

FRENCH VETERINARY ACADEMY



«HUMAN-ANIMAL RELATIONSHIPS»
COMMISSION

REPORT

SCIENTIFIC RESEARCH
AND ANIMAL
EXPERIMENTATION
STATE OF AFFAIRS

MAY 2012
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COMPOSITION AND VALIDATION OF THE REPORT

“Scientific research
and animal experimentation
State of affairs”

This report has been drawn up within the framework of a general study carried out by the Commission for «Human-Animal relationships» of the French Veterinary Academy.

It was conceived and coordinated by Claude Milhaud.

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The conclusion of the report is presented as a recommendation submitted for consideration to and adopted by the General Assembly of the French Veterinary Academy on June 21st 2012.

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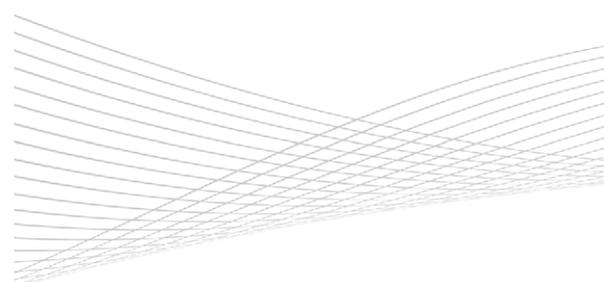
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SUMMARY

This report has been drawn up on the initiative of the human-animal relationships commission and includes three chapters entitled respectively : a social debate, animal models and replacement methods, practice of animal experimentation : bases of an academic approach. These three chapters are followed by a recommendation from the French Veterinary Academy of June 21st, 2012.



SOCIAL DEBATE

In order to meet popular demands with respect to health and longevity, research in biological and medical sciences is largely based on animal experimentation. Although historically justified, the use of animals for experimental purposes is called into question in our society in which the animal's position has considerably evolved.

Basically, three groups of contemporary views can be discerned which are at the root of this opposition; those who adhere to philosophical beliefs placing men on a strictly equal footing with all other animal species, those who express spontaneous compassion towards the animals, a sentiment they express with regard to any situation in which the latter are mistreated or risk being mistreated. Lastly, a limited number of scientists dispute the validity of animal models as a reliable source of knowledge for human and veterinary pathology. The expression of these convictions through violent actions, exceptional in our country, causes

security issues and problems with freedom of action which force researchers to put aside their reserve and to point out the legitimacy and the circumstances of animal experimentation practice.

The creation of national and international professional associations, the organization of specialized training, first spontaneously, later normalized by public authorities, the creation on a voluntary basis of regional and institutional ethics committees and finally the adoption of European and national regulations have largely contributed to the change in attitude of researchers and to their increased respect for the animal and its well-treatment whilst practicing their science.

The origin of the controversy which causes opposition to experimenters from a part of the community lies in convictions and attitudes that cannot be altered by rational discussion. Paradoxically, although demand for scientific progress and security have never been higher,



these convictions and attitudes are reinforced by global sentiments of defiance against science which tend to expand in contemporary society.

ANIMAL MODELS AND REPLACEMENT METHODS.

An in-depth study of animal models, their justification, their limits and their use in the principal disciplines of medicine and biology has been weighed against an equally in-depth study, performed following the same plan, of the justification, the limits and the use of replacement methods and alternative methods in the principal disciplines of medicine and biology. This comparative study led to the following conclusions:

The complexity of organisms cannot be modeled by a simple addition of elementary biological systems. The deeply integrative nature of Life requires biological science, and biomedical science in particular, to use - when necessary and in a reasonable and limited way - models of a complexity level similar to that of human beings: the laboratory animal.

Fundamental research, whether physiological, immunological or genetic, is currently orientated more towards the cellular and molecular approaches. It cannot help however resorting to laboratory animals when it needs to integrate the results obtained in vitro to the level of an entire organism. The same applies to research concerning the knowledge of physiopathological mechanisms which are the foundation of medical and surgical therapeutics.

In toxicology and in the safety of health products or in pharmacology, the in vitro or in silico approaches, with their own limits and aside from the satisfaction of the associated increased respect for life and for animal welfare,

allow to achieve important savings in time and money. The spontaneous development of their use and their introduction into regulations presently runs into the insufficiency of proposals issued by research and the duration and complexity of validation operations.

The very limited scope of the in vitro and in silico methods, as well as economical and ethical motives, have compelled the international scientific community and public authorities to make an important human and financial effort in order to develop, thanks to progress in bioinformatics, the so-called combinatorial methods. These methods aim to associate the analysis and synthesis of earlier data bases with results obtained more recently through an experimental body bringing together in vivo, in vitro and in silico methods. Each of these approaches remains indispensable since each one contributes, through its specific revelations, to the synthetic knowledge of live phenomena of the global organisms, be it human or animal.

PRACTICE OF ANIMAL EXPERIMENTATION : BASES FOR AN ACADEMIC APPROACH.

It is recommended to base an academic approach on :

- the reaffirmation of a vital prerequisite : recourse to animal experimentation is essential to the progress of knowledge and of medicine in the current scientific situation;
- the expression of respect towards laboratory animals on the grounds of their nature as a sentient creatures and on their phylogenetic origin, common to that of humans; this respect has been put into practice by the 3 R's principle, by taking into account the relationship between the harm to animals and the benefit for humans, by the generalization



of ethics committees and by the development of several well-treatment measures : environmental enrichment, standardization of euthanasia methods, post-experimental rehabilitation,

- the acknowledgement that in biology in general and in biomedicine in particular, the

experimental approach should use the whole range of methodological possibilities it has created without prejudice and in an objective manner;

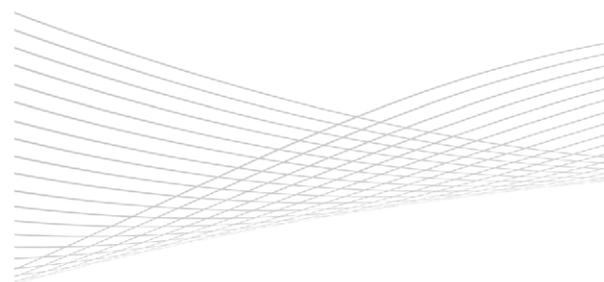
- the definition of and the proposal for a social dialogue based on mutual knowledge and respect.





INTRODUCTION

Since their first experimental work using animals, François MAGENDIE (1783-1855) and Claude BERNARD (1813-1878), two physiologists who were inspired by the rationalist approach of physicians and chemists, both had to face the hostility of some of their contemporaries. Thereafter, for nearly one century, the opposition to the use of animals for experimental purposes will remain the prerogative of minorities, ultimately without much influence in France.



During the last sixty years, the increasing distance from the objective reality of farm animals, the spectacular increase of pets, or again, the influence of the anthropomorphic representation of animals in cinematic or television fiction, have overturned the traditional image of the animal in Western society. This profound evolution in society has found connections and support in the philosophical approaches related to the utilitarian moral which was developed in the 19th century by Jeremy BENTHAM (1748-1832) and revived in the 20th century by Peter SINGER (1946 -), this philosophical trend converging with the so-called « continuist or antispeciesist » trend in order to question the relationships between humans and animals and to feed the debate on the existing

continuity or discontinuity between humans and animals. From a legal statute as an object, the animal has implicitly and explicitly evolved to that of a subject with its own rights¹²³. And, although animal rights remain controverted, today man's duties towards them are commonly acknowledged⁴⁵.

During the last thirty years, the protest against the use of animals for research purposes has found in this examination and questioning of human-animal relationships, philosophical support and a justification of its point of view. In general its effectiveness has been largely bolstered by the major disasters of the 20th century (local and world wars, torture, famine, depletion of natural resources, the relative delay, due to difficulties

¹) Anonyme. *Droit Animal, Éthique, et Sciences*, n° 69, avril 2011, p2

²) DENOIX DE SAINT MARC Renaud. « *Les animaux ont-ils des droits ?* » Communication présentée à la séance du 23 mai 2011 de l'Académie des Sciences morales et politiques.

³) MARGUENAUD Jean-Pierre. *Expérimentation animale entre droit et liberté*. Ed Quae, Versailles, 2011

⁴) CHAPOUTHIER Georges. *Les droits de l'animal par rapport aux droits de l'homme aujourd'hui*. In : Quedraogo A. P., Le Neindre P. (eds). *L'homme et l'animal, un débat de société*. Paris: INRA, 1999, 33-40.

⁵) FAINZANG Sylvie. *Le rapport à l'animal dans la recherche médicale. Esquisse d'un projet de recherche*. In : Quedraogo A. P., Le Neindre P. (eds). *L'homme et l'animal, un débat de société*. Paris: INRA, 1999, 169 -174



encountered in the development of prophylaxis or therapeutics, in combating certain major diseases such as cancer or AIDS) which contributed to challenging the notion of progress, and further, of science and of scientists.

In this context, it is not surprising that so-called «antivivisectionist» associations develop activities with the final objective of abolishing animal experimentation by mostly legal means but sometimes also with violent actions. This position,

based on emotion and not on reason, upsets a very large majority of the scientific community.

Aside from philosophical disputes, but without ignoring them, and within the framework of social reflections of our academy, the objective of this report is to establish as objectively as possible the reasons and conditions of laboratory animal experimentation as well as the rationale of the development of methods which might substitute them.

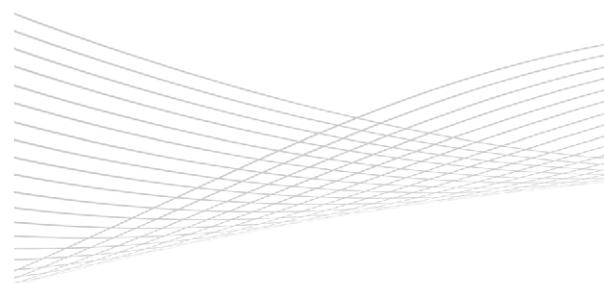


CHAPTER I

A SOCIAL DEBATE

1) BIOMEDICAL RESEARCH : A NECESSITY FOR SOCIETY

Although one could assume that its origin was concomitant with that of the first organized societies, biomedical research in its present form originated in the 18th century. It then developed almost exponentially to reach a volume of 43,770 publications in 2006. This growth is associated with a triple determinism : widespread demand to ensure the best possible health and maximum longevity for everyone ; sufficient material resources for the development of research both for humans and animals, increasingly effective therapeutic and prophylactic methods ; general improvement of the population's level of education providing the necessary human resources for biomedical research.



In parallel, the social demand regarding health has increased and the notion of the right to health was imposed. The precautionary principle and its consequence was added to this fundamental right : the necessity to evaluate more thoroughly the health risks of any technological innovation. While responding to these two fundamental demands of our society, biomedical research must also take into account the economic importance of any progress achieved in the field of prevention.

Experience of more than two centuries and every-day experience show that, when necessary, every progress both in fundamental disciplines as well as in the development of new

therapeutic or prophylactic means, has been based on the recourse to animal experimentation and due to the impossibility of experimenting on humans (chapter 1 § 2.2).

2) Animal experimentation : foundation of a scientific approach to health.

