric organs,
  2. there is no alternative therapeutic method and
  3. the procedure does not constitute serious harm to the life or health of the donor (art. 10 para. 1).

The harvesting of organs from a living donor is allowed if they are to be taken from an adult and if they are to be transplanted to the spouse or a close relative (atr. 10 para. 2). This limitation, however, does not refer to the case of bone marrow transplantatio, which may be also harvested from a minor, if following conditions are met:

1. The intervention is intended for his/her brother or sister,
2. Tissue compatibility cannot be found in any other transplant,
3. The transplantation is absolutely necessary for the patient and
4. Both parents are consenting (article 10 para. 3).

The adult donor should have the ability to validly express his will and give freely his consent, after being previously informed by a physician about the possible consequences of the organ removal and the transplantation (art. 10 para. 4). For the protection of the living donor it is further foreseen that the declaration of consent should be in writing (by a notary act or a private act, whereby the signature must be authorized by the police authorities). Such declaration may also be given orally but, in this case, it must be registered in a special book kept at the hospital where the transplantation is to take place in the presence of two witnesses, who sign in the book along with the donor (article 10 para. 5). The consent may be freely withdrawn, until the moment of the removal (art. 10 para. 6).

- In the case of *cadaveric organs* following principles are laid down in article 12:
  1. The removal of organs is permitted in the case of brain death, which occurs when the brain stem is presumed dead, even when other organs, apart from the brain, are maintained alive with technical support (para. 1).
  2. The brain death will be testified by a team of physicians, comprised of the physician treating the donor, a neurologist or neurosurgeon and an anaesthesiologist. None of these physicians may participate in the team which will carry out the transplantation (para. 6).
  3. Condition for the harvesting of an organ is that the donor has already given his/her written consent during the general census of the population. The respectiv written declarations will be forwarded to the National Transplantation Organization, which coordinates the transplantation procedures in Greece (para. 3)<sup>27</sup>. If there is no such

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<sup>27</sup> Transplantation Units operate by license of the Minister of Health and Providence, granted upon the proposal of the National Transplantation Organization and the opinion of the National Health Council. (Art. 4 of the Law). The license is initially granted for three years, and after evaluation of the results the permanent license may be obtained.- The transplantation procedure is promoted by Transplantation Coordinators, who work at the National Transplantation Organization and at the Transplantation Units of the Hospitals (Art. 5 of the Law).- Transplantation Tissue Banks are founded by decision of the Minister of Health and Providence after proposal of the National

declaration, then the municipalities and the public insurance organizations may take the necessary steps in order to obtain the a.m. written declaration from their citizens or insured individuals.

4. The removal of organs is forbidden if the person concerned has objected thereto in written form (para. 2).
5. If the potential donor has not expressed his will on the matter (i.e. there is no written consent or objection), then the organs may be released if his/her family does not object thereto (para. 4). If there is no family of the deceased, then the principle of „presumed consent“ stipulates that organs suitable for transplantation may be released.
6. National Registry about potential receptors operates in the National Transplantation Organization (art. 7). All data related to donors, their consent/ refusal to the removal of organs, etc. are kept at Registry, operating under the National Transplantation Organization (art. 8)
7. All data about transplantations are characterised as „sensitive“ and are subject to special treatment (art. 9 of the Law on transplantation in conjunction with art. 7 of the Law 2472/97 about Data Protection).

If xenotransplantation were to become current therapy then some of the a.m. dispositions could apply analogically thereto, after adequate modification. Xenotransplantation units and Tissues Banks should operate upon special permission of the Minister of Health and Care, national registries about the donors should be created, national registries about the animals – sources of xenografts should be kept .

Consent should be obtained upon written information available to the xenograft receptor.

Data protection regulations should also be adapted to the special problems accompanying the xenotransplantation procedure, i.e. not only data about the patient should be collected, but also about his/her relatives and the medical staff.

The creation of a special register will facilitate the early discovery of infections and enable monitoring and implementations of adequate measures .

The principle of gratuitness concerning xenografts and the principle of equal access to health care should be observed: There should be, therefore, no discriminatory policy among the patients as to their chance to receive a xenograft, based on their financial status.

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Transplantation Organization. They operate in Public hospitals or in Hospitals of public character or in the Research Center “Democritus” (Art. 6).

The potential receivers are registered at the National Registry, founded by the National Transplantation Organization. The allocation of the available transplants is undertaken following various criteria such as: compatibility, emergency, age, weight etc. (Art. 7).



## **4. Animal Protection Laws**

### **4.1 Legislation on Animal Protection**

In 1981 a law on the protection of animals was implemented, which already enforced some regulations with respect to animal experimentation. This law gives definition of animal experiments and specifies animals that may be used for experimental purposes. Also, specifications are given on the competence of the persons performing animal experiments.