2.1) Historical overview

Since the initial work at the end of the 18th century, animal experimentation has produced indisputable results both in scale and in productiveness. This approach of Life mechanisms forms the incontrovertible base of present-day biology and medicine. In order to confirm this statement, one can refer to the list



of the winners of the Nobel prize for physiology or medicine from its creation in 1901 until today. This list becomes particularly revealing if one starts to add to it the one or more species that the laureates used for their work⁶.

In order to determine some main themes, 4 tables have been extracted from the global list of laureates. They illustrate respectively, the role of the animal models in some of the important

advances in medicine since the beginning of the 20th century as well as in the development of three fundamental disciplines : physiology of the nervous system, genetics and immunology (fundamental work on viruses and bacteria, although these are also at the origin of major discoveries in genetics and have been distinguished by several Nobel prizes, are not reported here).

TABLE 1.
SOME OF THE GREAT ADVANCES IN MEDICINE SINCE THE BEGINNING OF THE 20TH CENTURY

YEAR	LAUREATES	THEME	ANIMAL MODELS
1905	R. Koch	Agent causing Tuberculosis and cholera	Cow, Sheep
1907	A.Laveran	Agent causing malaria	Bird
1923	F.G. Banting J.J.R. Macleod	Discovery of insulin and mechanism of diabetes	Dog, Rabbit, Fish
1945	A.Fleming et E.B. Chain	Discovery of penicillin	Mouse
1951	M. Theiler	Vaccine against yellow fever	Monkey, Mouse
1954	J.F. Enders, T.H. Wellers, F.C. Robbins	Vaccine against poliomyelitis (in vitro culture of the virus)	Monkey, Mouse
1966	F.P. Rous et C.B. Huggins	Virus induisant des tumeurs et traitement treatment of prostate cancer	Rat, Rabbit, Chicken
1976	C. Gajdusek, B. S. Blumberg	Origin of Kuru	Chimpanzee
1990	J.E. Murray et E.D. Thomas	Techniques and transplantation of organs (homozygous twins)	Dog
1997	S. Prusiner	Discovery of Prions	Mouse, Hamster
2005	B.Marshall, R. Warren	Role of H. pylori in gastric ulcers	Gerbil, Pig
2008	H. zur Hausen, F. Barré-Sinoussi, L. Montagnier	Discovery of HPV and HIV viruses	Mouse, Primate
2010	R. Edwards	Development of in vitro fertilization	Mouse, Rabbit

⁶ www.animalresearch.info



TABLE 2.
SOME GREAT STEPS IN THE DEVELOPMENT OF NEUROPHYSIOLOGY

YEAR	LAUREATES	THEME	ANIMAL MODELS
1906	C.Golgi et S. Ramon y Cajal	Structure of the nervous system	Dog, Horse
1932	C.S. Sherrington et E.D. Adrian	Function of neurons	Dog, Horse
1936	H.H. Dale et O. Loewi	Chemical transmission of the nerve impulse	Cat, Frog, Bird, Reptile
1944	J.Erlanger et H.S. Gasser	Neuron properties	Cat
1963	A.L. Hodgkin, A.F. Huxley et C. Eccles	Ionic mechanisms and nerve cells	Cat, Frog, Crab, Squid
1970	J. Axelrod B. Katz et U. von Euler	Physiology of neurotransmitters	Cat, Rat
2.000	A. Carlsson, P.Greengard et E.R. Kandel	Signal transduction in the nervous system	Mouse, Slug

TABLE 3.
SOME GREAT STEPS IN THE DEVELOPMENT OF GENETICS

YEAR	LAUREATES	THEME	ANIMAL MODELS
1933	T.H. Morgan	Role of chromosomes in heredity	Drosophila
1935	H. Spemann	E«Organizer»-effect in embryonic development	Frog, Newt
1968	R. Holley, G. Khorana et M. Nirenberg	Interpretation of the genetic code and protein synthesis	Rat
1995	E. B. Lewis, C. Nusslein Volhard et E.F. Wieschaus	Genetic control of embryonic development	Drosophila
2002	S. Brenner, J. Sulston et R. Horvitz	Genetic regulation of organ development and cell death	Nematode
2009	E. Blackburn, C. Greider et Jack Szostak	Chromosome protection by telomeres and telomerase	Mouse, Frog



TABLE 4.
SOME GREAT STEPS IN THE DEVELOPMENT OF IMMUNOLOGY

YEAR	LAUREATES	THEME	ANIMAL MODELS
1908	P. Ehrlich, E. Metchnikov	Immune responses and phagocyte function	Bird, Marine invertebrates, Guinea-pig
1913	C. Richet	Mechanism of anaphylaxis	Dog, Rabbit
1919	J. Bordet	Immune mechanism (the complement)	Guinea-pig, Horse, Rabbit
1960	F. M. Burnet, P. B. Medawar	Comprehension of acquired immune tolerance	Rabbit
1972	G. Edelman, R. Porter	Chemical structure of antibodies	Guinea-pig, Rabbit
1980	J.D. Snell et B. Benacerraf	Description and function of the major histocompatibility complex	Mouse, Guinea-pig
1984	N. Jerne, G. Kohler et C. Milstein	Monoclonal antibody production	Mouse, Rat
1987	Tonegawa Susumu	Genetic antibody structure	Mouse
1996	P. Doherty, R. Zinkernagel (Suisse)	Recognition by the immune system of virus-infected cells	Mouse
2011	J. Hoffmann, B. Beutler et R. Steinman	Innate immune system	Mouse

A careful examination of these four tables allows us to identify a number of areas for further study.

Firstly, whatever the nature, applied or fundamental, of the rewarded work, recourse to animal experimentation is a constant. The species used prove to be diverse and include invertebrates, vertebrates and poikilothermic or homoeothermic animals. In the four tables, 22 species are named in relation to the reported works. This diversity, which is necessary to understand the basic mechanisms of living beings, demonstrates at the same time how much attention has been given to the choice of the experimental model.

When these animals, usually mammals, have been used as general models, they have for instance enabled the development of essential vaccines (yellow fever, poliomyelitis) without the necessity of having at one's disposal all the fundamental knowledge that is currently involved with the control of immunological mechanisms underlying vaccination (tables 1 and 4).

Both in the fundamental and applied disciplines, most frequently, the animal is put at risk and its life is endangered : viral or microbial contamination, hormone therapy trials, organ transplantations or shock to the immune system (tables 1 and 4).

In addition to avoiding even minimum risks to human beings, the aim of having recourse



to animal models is to avoid the severe distress which is or would be condemned by bioethics and common sense if this were applied to human beings: sections and stimulations in neurophysiology (table 2), manipulation of genomes and embryos in genetics (table 3).

Finally, it can also be observed in these tables that, very often, the choice of study models is based on user convenience criteria. This is the case with the drosophila, whose very small size, easy breeding conditions and very short life cycle allow rapid generation renewal of statistically satisfactory importance as is required by geneticists. Along these same lines, the squid's giant axon represents, due to its size, one of the models chosen by physiologists for nerve conduction.

On the other hand, the accumulation of essential knowledge regarding the biology of species such as the drosophila or the mouse, leads to a near-monopoly of their use in certain disciplines or fields of study, for instance : genetics for the drosophila or transgenic models in experimental pathology and immunology for the mouse.

Past achievements are not guarantees for the future. Nevertheless, they contribute to a large extent to the validation of past experiences, in this case, those of experimental methods and concepts based on animal models and which have been used by biomedical disciplines for more than a century.

2.2) QUANTITATIVE IMPORTANCE OF RESEARCH USING ANIMALS

In France, 60,000 biologists are directly or indirectly involved in the use of laboratory animals. In the whole of the developed world, this number amounts to approximately a million. One can assume that, with the current

emergence of large nations such as India, China and Brazil, the number of researchers likely to use animals within the framework of fundamental or applied research, will increase to approximately two million in 20 years⁷.

In 2008, animal experimentation in Europe was applied 38.1% in basic biology, 22.8% in research and development of medicines for humans and animals, 14.9% in production and control of prophylactic and therapeutic resources for humans and animals, 8.7% in toxicology and safety, 1.7% in education and training, 1.6% in diagnostics and finally 12% classed as « other »⁸.

The number of animals used for these different purposes in Europe in 2008 is 12 million, of which 3 million in the United Kingdom, 2,330 million in France, 760,000 in Switzerland. These figures can be compared with those of the United States, ranging between 22 and 25 million animals (where only the number of rodents was evaluated). Globally, rodents and lagomorphs represent 80% of the animals used, cold-blooded animals 15%, birds 5%. The proportion of carnivores (0.3%) and of primates (0.1%) continues the progressive decline these groups have seen during the last decade. Details regarding species used, the nature of the models or the aim of the experiments, in a country comparable to France in this field, the United Kingdom, are published in an OPECST report⁹.

The global numbers mentioned rightfully give cause for alarm. They need to be put into perspective taking into account at least the species concerned, the category of distress levels imposed and the purpose of their use. Equally, these numbers should be viewed in their historic context. Indeed, the efforts to develop alternative methods of the last decade, particularly with

⁷ KOURILSKY Philippe « *Changements d'échelle et mutualisation mondiales des moyens en biologie* » « Mondialisation de la Recherche » Colloque Collège de France 14 et 15 octobre 2010.

⁸ www.ec.europa.eu/environment/chemical/lab_animals/reports

⁹ LEJEUNE Michel, TOURAINE Jean-Louis. Rapport « *Sur l'expérimentation animale en Europe. « Quelles alternatives ? Quelle éthique ? Quelle gouvernance ? »* » Office Parlementaire D'évaluation Des Choix Scientifiques Et Technologiques. Décembre 2009. n°2145 (Assemblée nationale) et 155 (Sénat) pages 24et25



regards to toxicology and safety of medicines have been counterbalanced by the parallel increase of the use of genetically modified or transgenic models (Annex 3). Simultaneously, the perspectives offered by combinatorial strategies (Chapter II § 4) create expectations for a medium-term substantial reduction of the number of animals used.

The essential effort of providing the explanation that should accompany these numbers is rarely made. This is the cause of the mistrust or even hostility from a section of the public and explains, alongside ethical, scientific and economic considerations, the political importance of this problem in certain countries such as the United Kingdom or Germany. In these countries, animal protection and, as a consequence, animal experimentation are already issues of electoral controversy. In France this happens to a lesser degree as is demonstrated by the part played by animal experimentation in the debates and in the conclusions of the « Animal et Société »-meetings¹⁰.

2.3) REGULATORY FRAMEWORK

The practice of animal experimentation is strictly controlled by national, european and international laws. The Ministries of Agriculture and Research primarily, and the Ministries responsible for Health, Industry and the Environment on a secondary level, are, in different capacities, in charge of the composition and application of the regulations.

Generally, the recommendation of the Helsinki Declaration (2000) should be incorporated into this regulation¹¹:

« 11. Medical research involving human subjects must, conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and

adequate laboratory and, as appropriate, animal experimentation. »

Moreover, the practice of experimentation should respect the sentient nature of domestic animals and wild animals tamed or kept in captivity, recognized in France by the 'Code Rural' (Rural Code) (art. L.214.1 to L.214.25). This regulation is a follow-up of and corresponds to the law on nature conservation of 1976 (ex article 276 of the Code Rural). In Europe, the protocol on animal protection and welfare, annexed to the Treaty of Amsterdam signed in 1997 and incorporated in the « mini-treaty » of Lisbon lays down the principle of « *an improved protection and respect for the welfare of animals as sentient beings* ».

Since the adoption of these treaties, animal protection is an integral part of European Union policy. The member states must take into account the protection of animals as sentient beings when formulating and adopting communal rules except for issues related to cultural, regional and/or religious customs for which the responsibility remains with the member state (subsidiarity principle).

As for all legislation, this regulatory framework is subject to discussions by the elected representatives of the people : the national or European parliaments.

In France, animal experimentation practice is subjected to a specific national regulation which is merely a transcript of the European laws as well as certain more general texts of the 'Code Pénal' (Penal Code) (condemnation of acts of cruelty towards animals: article 521-1, condemnation of animal experimentation performed by a non-authorized person : article 521-2, and condemnation of ill-treatments : articles R 653-1, R 653-2, R 655-1), of the 'Code de la Santé Publique' (Public Health Code) (knowledge needed prior to clinical experimentation : article L 1121-2) and of the 'Code Rural' (cf. supra).

¹⁰ www.animalsociete.fr/propositions/les%20rencontres%20animal%20etsociete%20rapport%20rapporteur%20general.pdf

¹¹ www.Genethique.org/carrefour_infos/textes_officiels.



From an entirely free activity in 1968, animal experimentation saw its regulatory framework evolve gradually and in parallel with the evolution of sensitivity within our society and the underlying controversy^{12 13}.

First stage : 1968. Decree 68 /139 implementing the law of November 1963. An individual authorization is needed in order to perform experiments.

Second stage : 1986. Creation of a specific directive by the European Community, directive 86 /609 EEC of November 24th 1986, transposed by decree 87-848 of October 19th 1987 and the decrees of April 19th 1988. These European texts set out the principle of authorization of the experimenter, license of the establishment where he works and the origin of the animals used. They describe a certain number of practical guidelines with regard to the housing conditions of animals. In 1992, ten measures, proposed by Prof. H. CURIEN then Minister of Research and Technology, have been included in these provisions. These measures formed the framework of a voluntary and responsible policy promoted by the Minister of Research and Technology, in the name of the scientific community.

Third stage : 2013. The new European provisions, directive 2010/63/UE of September 22nd 2010, transposed into the French law by the decree 2013-118 of February 1st 2013 (J.O. of February 7th 2013) and its five implemented decrees of that same date, add the approval of each experimental protocol to these three previous authorizations, they limit the use of primates and include invertebrates, the cephalopods in the regulations. The creation of committees to review animal welfare (the so-called « ethics committees ») is made compulsory and the former guidelines on animal

housing are modified taking into account recent knowledge on ethology with regard to the notion of « behavioral enrichment ».

Furthermore, since the « animal welfare »-notion has been taken into account by the World Organization for Animal Health (OIE) in 2001, specific working groups of this organization are studying the formulation of texts specific to laboratory animals¹⁴.

2.4) UNANIMITY OF RESEARCH ORGANIZATIONS

In the whole world, all public or private research institutions, independent of the dominant philosophical culture in their respective countries, are having recourse to animals in order to extend fundamental knowledge as well as to develop new therapeutic resources or to perform toxicological controls. The only perceptible differentiations are not related to methodology but to the practical application of fundamental ethical rules which however are rapidly being generalized and standardized.

2.5) ADDITIONAL PROBLEM OF THE USE OF LIVE ANIMALS FOR EDUCATIONAL PURPOSES

The justification of the use of laboratory animals for educational purposes, which is less obvious than that of biomedical research, is frequently put into question. Its pedagogic usefulness, greatly varying in importance and nature, needs case by case consideration. The quality of increasingly sophisticated educational models, computer simulations or video applications should result in a reduced use of animals for educational purposes.

Thus, of the 2,328,380 laboratory animals used in France in 2008, 55,573 (i.e. 2.3 %) were used for training purposes in universities or colleges and technical institutions.

¹² MARGUENAUD Jean-Pierre. *Expérimentation animale entre droit et liberté*. Ed Quae, Versailles, 2011

¹³ RONDAUD Annabelle. *L'expérimentation animale : une controverse stagnante ? Approche communicationnelle*. Thèse en sciences de l'information et de la communication. Paris IV – Sorbonne –Celsa. 2011

¹⁴ KHAN Sarah, *The role of the World Organization for Animal Health (OIE) in the development of international standards for laboratory animal welfare* p 727-730 Proc. of 6Th world congress on alternatives and animal use in the life sciences august 21-25, Tokyo, Japan.



This proportion is within the upper part of the European range (0.1 to 2.9%)¹⁵. It should deserve appropriate examination which falls somewhat outside the scope of this report.

3) OPPOSITION TO ANIMAL EXPERIMENTATION

3.1) A SOCIAL ISSUE

As mentioned in the introduction, the opposition to animal experimentation has developed in all Western countries over the last thirty years. Although at the origin of modern medicine and its development, the experimental method and its merits are ignored by certain categories of the population who increasingly express their defiance of scientifically based medical approaches. On this basis, an active, structured opposition has developed, with substantial financial resources, producing abundant militant literature and making the best possible use of the opportunities offered by the internet¹⁶. It demonstrates a capacity for violent actions and raises ever increasing awareness within a section of the public.

However, the reactions of the latter may appear paradoxical. The detailed regulations concerning the safety of drugs, cosmetic products or, presently, any chemical substance (REACH regulations : Registration, Evaluation, Authorization and restriction of Chemical substances) are indeed the outcome of two apparently contradictory concerns. The European consumer demands maximum safety regarding the products or medicines he uses, which implies the performance of tests which, to a large degree, involve laboratory animals. And at the same time, part of public opinion expresses its desire for a reduction or even the abolishment of distress imposed on animals.

One notices the same contradiction between health concerns with a demand for constantly more efficient treatments, and the negation of animal experimentation as a major source of biomedical knowledge.

Faced with these contradictions, manifestations of public opinion are scarce. It seems to remain barely concerned, to the point that even the results of the few surveys that have been made, reveal to be contradictory. This phenomenon can be found in other controversies concerning human-animal relationships : such as those concerning « productivist » breeding techniques or ritual slaughter.

This kind of contradiction is illustrated by the differences observed in Great Britain between two surveys, one conducted in December 2009 for the Government (by Ipsos-Mori) which demonstrates that 71% of public opinion is in favour of using laboratory animals for biomedical research, whereas the other survey conducted in August 2010 for the Animal Aid association (by GfK-NOP) establishes that 82% of the respondents are opposed to animal experimentation and 16% are in favour¹⁷.

How to explain these contradictions? The questions asked were not strictly identical and it is possible that their formulation influences the persons who were questioned, especially when the ins and outs of a problem area like the one discussed in this present report, are not well known by the public.

3.2) NATURE AND METHODS OF THE OPPOSITION TO ANIMAL EXPERIMENTATION

3.2.1) Global opinion sincerity

Apart from exceptional cases, the commitment of the members of the so-called « antivivisectionist » associations appears to be

¹⁵ Anonyme .Droit Animal, Éthique, et Sciences, n° 69, avril 2011, p2

¹⁶ RONDAUD Annabelle. *L'expérimentation animale : une controverse stagnante ? Approche communicationnelle*. Thèse en sciences de l'information et de la communication. Paris IV – Sorbonne –Celsa. 2011.

¹⁷ ANIMAL AID. *Victims of charity. A report on the cruel and scientifically invalid experiments funded by medical research charities*. www.animalaid.org.uk



free and indisputably genuine; it is most often based on a personal philosophy which reconsiders the human-animal relationships and which is not limited to opposition to animal experimentation. Generally, these persons are also committed to other issues in defense of animals : animal rights, opposition to « productivist » breeding techniques, to the use of animal furs, to meat consumption, to the practice of ritual slaughter, etc. As with all organized social activity, there are some professionals managing these associations, who are making their living from this activity and whose sincerity could be questioned.

3.2.2) Philosophical opposition : current trends

During the last decades, considerations relating to the position of mankind relative to animals have evolved considerably. For millennia, an impenetrable wall separated men from animals, resulting in men scrupulously using the latter to meet his needs since, they, just like the whole of Creation, were supposed to be at his service. The decline of religious sentiment and the (partial) spreading of modern biology concepts, Darwinism and genetics (in its simplistic interpretation), have contributed to the awareness that mankind belongs to the animal kingdom, creating a feeling of greater proximity, or even equality, and the conviction that the fact of using animals endangers its sentience and harms biodiversity.

More precisely, the convergence of two philosophical movements, the utilitarian trend and the so-called « continuist or antispeciesist » trend, challenges the framework of human-animal relationship as it was perceived even in the middle of the 20th century. It particularly poses the general problem of the use of animals by humans. Starting from the acknowledgement of animal sentience and consequently of the moral value of each animal being at the same level as that of each human, the utilitarian

movement places human-animal relationship in an egalitarian perspective. Followers of the « continuist or antispeciesist » trend reinforce this movement with a vision, inspired by discoveries in biology in general and ethology in particular, aspiring to demonstrate the biological and philosophical relationship that exists between men and animals, downgrading or ignoring the singularity of culture and human spirituality. This double egalitarian perspective challenges all human-animal relationships as we still know them today both at the individual and the collective level.

It forms the philosophical foundation of two principles widely popularized in our society and just as widely cited by the so-called « antivivisectionists » : animal rights¹⁸ and animal welfare.

3.2.3) Opposing associations

Initially somewhat isolated and motivated by emotional, sometimes legitimate, judgment, the so-called « antivivisectionist » associations have been progressively included within the more general, « pro-animal » sphere as it is named by some. There they found rational arguments and action methods. Besides the natural compassion towards the animals concerned, and submerged in a society that partially doubts science and its progress, opponents to animal experimentation are convinced of the aggressive nature of all experimentations, of their uselessness as well as of the bad faith, the cruelty or the greed for profit of the experimenters or the institutions that employ them.

Their credo consists in the almost magical invocation of the so-called *in vitro* experimental methods as superior substitutes for animal use. Associations for animal protection mostly act with passion but most often within the legal framework, often with international cooperation. Beyond permanent protest against the methods of, and results from, animal experimentation, their current targets of action focus on the

¹⁸ MARGUENAUD Jean-Pierre. *Expérimentation animale entre droit et liberté*. Ed Quae, Versailles, 2011



cessation of laboratory animal transport by airlines (which intends to limit the use of dogs, primates and transgenic animals) and the development of a campaign to convince the public to refrain from donating to charitable associations which are supporting medical research¹⁹.

Some of the French associations developing within pro-animal activism not only respect legality but also show readiness for a certain dialogue with the researchers. They regularly take part in activities of think tanks concerned with animal experimentation, the 'Commission Nationale de l'Expérimentation Animale (CNEA)' (National Committee on Animal Experimentation) and the 'Comité National de Réflexion Éthique en Expérimentation Animale (CNREEA)' (National Committee for consideration of ethics in Animal Experimentation) (Chapter I §4.2.5).