Under this law, an authorization from the Prefecture was already needed for the performance of animal experiments that included severe pain or stress.

The European Convention on the Use of Animals for Experimental Purposes has been ratified by Law 2015 of 27.2.1992. Further, the Presidential Decree 160 of April 1991, which implements the EC- Directive 86/609 on animal experimentation, specifies the application of this Law.

In this decree “experiment” is considered any use of the animal for experimental and/or scientific purposes related to pain, suffering or damage (art. 2 d). The aim of the experiment may be the prevention, therapy and diagnosis of diseases to human, animals or plants, or the evaluation, regulation and modification of the physiological characteristics of human beings, animals or plants. Experiments with and on animals with the purpose to procure xenografts should respect the provisions contained in this decree.

Apart from some administrative provisions, the Presidential Decree is an almost exact translation of the said Directive. Some adaptations in articles 6 and 7 were necessary to make the regulations fit with Greek legislation.

Article 6 specifies that the Regional Veterinary Services are the competent authorities that should be addressed for issues concerning authorization and registration. These Services are coordinated by the Ministry of Agriculture, The same article also specifies the possibilities to ask for a second opinion from an expert scientist on the experimental protocols, for which an application for authorization has been received. Article 7 deals with the authorization of persons and experiments and article 12 specifies regulations for the registration of statistics.

The authorization of persons and experiments is inseparable and results in only one license. An application can be awarded only when the applicant can demonstrate that he/she was never officially sentenced for an offence against the Law on Animal Welfare. Further, the application should contain all information on the persons who have first and second responsibility for the experiment for which an authorization is requested (i.e. name, university degree, quality of employment, relevant additional

training, address, previous application for an authorization of similar studies and name of the competent veterinarian). Full details should be also given on the study, for which the authorization is requested (i.e. information on the purpose and necessity of the experiment, information on experimental methods, number of animals to be used and expected pain or stress, a justification of the necessity to repeat an experiment -if applicable-, the opinion of the competent veterinarian, a justification of the necessity to conduct an animal experiment instead of an alternative method). Information should be also given on the choice of the specific animal, the origin of the animals and the supplier establishment, the condition of the animals after the experiment and the number, sex, strain etc, of the animals. An annex should contain details about the institute, the facilities, in which the animals will be housed before and during the experiment, the name of the person responsible for the Institute' s administration and the name of the persons involved in the experiment.

The license actually is a decision of the Prefecture granted upon opinion of the Regional Veterinary Service and is valid for one year. Once a license is given to the person who is first responsible for an animal experiment, this person is obliged to communicate to the regional Veterinary Service one month before the study actually begins. This obligation is specified in Article 12 of the Presidential Decree. The license holder should provide information on the purpose of the experiment, the experimental methods to be used, the duration of the experiment, the number and species of animals to be used, the respective institute and the names of the responsible persons. This information is used by the Regional Veterinary Services for registration of statistics.

#### **4.2 . Legislation on genetically modified microorganisms and organisms**

4.2.1. Presidential Decree 186/1995 (30.5.1995) about the protection of the individual with regard to biological risks (as a result of the European Directives 90/679 and 93/88).

4.2.2. Ministerial Decision 952/1995 (14.12.1995) about contained use of genetically modified microorganisms (as a result of the European Directive 90/219/23.4.90). Contained use, means mainly application in the laboratory. The Decision regulates the safety of individual and environment when using genetically modified microorganisms. Since a genetically modified animal cannot be considered as a microorganism, these regulations do not apply to the creation of xenografts. The safety measures, however, contained therein, should be taken into consideration *analogically* at the respective experimental procedures.

4.2.3. Ministerial Decision 88740/1995 (11.12.1995) about the deliberate release into the environment of genetically modified organisms (as a result of the European Directive 90/220 and 94/15).

Art. 2 para.1 defines an organism as a biological unity able to multiply or transmit genetic information. A genetically modified organism is one, the genetic material of which has been modified in a way that does not occur naturally .

An animal, the genetic material of which has been modified in an unnatural way, may fall under these regulations. This Decision is applicable in the field of xenotransplantation, since it specifies the genetically modified organisms as biological entities able to transmit genetic information. This decision does not apply to organisms created through the following techniques of genetic modification, on condition that they do not involve the use of recombinant DNA molecules or GMOs:

In vitro fertilization; conjugation, transduction, transformation or any natural process; polyploid induction (Annex I A , Part 2).

Other techniques of genetic modification to be excluded from this Decision, on condition that they do not involve the use of GMOs as recipient or parental organisms are:

Mutagenesis; Cell fusion (including protoplast fusion) of plant cells where the resulting organisms can also be produced by traditional breeding methods (Annex I B).