3.2.4) Radical opposition

Unfortunately, it becomes apparent that within « pro-animal » activism a by-product of small radical minorities has emerged which are almost sectarian or even isolated individuals, closed to all dialogue and using violence trying to impose their point of view on all citizens. The gravity of their actions falls under the definition of terrorism. Acts of an illegal and violent nature are thus carried out in the name of an ideology : they mainly include criminal arson of institutions or companies, acts of violence against experimenter's property or threats addressed to their families. This disturbing violence which is difficult to understand and define, is troubling public authorities in Europe and the United States. In early summer 2011, it was the subject of an important work session of the European institutions that are in charge of citizen security : Europol and Eurojust²⁰.

3.2.5) Methodological opposition

Within the biomedical community in France and

abroad, a minority of personalities, researchers or doctors, or groups of personalities (Safer Medicine, Physicians Committee for Responsible Medicine, Pro-anima in France) condemn animal experimentation in the name of their clinical and scientific experience, despite its unquestionable record. They proclaim its inefficiency in certain areas such as cancer research, its ethical and financial costs and above all the risks that this approach to therapeutics and toxicology causes to the population (Chapter I § 5.3). In their opinion, the association of measurements and observations conducted on humans with the results of research conducted with the aid of *in vitro* and *in silico* techniques should contribute at low cost to unparalleled reliability of therapeutics, toxicology and drug safety²¹.

4) POSITION OF THE RESEARCHERS

4.1) EVOLUTION : DISCRETION IN COMMUNICATION

One could assume that patients, researchers, doctors or vets would have the highest legitimacy for being invited to the debate concerning animal experimentation. These four communities are indeed particularly concerned and awaiting decisive advances. They are however seldom heard. Historically, up to the 1980's, research teams, who were seldom criticized and who were reassured by the application of their own regulations, considered it unnecessary to respond to demonstrations whose importance and media impact were limited. This attitude of « vivons cachés » (let's not draw attention to ourselves) has prevailed during several decades, giving biomedical research an image of being averse to transparency.

The arrival of television, followed by the internet, the rejuvenation of the members of the so-called « antivivisectionists » associations, the action of media personalities and the onset of

¹⁹ ANIMAL AID. Victims of charity. A report on the cruel and scientifically invalid experiments funded by medical research charities. www.animalaid.org.uk

²⁰ www.europol.europa.eu/content/press 3 septembre 2011

²¹ The Lancet, volume 377, issue 9781, page 1915, June 4 2011



violent actions have motivated the biomedical community and those in charge of the large research institutions to create an organization in order to explain their point of view to the public. In 1991, the 'Groupe Interprofessionnel de Réflexion et de Communication sur la Recherche' (GIRCOR) (Interprofessional Group on Reflection and Communication on Research) was thus created. It presently unites the entire biomedical research community, both public and private. In addition to communications, specifically designed for large public institutions involved in research, this non-profit organization strives for the promotion of communication and the defense of researchers' viewpoints. While acknowledging the merits of animal experimentation, patient associations or professional medical associations seldom and reluctantly commit themselves on this issue.

4.2) CURRENT ORGANIZATION OF CONSIDERATIONS REGARDING ANIMAL EXPERIMENTATION

4.2.1) Among the research organizations

At the managerial level, all the large research institutions in France and abroad possess a structure charged with the responsibility of animal experimentation within the organization and which may present itself in different forms (specialized bureau, responsible nominee, committee).

4.2.2) The professional associations

Since the beginning of the 1960s, the quality of laboratory animals and that of their environment have proven to be essential factors towards the success of experimental procedures, in particular with regard to the reproducibility of their results. The breeding and care of these animals have therefore been professionalized. In search of technical information, researchers have formed associations which not only exist to promote good practices, they were also at the origin of the ethical reviews on this matter.

In France, such an association 'Association Française pour les Sciences et Techniques de l'Animal de Laboratoire' (French Association of Laboratory Animal Sciences and Techniques) was created in 1972. Associations of this type have regrouped on a European (Federation of Laboratory Animal Science Associations, FELASA, 1978) and world (International Council of Laboratory Animal Science, ICLAS, 1956, International Association of Colleges of Laboratory Animal Medicine, IACLAM) level. Their mission statements clearly demonstrate their concern for the ethical treatment of laboratory animals²².

4.2.3) Education : spontaneous initiatives, regulatory training

In our country, at the request of the biomedical community, Professor Michel BERTRAND created in 1967 the 'Centre d'Information sur les Animaux de Laboratoire' (Laboratory Animals Information center) based at the 'École Nationale Vétérinaire' (National Veterinary School) in Lyon. His education, composed for more than twenty years of 15-day training sessions, included both ethically-orientated deontology and technical aspects. In 1972 a multi-level training session was set up at Créteil University targeting technicians and researchers. Academic year 1973 – 1974 : first official academic training in France at the Vendôme 'Lycée Agricole' (Agricultural College) with a national certificate of the CAPA-type ('Certificat d'Aptitude Professionnel Agricole' (Certificate of Professional Agricultural Competence)) Laboratory animal caretaker option. This training, which was created at the request of the professionals, will further develop :
- 1977, addition of a National Certificate of the B.E.P.A.-type ('Brevet d'Enseignement Professionnel Agricole' (Certificate of Professional Agricultural studies)) Option : Animal care, specialty laboratory – 1989, B.T.A. type National Certificate ('Brevet de Technicien Agricole' (Agricultural Technician Certificate)) Laboratory

²² www.afstal.com/L-association-Representation



Animal Technician option – 2011 : National Certificate type 'Bac Professionnel : Technicien Expérimentation Animale (T.E.A)' (Professional Baccalaureate : Animal Research Technician) over 3 years²³.

The regulation enforced in 1987 made the completion of a certified training degree obligatory in order to be allowed to conduct experiments on animals. Consequently, general and specialized trainings, divided into three levels, have multiplied throughout the country and are under the control of the 'Commission Nationale de l'Expérimentation Animale (CNEA)' (National Commission on Animal Experimentation^o). More recently, a high-level training has been created targeting specialized vets within the framework of the « Collèges Vétérinaires Européens » (European Veterinarian Colleges).

4.2.4) Self-regulation : the ethics

The first deliberations generating tangible improvements to the conditions of laboratory animals emanate from British universities. To start with, in 1926, Charles HUME created the ULAWS (University of London Animal Welfare Society). In 1938 the association was renamed UFAW (Universities Federation for Animal Welfare) extending its influence to the entire academic world of the United Kingdom. This association, all the more credible because it translated scientists' opinions, was the first to contribute to improvements of all aspects regarding the housing and the use of laboratory animals.

In 1959, working within the framework of this association, William RUSSEL (1925-2006) and Rex BURCH (1926-1996) proposed the « 3 R » principle (Chapter 3 § 2.2.1) : the adoption of an « alternative » attitude striving to replace the animals (« Replacement »), reduce the number of animals used (« Reduction ») or to improve the experimental conditions (« Refinement »)²⁴. With

a similar concern to improve ethical conditions of experimental animals, Canadian researchers of the Canadian Association for Laboratory Animal Science in cooperation with the Canadian Council on Animal Care, proposed in 1969 the concept of the ethics committees for animal experimentation. Simultaneously, in August 1969, a group of European researchers, brought together for the centenary of the death of Claude BERNARD by the European Center of Tufts University and the Marcel MERIEUX foundation, adopted the « *Principles of ethics in animal experimentation* » also known as the Talloires Declaration.

European legislation waited until 1986 to approve an official directive on this matter (Chapter I, § 2.3). Researchers, conscious of the sentient nature of animal models, anticipated this move on the part of the legislators with all the more attentiveness because they observed on a daily basis the influence that well-treatment of the animals has on the quality of their results²⁵.

The application of « Good laboratory practice », voluntary national or international accreditation pursued by the pharmaceutical and toxicological laboratories, the generalization of ethics committees independent of all regulations or even the editorial policies of scientific journals who spontaneously agreed not to publish works unless they were submitted to ethical evaluation or were at least compliant with national legislation, all these initiatives contribute beyond legislation, to a use of laboratory animals which aspires to be respectful, reasoned and optimized.

4.2.5) Official organizations

In the context of successive regulations, two official institutions have been established:

- first, the 'Commission Nationale de l'Expérimentation Animale (CNEA)' (National Commission on Animal Experimentation) was

²³ www.legta41.educagri.fr/nos-enseignements-optionnels.html

²⁴ RUSSEL William , BURCH Rex. *The principles of humane experimental technique*. Springfield, Illinois Charles Thomas, 1959.

²⁵ MILHAUD Claude. *Vers le bien-être des animaux de laboratoire par la bientraitance*. Sci. Tech. Anim. Lab (2006),2,135-140



created at the occasion of the transposition of directive 86/609/EEC. It was primarily responsible for ensuring the application of articles R-214 to 216 of the 'Code Rural' (Rural Code) pertaining to animal experimentation and more precisely for promoting the replacement methods, good practices in breeding, care and handling of laboratory animals, as well as the accreditation of training courses in this field. This commission is composed of representatives of the different ministries concerned, of professional associations, researchers from the public and private sector as well as the animal protection associations²⁶.

- later, in 2005, in order to formalize the ethical initiatives in biomedical research, in particular the ethics committees, a 'Comité National de Réflexion Éthique en Expérimentation Animale (CNREEA)' (National Committee for consideration of ethics in Animal Experimentation) was created pursuant to articles R 214-122 to 129 of the 'Code Rural' (Rural Code). It was initially responsible for the development of an ethical charter : « National charter on the ethics of animal experimentation » adopted on June 22nd, 2009 jointly by the departments in charge of Agriculture and of Research (Chapter III § 2.2.2). The permanent mission of this committee is to make to the CNEA any recommendation with respect to the ethics of animal experimentation. Its composition is essentially identical to that of the CNEA, with personalities qualified in philosophy, sociology and judicial sciences.

5) THE CONTROVERSY

5.1) IS THERE A RATIONAL BASIS ON WHICH TO JUDGE ANIMAL EXPERIMENTATION?

It might be argued that one of the problems faced by contemporary culture is that of the

equivalence which tends to establish itself ever more between all forms of belief. These are not appraised on the basis of their content, on the reasoning and arguments in their favor nor on their chances of being true. Their criteria for admission are rather notions such as the sincerity and degree of conviction of their followers, the satisfaction and comfort offered to their members or even simply the number of their believers. The protest against animal experimentation per se, and therefore its opponents and their argumentation are to a large extent subject to this phenomenon. As a result, the question of a rationalization of the discussions on this issue arises.

5.2) THE ANSWER FROM J. HABERMAS

The core argument of Jürgen HABERMAS is that informed and rational discussion of a controversial issue results in a consensual, universally acceptable solution provided that the discussion is conducted without constraints between all interested parties and if all are committed to achieve a consensus. This author is an advocate of liberty and pluralistic tolerance, since he postulates that they lead to the rational unification of views²⁷.

However he observes that the pluralistic and multidisciplinary (think of euthanasia, the status of the embryo, cloning, etc.) debate on bioethics negates this argument and presents a philosophical diversity and unyielding morals²⁸.

5.3) REJECTION PARTIALLY EXPLAINED BY NON-DISCLOSED BIG CHALLENGES AND BY CERTAIN FAILURES

In the context thus established, characterized by a substantial escalation of global apprehension towards science, the arguments of the so-called « antivivisectionist » associations are all the more effective since the common methodology used in biomedical research, based on animal models, has experienced some regrettable failures and

²⁶ www.ethique.ipbs.fr/ Commission Nationale de l'Expérimentation animale.

²⁷ HABERMAS Jürgen. *L'avenir de la nature humaine. Vers un eugénisme libéral ?* Gallimard. Essais Paris. 2002.

²⁸ HOTTOIS Gilbert. *La philosophie à l'épreuve de la bioéthique* « Un monde meilleur pour tous » Colloque européen 2006, Collège de France, Odile Jacob, Paris, 2008.



sometimes appears to stagnate with regard to certain diseases, showing no apparent progress. Negative results however, although they are not published, are a step forward, even if they are only known by the team concerned.

Amongst the failures of the predictive quality of animal experimentation, it is often pointed out that, if the current control methods had been used, aspirin would probably never have been authorized and that, in contrast, thalidomide and diethylstilbestrol (Distilbene) never should have been allowed on the market with their initial indications.

More in relation to evolution within our society, three important diseases : cancer, Parkinson's disease and Alzheimer's disease are the most quoted by the so-called « antivivisectionist » associations as examples of failures of animal experimentation²⁹. As proof of the « western » nature of this impatience, one can observe that malaria, one of the major unresolved causes of world mortality, is never quoted by these associations. Yet, in 2010, this disease has affected 225 million people in 106 countries, causing 781,000 deaths³⁰.

In cancerology, researchers from the Mouse Model of Human Cancers Consortium (2010) and those of the National Cancer Breast Coalition (2008) claimed molecules successfully tested in mice carrying human cancer transplants proved to be clinically ineffective, thus pointing out the very low predictive quality of the mouse model in this area [18]. Similarly these researchers invoke the inefficiency of Parkinson's disease models which have been developed to-date, such as genetically modified rats or primates treated with neurotoxin regimens³¹.

5.4) SOCIETAL INCOHERENCE

The fraction of society that rejects recourse to animal experimentation based on a more or less confirmed philosophical background, reacts largely out of compassion for the animals and out of concern for the preservation of life and biodiversity. At its most extreme, this position presents, as already indicated (Chapter I § 3.1), in its opposition, a certain incoherence between the profound desire, shared by all, to enjoy the right to health, and the rejection of animal experimentation, to-date the principal source of progress in the biomedical disciplines.

Apart from animal experimentation, a new proof of societal incoherence towards the scientific approach can be found in the results of a recent inquiry made in France. If 75 % of the respondents are of the opinion that Science and Technology should solve the problems of our civilization, only 50% trust the information given by the researchers, particularly in the fields of nuclear energy and GMOs to which only 1/3 of the respondents lent some credence. For the public, the main reason for this defiance could be found in the insufficient independence of the scientists both employed in the public and private sectors³².

In parallel, this same population demands a rapid solution to newly emerging health problems, while insisting that the use of prophylactic or therapeutic methods that are proposed by research to solve them, do not carry any risks. Strong movements in public opinion based on emotion and not on knowledge and deliberation, are leading public authorities to decisions that lack rationality, especially when concerning vaccinations. Decree

²⁹ ANIMAL AID. *Victims of charity. A report on the cruel and scientifically invalid experiments funded by medical research charities*, www.animalaid.org.uk

³⁰ www.who.int/malaria/world_malaria_report_2010

³¹ www.safermedicines.org

³² LE HIR Pierre. *Les français se fient à la science pas aux chercheurs*. Le Monde, 06 Juin 2011



of November 4th, 2009 pertaining to the vaccination campaign against the influenza virus A (H1N1)³³.

5.5) ATTITUDE OF THE MEMBERS OF PARLIAMENT

Reflecting the whole of public opinion, national and European members of Parliament, true referees of controversy, have until now shown wisdom and moderation in their votes of approval of regulatory measures proposed by French and European public authorities.

A parliamentary deliberation report, entitled « *Sur l'expérimentation animale en Europe*.

Quelles alternatives ? Quelle éthique ? Quelle gouvernance ? » (Animal experimentation in Europe. What alternatives? What ethics? What governance?) by Michel LEJEUNE and Jean-Louis TOURAINE, shows the commitment of our elected officials to take into consideration and to further explore this issue³⁴.

Certain members of Parliament however, pressurized by the so called « antivivisectionist » associations or driven by electoral preoccupations, do not hesitate to exceptionally present legislative proposals that are devoid of the most elementary realism^{35 36}.

³³ www.academie-medecine.fr/mission_de_conseil_de_l_academie.cfm

³⁴ LEJEUNE Michel, TOURAINE Jean-Louis. Rapport « *Sur l'expérimentation animale en Europe*. » « *Quelles alternatives ? Quelle éthique ? Quelle gouvernance ?* » Office Parlementaire D'évaluation Des Choix Scientifiques Et Technologiques. Décembre 2009. n°2145 (Assemblée nationale) et 155 (Sénat)

³⁵ www.academie-veterinaire-defrance.org/avis-rapports.html

³⁶ FLORY Jean-Claude. Proposition de loi relative "Au recours à la vivisection et à l'utilisation des animaux domestiques en laboratoires" déposée le 15 février 2007 par M. le Député J-C. FLORY.





CHAPTER 2

ANIMAL MODELS AND SUBSTITUTIVE METHODS

1) ANIMAL MODELS

1.1) COMPLEXITY OF ORGANISMS

As we have already discussed in the previous chapter, the relative disequilibrium between the necessary progress in biomedical disciplines and the expectations of society concerning health control, is one of the causes fueling the controversy on animal experimentation. However, it is commonly known that progress in medicine is intimately linked to that of basic science and technology. The first keys to modern medicine were the principle of stability of the internal environment concept established by Claude BERNARD, the refutation of the theory of spontaneous generation by Louis PASTEUR (1822-1895), or again the development of the stress theory by Hans SELYE (1907-1982). Experimental physiology and microbiology have opened the doors to medical progress of the 20th century.

In the last twenty years, advances in molecular biology have been spectacular. Amongst those, knowledge of the genome and of a large number of mutations is largely contributing to the mechanistic study of diseases. The new disciplines in cell biochemistry and physiology, the « omics », reveal an organization with a high degree of complexity of which the total control of interrelations among molecules remains reserved for the future. Once the molecular components of Life have been dissected, the big question is raised of finding coherence

between these elements in order to understand the logic of all levels of life, from the molecule to the entire organism. Facing the many uncertainties, the study and simulation of the biological mechanisms necessitate the use of integration models such as *in vitro* cell cultures, isolated *ex vivo* organs, or the entire organism, the so-called *in vivo* experiments.

That is why, when trying to understand a physiological mechanism, for example the functioning of memory, this cannot be done on isolated cells, even though *in vitro* studies, in



combination with the *in vivo* studies may advance the progression of knowledge in this field. Superior neurological functions are preeminently *Terra Incognita*, and their discovery cannot be made without the object it seeks to understand.

Similarly, the infection of a mammalian organism by even a very simple infectious agent, for example influenza, triggers a cascade of reactions in the infected organism of which, at present, we only have the vaguest outline but we know it to be complex and impossible to reproduce *in vitro* on a mere cellular level.

Neither can genetic experiments involving the entire organism, or even entire populations, be conducted *in vitro* since it is impossible to simulate meiosis nor genetic recombination.

How can one attain knowledge using only *in vitro* experiments of, for instance, the etiology of autoimmune diseases, of diabetes or simply the more or less high sensitivity of animals (and humans) to infectious diseases that involve several genes acting simultaneously but at very different levels or understand the global nature of the mechanism of transplant rejection?

Another common problem for humans and higher animals is pain. Is it useless, in order to avoid studies involving laboratory animals, not to try and reveal its physiological mechanisms, the knowledge of which progresses painfully slowly despite progress in medical imaging systems?

Finally, the toxicological evaluation of chemical products, such as those outlined by the European REACH (Registration, Evaluation, Authorization and restriction of Chemical substances) program, cannot be fully accomplished at certain of its stages without also involving the totality of cells in an organism and their interactions. The results of one or more *in vitro* models only, cannot

guarantee the reaction of the entire organism, which obviously behaves differently from this type of model. Consequently, a basic precautionary approach justifies recourse to studies involving the entire organism (Chapter II, § 3.2, 3.6, 4).

1.2) ETHICAL AND SCIENTIFIC LIMITS TO THE USE OF HUMANS IN BIOLOGICAL AND MEDICAL EXPERIMENTS.

In the first place, the limits of experimentation on humans are based on commonly shared intuitive judgment. They are based on four moral principles accepted by bioethics : respect for autonomy, non-maleficence, beneficence and justice³⁷. The unknowns that underlie the search for basic knowledge or the pharmacology or drug safety trials involve drastic precautions as confirmed in the Declaration of Helsinki (2000) : « 11. *Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation* »³⁸.

These essential precautions, ratified by the hospital ethics committees, strictly control trials involving human subjects. They are based on the verification of the scientific and ethical relevance of each experimental protocol.

1.3) DUAL RELATIONSHIP WITH ANIMALS

Beyond the immediate evidence of the relationship linking humans and animals, both belonging to the same realm, the scientific foundations of this concept, which was purely intuitive until then, have been established during the 19th century. It concerns the common constitutive roots (of animals and humans) with the establishment of the principles of a common structure in all animals : the cellular

³⁷) BEAUCHAMP Tom L., HILDRESS James F. « *Les principes de l'éthique biomédicale* » Editions Les Belles Lettres, 2008

³⁸) www.Genethique.org/carrefour_infos/textes_officiels .



structure associated with a second relationship, the « tree of life model » established in the developments of Charles DARWIN's (1809-1882) Evolution theory. The zoological foundations of the filiation relationship have been reinforced for about 50 years by the spectacular progress in genetic knowledge. This dual relationship justifies, if necessary, the wordings of the Declaration of Helsinki. It establishes the principle of rational recourse to animal experimentation.

1.4) AWARENESS OF THE LIMITATIONS OF ANIMAL MODELS

Does this dual relationship guarantee the potential results of extrapolation to humans from observations performed on animals? The so-called « antivivisectionist » associations clearly respond to this question. They deny, in all its aspects, all validity of animal models. This objection, in reality a pretext, suggests that, should a reliable animal model of humans exist, animal experimentation would be acceptable for these associations. As declared by Claude BERNARD, the extrapolation to humans or the identification of a physiological mechanism may sometimes "result from the choice of the right model" but, in the majority of cases, the "right model" is not readily available to the researcher. In reality, the absence of this absolute model forms a major difficulty that can only be circumvented by approaches which will always include a degree of uncertainty (Chapter I § 2.1).