Article 5 para. 1 of the said Decision states that any person, before undertaking a deliberate release of GMOs must submit a notification to the competent national authority, the General Direction of Environment at the Ministry of Environment, Development Planning and Public Works (art. 4, para. 1). The notification shall include a technical dossier supplying the information necessary for the evaluation of foreseeable risks, immediate and future, which the GMO or combination of GMOs may pose to human health or the environment, as well as the methods used and the bibliographic references. The dossier contains in particular: general information, information on personal and training, information about the GMOs, information relating to the conditions of release and the receiving environment, information on interaction with other organisms in the environment, information on monitoring, control, waste treatment and emergency response plans.

The notifier shall also include in the notification a statement assessing the impacts and risks posed by the GMOs to human health or the environment and information known to him/her from releases of the same GMOs or the same combination of GMOs, previously or currently notified or carried out by him/her inside or outside the European Union (art. 5 para. 2).

The competent authority, the General Direction of Environment, shall answer in writing to the notification within 90 days upon receipt thereof. The answer will either permit the deliberate release of GMOs or will reject it, if it poses a threat for public health and the environment (art. 6 para. 1).

A notification is also to be submitted at the general Direction by the importer or manufacturer, if a GMO or a combination of GMOs is placed on the Greek market as or in a product. The notification shall contain information about the name of the product and of the GMOs contained therein, the name of manufacturer or distributor and the specificity of the product. The notification will contain information about the places, where the product is to be distributed, information about potential dangers,

emanating from the product and affecting ecosystems and assessment of potential dangers for health and/or environment related to GTOs or combination of GTOs(art. 8 para. 1, I ii). The notifier shall submit a new notification for every product consisting of the same GMOs but intended for a different use (art.8 para. 4). Annex III lays down the conditions required for the placing of the product on the market, including conditions of use, handling and packaging.

If new information is available with regard to the risks of the product to human health or the environment, the notifier shall inform immediately the General Direction of the Environment, revise the evaluation of the foreseeable risks and take the necessary steps for the protection of human health and environment (art. 8 para. 5).

The regulations of this Decision can apply to the creation and purchase of xenografts, but its provisions should be further elaborated, in order to meet specific safety demand (i.e. the decision about the deliberate release of GTOs , in the case of xenografts, should be taken by the General Direction of Environment, upon concurring opinion of the National Board on Bioethics or the Ethics Committee of the medical establishment, where the research/therapy will take place).

#### **IV. Concluding Remarks**

The Greek legal frame addresses some of the issues common also to xenotransplantation, but not all of them. These new complex problems have not been properly assessed by the scientific community and have not been presented to the wider population. Since our new Law on Allotransplantation has been voted some years ago, the main attempt of the Ministry of Health is to endorse its implementation and to make its options widely known and understood.

Given that xenotransplantation poses new problems, connected mainly with the danger of infections (xenozoonoses) and the spreading of epidemics, some other questions have to be dealt with in association with this method:

1. The consent regulations have to be supplemented by rules referring to the risks/dangers not only to the person involved, but also to the society in general. The patient/research subject should receive written information about the method, the potential risks and benefits as well as the opinion of the ethics/deontology committee of the respective establishment about the general assessment of the procedure. Economic interests of the research scientists should be also revealed to the patient/research subject. These adaptations are necessary both in the experimental and in the therapeutic intervention.
2. The concurring opinion of the ethics/deontology committee should be a formal prerequisite for research<sup>28</sup>.

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<sup>28</sup> See M. Kourtis, op. cit. p. 225

3. Detailed regulations are needed concerning the creation of source animals. The existing provisions, based on Directive 220/90 are to be completed on the topic: Authorization by a competent body.
4. Research should be conducted upon the principle of subsidiarity, i.e. after the experimentation with and on animals cannot yield the requested information. Of crucial importance is the transplantation of organs from other animals to primates (i.e. from pigs to chimpanzees), given that the latter show many similarities with the human organism<sup>29</sup>
5. Research should not be conducted on minors and persons incapable of consent.
6. Data registries about the research subjects/patients, their families, and medical staff should be created. The data contained therein should not be anonymous, at least in the beginning of the procedure, in order to facilitate the early detection of potential side effects
7. Regulations about the protection of health in case of new infections should be elaborated.
8. Special registries should also be created with data of the source animals: country of origin, importer, scientific/medical establishment, responsible staff members etc.

In the face of so difficult problems, however, one should keep in mind one of the fundamental principles enshrined in the European Convention on Biomedicine, that is: “the interests and welfare of the human being shall prevail over the sole interest of society or science”.

In Homer’s Iliad the hero Bellerophon killed Chimaera,  
*“grim monster sprung of the gods, nothing human,  
all lion in front, all snake behind, all goat between,  
terrible, blasting lethal fire at every breath!”*<sup>30</sup>

The battle, however, goes on...

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<sup>29</sup> M. Kourtis, op. cit. p. 224, fn. 42.

<sup>30</sup> Iliad, Book 6, 213 - 215