It should be remembered that a model's validity is based on the similarity in the model and in humans of the mechanisms involved in the phenomenon that is being studied, from the cause to the expression of its effects, whether the mechanisms are studied at cellular or molecular level, in *in vitro* models or at the level of the entire organism in animal models *in vivo*. The phylogenetic relatedness of the species used is also *a priori* a criterion of the

logical choice. If the role of primates sometimes proves to be irreplaceable (nervous system disorders, infectiology, immunology), certain genetic or physiological characteristics typical of one or other species, mean that an ideal model does not exist and that models as far removed from humans as the drosophila or the chicken embryo have nevertheless been at the basis of some of the most important discoveries (Chapter I § 2.1).

The selection of one or more species to be used as a model can only be made based on previous data and using a process of successive trials/errors. Researchers, aware of the limits of their models, therefore exercise extreme caution, especially because their choice is influenced by additional factors such as economic issues, concern for the preservation of biodiversity or simply practical restrictions (weight, size, availability...). For this reason, evaluation studies in the essential fields of toxicology and safety of health products, will involve several species. The use of three species, of which one « *other than rodents* » has thus been set in the regulations.

Genetic homogeneity, another criterion for the choice of a model, poses a permanent question for researchers. High genetic homogeneity ensures improved reproducibility of results. On the other hand, it can cause effects to be ignored that would only appear in a certain section of heterogeneous populations, as is the case with the human species, the final object of the study.

Other than the well-known effects on age and gender, several medicinal accidents can indeed be explained by the genetic variability of the human species, which led to the discipline that has been named « pharmacogenetics ». Key elements for the effectiveness of medicines, their targets, the transporters, the enzymes (prodrug activation or metabolic inactivation) can present a



variability that can produce many different effects³⁹. Even a human subject can therefore not be the perfect model for all other human beings.

If today it is somewhat admitted that few animal models can reliably reproduce human disease in all its aspects, it also has been well established that an animal model, even a not very adequate one, can nevertheless be of great importance if it is used correctly. The examples qualified to illustrate this declaration are numerous but we only have chosen one which is, in our opinion, adequate enough to be convincing : it is the modeling of the disease named Duchenne de Boulogne, a very severe muscular dystrophy that essentially affects young boys of approximately 2 years of age and leads to death, generally before the age of 20. Two animal models of this disease exist : the "Golden Retriever" breed dog (Chapter II § 2.2.1) and the *mdx* mutant mouse. The mouse is not clinically affected and lives a relatively normal life into old age. On the contrary, the dog presents a fairly congruous symptomatology to that of humans and this was sufficient for this species to be declared a "right model" and the mouse a "wrong model".

In fact, this conclusion is erroneous and dangerous⁴⁰. It should therefore be qualified. The first reason is the fact that the comparison human-dog-mouse, brought to its logical conclusion, will allow to discover one day why the symptomatology is so different for diseases that yet have the same genetic origin. Understanding this difference, which is of genetic origin itself, will uncover the pathogenesis of this human disease and will probably lead to new perspectives of the treatment. Another reason, equally important, is the fact that the mouse is the only species in which cellular transplantations can easily be performed without risk of rejection, to-date at

the forefront of therapeutic approaches. Finally, and as imperfect as the similarity of the model may be, the use of the mouse forms a parallel approach to the « Golden Retriever » model and is just as effective, more fundamental but less onerous and more ethical due to the absence of the induction of pathological signs in the mouse.

2) USE OF ANIMAL MODELS

2.1) ANIMAL MODELS IN BASIC RESEARCH

Already in 1628, William HARVEY (1578-1657), pioneer of the study of blood circulation, wrote : "*One should confirm what is true, set right what is false, look for the truth using anatomical dissections, many experiments and careful attentive observations*". Thus he established the principle of physiological experimentation, going beyond mere observation, which was often limited to fortuitous coincidence. This principle, introduced and remarkably illustrated by the physiologists François MAGENDIE, Claude BERNARD or Hans SELYE, was also accepted in all the basic disciplines including genetics, microbiology, immunology.

2.1.1) An example of experimental approach : the physiology of endocrine glands

Although to-date the relationship between membrane receptors and hormones and its medicinal control can be studied *in vitro*, the discovery of the different hormone systems was made using *in vivo* experimentation.

Clinical observations have led doctors to formulate hypotheses regarding the role of certain glands. In various animal models, their ablation, followed by the compensation of the effects of these ablations by transplants or by cross circulation with an undamaged animal, has revealed the physiological role of the endocrine glands. Later, the injection of glandular extracts, then of different identified

³⁹ BOUREL Michel et ARDAILLOU Raymond. *Pharmacogénétiq ue et Pharmacogénomique*. Rapport adopté par l'Académie Nationale de Médecine le 31 janvier 2006. Bul. Acad. Natle Méd. (2006) 190, n°1, 9-24.

⁴⁰ GUENET Jean-Louis. *Animal models of human genetic diseases: do they need to be faithful to be useful?* Mol. Genet. Genomics, (2011) 286:1-20.



and purified hormones, have allowed describing the hormonal systems in animals, confirming the doctors' hypotheses. These systems form the foundation of the therapeutics of hormonal disorders but also of certain hormone dependent cancers in humans and animals. Especially the dog and the pig have contributed to these efforts. One could describe in a similar way, the methodological approach aiming to unveil the functioning of all physiological systems : central and peripheral nervous, digestive, musculoskeletal, cardiovascular systems, describing the human characteristics of each system by associating the clinical observations with the non-invasive measuring methods that are currently used on animals (Chapter II § 2.3.1).

2.1.2) Statement of researchers

on the experimental approach

François JACOB, Professor at the 'Collège de France' (College of France) (chair of cellular genetics – 1964-1991) Nobel prize in physiology or medicine (1965) member of the 'Académie des Sciences' (Academy of Sciences) (1977) and the 'Académie Française' (French Academy) (1996) :

"To tackle an important problem, to have a reasonable chance of finding a solution to it, the biologist must use the suitable material. A material that enables to carry out certain types of experiments required for the proposed study. When Morgan wished to study heredity at the beginning of this century, he used the drosophila fly which allowed him to resolve questions about the transmission of characters. In the middle of the century, attention focused on the identification of the chemical nature of heredity, the analysis of the basic functions of the cell. For this purpose, molecular biologists had to resort to bacteria which are uniquely suited for such studies. Later, when genetic engineering gave access to genetic material of any arbitrary organism,

the drosophila came back into favor. For the first time it offered the possibility to study the genetic bases of embryonic development and the major functions of the organism. After this, the astonishing discovery of the persistence of the same regulatory structures over the whole range of evolution made it possible to study mammals, in this case, the mouse. [...] This small animal (the mouse) was appropriate for research on immunity but the immunologists used the rabbit. It could be infected with certain bacteria or pathogenic viruses but bacteriologists mostly studied guinea pigs. In the end, this was the animal that was best suited for research on certain cancers and on transplantations " 2000⁴¹.

Nicole LE DOUARIN, Professor at the 'Collège de France' (College of France) (1988-2000), Perpetual honorary secretary of the 'Académie des Sciences' (Academy of Sciences) (2001-2005) :

"Be as it may, from Aristotle to Malpighi or Gaspar Friedrich Wolf, we can observe that the chick embryo will not go out of fashion.[...] The adoption of the chick embryo as experimental material is based on several good reasons. First, it remains easily accessible during the entire period of its development (which is not the case for viviparous species). Next, like the mammals, birds are homoeothermic vertebrates: after all, the ultimate objective of biological research is to understand how the human being functions in order to better protect his health, his well-being and to increase his longevity. In addition, another point that birds have in common with mammals is that they are amniotic vertebrates : for their protection, their embryos are enclosed in a sac filled with liquid, the amnion.

In this modern age, the embryo of the bird has been at the source of several far-reaching discoveries. I will mention one which, in my

⁴¹) JACOB François. *La Souris, la Mouche et l'Homme*. Odile Jacob, Paris, 2000



opinion, is the obvious result of the advantages offered by this experimental model. It relates to immunology and, thanks to a strange anatomic peculiarity of birds, has allowed the discovery of the exact origin of two large groups of immune cells that ensure the integrity of the organism". It concerns the recognition of the division of lymphocytes into two distinct populations whose roles in the immune response are different. This stage is remarkable since it marks the beginning of the understanding of the cellular mechanisms underlying the immune response to infections. It has enabled the identification of the cellular interactions that control the production of antibodies and the response to viral infections. As a consequence, the delicate physiological problem of the existence of two distinct populations of lymphocytes which are distinct in separate cellular environments, has been solved, somewhat by chance but mainly due to the anatomic peculiarity of an experimental model » 2000⁴².

Michel JOUVET, neurobiologist, Emeritus professor at the Claude BERNARD University (Lyon), Member of the 'Académie des Sciences' (Academy of Sciences) (1977), Gold medal of the CNRS (1989) :

«But it is due to the cat that the dream made its appearance in neurophysiology. The polygraphic study of the sleep-wake cycle by chronically implanted electrodes in the principal cerebral structures, and the different muscular groups, indeed allowed the chance discovery of the categorization of sleep into two completely different stages : one, the slow wave sleep, which is associated with slow cortical large-amplitude waves and the conservation of the muscular tonus; the other, the deep sleep paradoxically characterized by electric cerebral activity similar to that during wakefulness by rapid ocular movements and by the total disappearance of the muscular tonus. These periods, which I named

"paradoxical sleep" in 1959, last approximately 6 minutes and occur every 25 minutes during sleep. (In humans, the periodicity of paradoxical sleep is 90 minutes).

Very soon, it was observed that the criterion of muscular atony also exists in the human subject and that the dream in man and the paradoxical sleep in the cat have the same neurobiological substrate (at least on a physiological level). The dream became the third state of the brain, as different from sleep as sleeping is from waking »1992⁴³.

2.2) ANIMAL MODELS IN APPLIED RESEARCH

2.2.1) Medecine

The key to understanding diseases and their future therapeutics, modeling their causes or their innermost mechanisms, involves experimentations that cannot possibly be conducted in human subjects. In the case of infectious diseases, Pasteur's approach using animal models still applies. In organic pathology, the classic method is to induce metabolic disorders with appropriate diets or by direct intervention on the organs, as is the case for cardiac disorders. To-date, as they are more productive and closer to clinical reality, there is a steady increase in the use of spontaneous pathological and transgenic models.

Meticulous observation of laboratory animals or the processing of veterinary data has led to the identification of spontaneous disorders in animals that are similar or even identical to those observed in humans. These are therefore the research models for the causes and possible treatments of these diseases. These models are helpful to comprehend the pathological mechanisms and to evaluate and propose therapeutics, all information that can later be used in human pathology. For example, within the dog breed of the « Golden

⁴² LE DOUARIN Nicole. *Des chimères, des clones, des gènes*. Odile Jacob, Paris, 2000

⁴³ JOUVET Michel. *Le sommeil et le rêve*. Odile Jacob Paris, 1992



Retriever », a certain number of subjects are affected with a type of myodystrophy presenting great similarities with the Duchenne myopathy (association of muscular, respiratory and cardiac disorders). The extensive study of this disease in the dog demonstrates that its origin is identical. It concerns a mutation, equivalent to that observed in humans and in mice (Chapter II § 1.4). By experimenting on dogs carrying the mutation, this identification has already contributed to significant progress, especially in the field of gene therapy and the use of stem cells. The same applies to certain types of Leber's congenital amaurosis, a disease that affects both children and dogs. Therapeutic research has enabled the development of a gene therapy, which was developed and validated on the dog and is now applied to children from birth, restoring their vision⁴⁴.

These two examples highlight the importance of the contribution of veterinary medicine and of clinical research in the animal. They illustrate that there is only one single medicine (« *one health, one medicine* »). In this light, the benefits of animal experimentation are shared on a daily basis between humans and the animals that surround them. Biology, the foundation of medicine, is obviously common to humans and animals when it concerns the great physiological principles. A happy illustration of this is the field of medically assisted procreation. Since the 1950's the techniques of artificial insemination, *in vitro* fertilization (Prof. C. Thibault, INRA) or embryo transfer have been progressively applied in the field of domestic animal breeding. This long experience of human intervention in the natural mechanisms of animal reproduction has notably contributed to the development of the basic techniques of medically assisted procreation which today makes the happiness

of thousands of couples all over the world. Thanks to the knowledge of the genome of different species and that of the precise determination of some human genetic diseases, and in line with the spontaneous pathological models, the transgenic models which are created by genetic engineering have the advantage of being able to reproduce these diseases in certain species of laboratory animals (the so-called *knock out* and *knock in* techniques) and to facilitate the analysis of the innermost, molecular, tissue and organic mechanisms. Although absolute similarity between the responses in transgenic animals and those of the human organism cannot be guaranteed, these approaches enable precise evaluation, with regards to genetic response, of the effects of aggressive or modulation factors. Once these innermost mechanisms are known, the development of gene or chemical therapeutics can be considered. Moreover, it was genetic engineering that triggered the « humanization » of mouse monoclonal antibodies which are used in the treatment of certain cancers.

The breeding of animals carrying hereditary lesions, whether spontaneous or induced by genetic engineering, poses an obvious ethical problem since it implies the perpetuation of strains of animals that are diseased. Its solution can not only be found in the systematic application of the 3 R's principle, but mainly in the ethics committee in charge of the evaluation, which, although subjective, should be as honest as possible, of the balance between the benefits for humans and the distress that would be imposed on the animals (Chapter III § 2.2).

2.2.2) Surgery

In this field, animal models are used in feasibility studies of new techniques (e.g. fetal surgery) but above all in the approach of

⁴⁴ JACOBSON S.G. et al. *Gene therapy for Leber congenital amaurosis caused by RPE65 mutations: safety & efficacy in 15 children & adults followed up to 3 years.* Arch. Ophthalmol. (2012) 130(1):9-24,



tolerance to restorative components introduced in the organism, from transplants of biological elements to prostheses made of biomaterials such as artificial hearts, ocular implants or hip prostheses.

2.2.3) Toxicology and safety of health products, pharmacology

In toxicology and safety of health products, in order to ensure the broadest detection range of potential risks, the models that are employed are perfectly healthy non-consanguineous animals. They are subjected to significant exposure to the activity of the molecules that are studied, in accordance with regulated protocols, which determine the species used and the methods and duration of administration. The intended pathological effects themselves are covered by regulatory provisions. These provisions are subject to constant revisions, the objective of which is to limit the use of animal models and eventually substitute them as much as possible with *in vitro* techniques. In parallel with toxicology, pharmacology mainly uses healthy animal models as substitutes for humans for the development of new molecular therapeutics.

Specialized models corresponding to precise pathological disorders and which are derived from healthy models, are artificially obtained by surgical or chemical intervention. This is the case with pigs carrying coronary artery ligations used as cardiac pathology models, rodents or primates of which certain nervous structures have been damaged by surgery or by chemical process in order to obtain models that are homologous with chronic diseases of the human central nervous system. As they are not very successful from the physiopathological point of view, these models are essentially used for the initial evaluation of therapeutic substances.

2.3) LIMITATIONS TO CONDITIONS OF USE

The ethical considerations already discussed (Chapter I § 2.3 and 2.5) and the concern for efficiency, have led researchers to spontaneously limit the number of animals used and the distress inflicted on them.

2.3.1) Limitations to the number of animals used

Methodological progress, a permanent concern for researchers, not only opens new perspectives for research but also enables a substantial reduction of the number of animals used.

In this way, the classical methods of histology and pathological anatomy which were applied for studying a phenomenon or the metabolism of a substance, formerly required euthanasia of several groups of representative animals, spread over successive periods in time all along the evolution of the phenomenon. Medical imagery has now been adapted to small animals and only requires the use of a single group of animals from the start of the experiment to the end. Moreover they only suffer a limited amount of distress. These non-invasive techniques are indeed applied under restraint or under sedation. Adaptive imagery includes the so-called micro-PET (Positron Emission Tomography) techniques, the « micro computed tomography » (scanner), and also the use of bioluminescence (optical coherence tomography) and MRI (Magnetic Resonance Imaging) and fMRI (functional magnetic resonance imagery), all adapted to be compatible with the dimensions of small animals. The development of these techniques encourages the convergence of the animals' interests with that of the researchers (achieving time-saving, benefits and reliable results). More reliable and compelling statistical results can be achieved due to the ability to follow the evolution of a phenomenon in one single subject and therefore maintaining the same group of subjects all along this evolution.



From another earlier angle, a selective approach of the orientation of toxicological studies, like the one proposed by EFSA (European Food Safety Authority), the approach named *Threshold of Toxicological Concern* (TTC), responds at the same time to a necessity and desire to economize not only on financial means and human capacity but also on animal use⁴⁵.

2.3.2) Limitations to the distress imposed to the animals

Under *Refinement*, the third R of the Russel and Burch principles defining the limitation of the distress inflicted on the animals, the animals' welfare is a permanent, both ethical and practical, preoccupation. It concerns the pursuit of the quality of the results, their reliability and consequently the reduction of distress and the number of animals used.

The fundamental constant improvement of the animals' environmental quality which is the key to their health and homogeneity, was initiated in North America at the end of the 1950's and in Europe at the end of the 1960s with the creation of specialized professional associations and the publication of practical guidelines such as the « Guide for the care and use of laboratory animals » of the Institute of Animal Resources and the « UFAW handbook on the care and management of laboratory animals » which are regularly re-edited, the first one since 1947. These concerns have been incorporated in the regulations, in particular, in the annex of the European directive 86/609 which was revised from 1996 to 2006. Beyond the welfare regulations, the entire community has made special efforts to ensure environmental enrichment for the animals in order to optimize the expression of their specific behaviors⁴⁶.

In parallel, short of their replacement, stress and distress imposed on the animals have been reduced by the constant improvement of experimental techniques : progressively more

sensitive biomarkers, painless external investigation techniques such as telemetry and increasingly efficient local and general anesthetics. At the same time, these techniques contribute to improving the quality of experimental results.

2.4) ECONOMIC AND PRACTICAL ASPECTS

One of the objections against animal experimentation that is frequently raised by certain animal protection associations is that, from a technical point of view, this practice is outdated and that it is intended to ensure considerable financial revenues for the laboratories concerned.

This criticism combines an accumulation of a number of misunderstandings and errors, and it only could possibly be used against the pharmaceutical industry whereas animal experimentation concerns all fields of biomedical and biological research. The most important evaluation error is, of course, the notion that animal experimentation is a low-cost activity generating financial benefits. In reality, the purchase of laboratory animals requires a considerable investment because their selection and breeding required high-level intellectual and material means and the quality of the maintenance of their housing conditions of their food and care must meet a dual objective: the compliance with regulatory requirements and the prevention of any incident during the experiment. This investment cannot possibly be compared with the installation of a few rooms dedicated to cell cultures nor to the fitting of the computer equipment required for *in silico* methods. Moreover, for certain toxicity studies (generally imposed by regulation) very large batches of animals are required and the length of study can be spread over several years.

On top of these financial costs, all kind of difficulties must be considered, including the moral reservations the researchers are

⁴⁵ www.efsa.europa.eu/fr/calls-htm

⁴⁶ BAUMANS V. *Science based assessment of animal welfare: laboratory animal*. Rev. Sc. Tech. Off. Int. Epiz. (2005) 24(2), 503-514



confronted with and the physical risks (injuries, possible contaminations) they are taking while handling the animals. One can assume that if laboratories, whatever their objectives, nevertheless resort to animal experimentation, it is because, despite all these inconveniences, this is the only available approach to-date to scientifically answer most of the many questions they are asked or are asking themselves.

3) REPLACEMENT METHODS

3.1) INTRODUCTION : REPLACEMENT METHODS AND ALTERNATIVE METHODS

The two terms assigned to different methods : alternative or replacement are often associated and generally confused by non-specialists and by the public at large. The alternative approach is a direct result of the 3 R's rule of W. RUSSEL and R. BURCH (1959), and endeavors to globally improve the conditions of laboratory animals. The three principles proposed by these authors are alternative principles, challenging former practices. They are the reduction of the number of animals used (*Reduction*), of their substitution (*Replacement*) and the application of techniques which are as noninvasive as possible for the animal (*Refinement*). The term replacement is therefore limited to the methods of replacement whereas the term alternative refers to the three principles combined^{47 48}.

The confusion between alternative and replacement methods often creates a dialectical bias by confusing, or pretending to confuse, the significant results obtained in the improvement of the conditions of laboratory animals using alternative approaches and the perspectives offered by the limited number of methods that have been developed in the field of substitution.

On this matter, it should be remembered that the PubMed database registered a spectacular increase of publications on biomedical research (10,267 references in 2002, 22,343 in 2004 and 43,770 in 2006) whereas the number of animals used remained relatively stable (11.6 million in 1996 for 15 European member states, 12.1 million in 2005 for 25 European members, 12 million in 2010 for 27 European members). This observation is the direct result of the improvement of experimental protocols and of a better use of models, but only to some extent⁴⁹.

The relative decrease in the use of laboratory animals (ratio number of animals versus number of publications) can essentially be attributed to the development of molecular biology and to the tendency of research to be directed towards physiology and cellular pathology, disciplines based on *in vitro* techniques.

However, it should be remembered that, except for cell lines (immortal because of their origin or immortalized), these methods imply that most of the cells (with the exception of human cell cultures) and organs used are removed from an animal that has undergone biopsy or has been euthanized for the organ removal (primary explants).

3.2) EUROPEAN REGULATIONS : ECVAM «EUROPEAN CENTRE FOR VALIDATION OF ALTERNATIVE METHODS»

Whether the animal models are *in vitro* (cell or tissue cultures) or *ex vivo* (after organ removal from an animal) or even *in silico* (computer simulations), the reliability of replacement methods intended to replace them is crucial for disciplines whose results fall under the immediate moral and legal responsibility both of the experimenters and the legal authorities. On top of this dual one, the responsibility of

⁴⁷⁾ www.frame.org.uk/alternat.htm

⁴⁸⁾ Smyth D. *Alternatives to Animal Experiments*. Scholar Press London 1978

⁴⁹⁾ www.ncbi.nlm.nih.gov/pubmed/etec.europa.eu/chemicals/labanimals



the institutions in charge of the validation of replacement methods (ECVAM for Europe) and its committees of experts who have direct influence on the legislator, can also be put into question. In fundamental disciplines the modeling of substitutions is of considerable theoretical and practical importance but its failures do not make the experimenters or the legislator liable. The researchers risk no more than the rejection by their peers and, exceptionally, the judgment by their discipline's history.

It is therefore the pharmacology, toxicology and the safety of health products that are essentially concerned with the guarantees of reliability of the replacement methods and who are applying verification tests, most of them regulated. These tests use large quantities of animals, often under relatively severe distress conditions.

The replacement of this type of tests is the subject of an official research and validation process at a European level. Pursuant to articles 7 and 23 of the European directive 86/603 regarding the protection of live animals, a dedicated organization was created in 1991, ECVAM. Its central research unit, ESAC (ECVAM Scientific Advisory Committee), focuses on the scientific and technical evaluation of replacement methods and their formalization⁵⁰. At a global level, these methods are also recorded in the list of guidelines of the OECD (Organization for Economic Co-operation and Development). The ECVAM activities are not limited to the research for new methods to replace the use of animals, the organization also validates the *in vivo* methods that help in reducing the numbers involved, in particular through the use of appropriate statistical methods.

3.3) TOXICOLOGY AND SAFETY OF HEALTH PRODUCTS

Amongst biomedical disciplines, toxicology proves to be more advanced in the application of alternative methods and especially replacement methods.

Originally, regulatory methods for drug health and safety essentially guaranteed the examination of the safety of medicines and more generally of health products. However, the use in most industrial sectors of a continuously increasing number of molecules compels legislation to extend toxicological monitoring to all synthetic molecules, regardless of their particular field of application: household goods, hygiene, health, industry or phytosanitary.

In order to respond to the demands of society, this new regulatory development should go hand-in-hand with the promotion of methods which don't or hardly make use of animal models as is the case in toxicology where to-date, the most noticeable advances in the substitution of animal models have been achieved. This progress can not only be explained by the considerations of researchers and public authorities with respect to the ethical issues but also by the nature of the toxic phenomenon in itself. It is indeed easier to model the deregulation of a complex organism such as that of humans with a simple biological or artificial system than to simulate its functioning in detail by taking into account the entire structure of interactions. This statement is illustrated by the *in vitro* test which is presently being validated, called the EvaTOX test, which is the purpose of the Vitaltox program⁵¹.

Finally, the growing concern for individual or environmental toxicological risk management (ecotoxicology) has compelled Western countries to consider without delay, almost in emergency conditions, the regulatory examination of thousands of old and new

⁵⁰ www.ivtip.org/publications/validate.html

⁵¹ www.noveleads.com/index.php?page=dap&lang=



molecules. In the European Union the implementation of the REACH regulation⁵² with conventional toxicological methods would involve the use of millions of animals, which is ethically not acceptable and at the same time would be very costly and cause considerable delays. It is up to ECVAM in Europe, and to the OECD on an international level, to identify, validate, regulate and introduce the methods that are likely to replace or, failing that, reduce the number of animals used.

Since 1991, date of its creation, ECVAM has validated and introduced into the European regulations 14 tests including :

- seven in cutaneous toxicity
- two in ocular toxicity and acute systemic toxicology
- one in cutaneous sensitivity
- one in phototoxicity
- one in cutaneous absorption

The tests that currently have been validated include eight *in vitro* replacement tests and five alternative tests, two *ex vivo* and three *in vivo* (two in systemic toxicology and one in cutaneous sensitivity⁵³).

In the short to medium term, taking into account the tests that are in the process of being scientifically or administratively ratified, the following tests can be expected :

- in cutaneous toxicity, six ratified replacement tests and one replacement test still being assessed;
- in ocular toxicity, two ratified alternative tests and four alternative tests still being assessed (five *ex vivo* and one *in vivo*);
- in cutaneous sensitivity, one ratified replacement test and two alternative (*in vivo*) tests still being assessed;

- in mutagenicity, absence of ratified tests and one replacement test still being assessed;
- in acute systemic toxicology, two ratified alternative (*in vivo*) tests, five alternative (*in vivo*) tests and one replacement (*in vitro*) test still being assessed;
- in chronic toxicology, no ratified test, no test being assessed;
- in reproduction, absence of ratified tests, three replacement tests still being assessed (parents are sacrificed in the process);
- amongst the miscellaneous, two ratified replacement tests (phototoxicity and cutaneous absorption), one replacement test being assessed (estrogen toxicity)⁵⁴.

In 2011, in a short to medium term perspective and just as it has been doing since 1990 (Bridge project), the European Union supports 28 design and development projects of tests intended as replacement or at least alternative tests, with a budget of 50 million euros. These projects can be categorized under the following disciplines: toxicology (17), pharmacology (8), common technology (tissue culture, bioinformatics) (3). Twenty of the tests proposed in these projects are based on *in vitro* techniques, one on an *in vivo* technique and seven may use results obtained *in vivo*. It should be noted that 6 projects involve combinatorial approaches (« *computational toxicology* »).

At present no test relating to the major fields of toxicology which are chronic toxicology, reproduction toxicology or carcinogenesis, has been validated. Furthermore, those relating to systemic toxicology are merely alternative improvements of *in vivo* trials, with the exception of the EvaTOX test which is in the process of being assessed and validated by ECVAM⁵⁵.

⁵² LEJEUNE Michel, TOURAINE Jean-Louis. Rapport « Sur l'expérimentation animale en Europe. » « Quelles alternatives ? Quelle éthique ? Quelle gouvernance ? » Office Parlementaire D'évaluation Des Choix Scientifiques Et Technologiques. Décembre 2009. n°2145 (Assemblée nationale) et 155 (Sénat) pages 24 et 25.

⁵³ www.tsar.jrc.europa.eu/index.php?endpoint=2&method=1

⁵⁴ www.tsar.jrc.europa.eu/validation

⁵⁵ www.noveleads.com/index.ph?page=dap&lang=



In the present situation and based only on the tests validated by ECVAM, these very limited results don't allow us to anticipate important savings in animals and in time within the framework of the REACH program nor that of general toxicology. This deficit can partly be contained by the possibility to resort to a certain number of *in vitro* tests which have not been officially validated but are merely recommended by the OECD^{56 57}.

3.4) PHARMACOLOGY

Despite the difficulties that have to be overcome in order to reveal the pharmacological effects on simple systems, outside the organism and following the example of the physiologists, pharmacologists have been prompted to develop for their own use, more or less complex techniques of isolated organs that are kept alive artificially, the *ex vivo* models. Then, to make a more in-depth study of the effects of molecules at a cellular level, they resorted to *in vitro* models, consisting of reactive tissues produced from stem cells.

Experimental evaluation of pharmacological effects only starts after an initial stage of screening the molecules that are most promising with regards to efficiency and safety, the selection being conducted electronically, or *in silico*, using large databases on the relationship structure-activity.

It is obvious that when establishing the activity of a molecule, even when proven in *in vitro* trials, its potential for the organism should also be considered using *in vivo* pharmacokinetic trials, first in animal models, afterwards in humans. The simulation of the potential of a molecule for the human organism using elementary data obtained *in vitro* and bypassing *in vivo* models is one of the challenges that bioinformatics are trying to discover. Anxious to modernize the European

Pharmacopoeia by introducing ratified *in vitro* or *in silico* methods, the EDQM (European Directorate for the Quality of Medicines and Health Care), has introduced a biological standardization program encouraging the development and organizing the ratification of these methods in pharmacology and pharmacokinetics⁵⁸.

3.5) MONITORING EFFICACY AND SAFETY OF IMMUNOLOGICAL PRODUCTS

The monitoring of the manufacturing of biological products has been the target of important efforts from ECVAM and EDQM because these controls are consumers of large quantities of laboratory animals, especially due to the double controls (by the industry and by the administration). The procedures relating to general toxicology (human vaccines) and safety tests (veterinary vaccines) have been considerably relieved by the implementation of quality assurance procedures during manufacturing. In addition, three replacement tests have been ratified and incorporated in the European Pharmacopoeia : the bacterial endotoxin test in replacement of the apyrogenicity test conducted in the rabbit; dosage by HPLC of hormones to replace the *in vivo* tests performed in the mouse; lastly, the dosage of antigen with the ELISA test replacing the immunological tests which, until then, were performed on the mouse⁵⁹.

3.6) LIMITATIONS OF THE IN VITRO METHODS

3.6.1) Reminders

The *in vitro* methods which don't exclusively use human cells and tissues, as well as the *ex vivo* methods such as isolated organs, involve the euthanasia of a number of animals that can't be ignored.

In addition, it may not be forgotten that the development of *in vitro* techniques largely

⁵⁶ www.oecd.library.org

⁵⁷ FABRE Isabelle . *Méthodes substitutives à l'expérimentation animale: aspects réglementaires , état de l'art et perspectives*. Bull.Acad.Vet.France (2008) 161, (5),403-407

⁵⁸ FABRE Isabelle . *Méthodes substitutives à l'expérimentation animale: aspects réglementaires , état de l'art et perspectives*. Bull.Acad.Vet.France (2008) 161, (5),403-407

⁵⁹ FABRE Isabelle . *Méthodes substitutives à l'expérimentation animale: aspects réglementaires , état de l'art et perspectives*. Bull.Acad.Vet.France (2008) 161, (5),403-407



depends on advances in cellular and molecular biology.

3.6.2) Reproducibility

Although the « *Good Cell Culture Practices* » are largely followed, the standardization of strains and culture techniques, greatly facilitated by the cell-line banks, produces a general problem for the reproducibility of a certain number of *in vitro* techniques⁶⁰.

It should be remembered that cultures use modified cell lines, which implies that the cells have the characteristics of the stem cells or cancer cells. Not only are there limitations imposed on their use because of the nature of the cells itself, there is also the fact that, in most cases, keeping them alive necessitates either artificial (addition of various synthesis factors or products from genetically modified bacteria) or natural (fetal animal serum) intervention which is not devoid of health risks. The combination of these factors necessary for cell culture undermines the principle of their reproducibility and therefore the reliability of the proposed methods.

3.6.3) Duration of the validation process

The time needed to ratify *in vitro* methods is another limitation to their implementation. In the case of animal experimentation this approach is designed to demonstrate to the scientific community, the industrialists as well as the legislator, the aptitude of an *in vitro* method to replace, for the same objective of safety and effectiveness, a test conducted on animals which is generally being used or is regulated. It is important that the validation process of replacement methods is carried out by an independent institution, which is ECVAM in Europe, and that it should be internationally recognized by the OECD, if only out of respect for the international competition rules.

The validation process however takes a long time (nearly 20 years for the apyrogenicity

tests). Scientifically, it should not only prove its reproducibility but also its efficiency in detecting the toxic properties of as many molecular families as possible, which, if earlier data are insufficient or unavailable, could require long, costly and animal consuming studies. One should not forget the important work carried out by the successive committees of experts that was necessary to come to a consensual and reliable opinion.

In all cases, experience shows that, in the current scientific situation and technical administrative organization, at least 10 years are required for the validation of *in vitro* tests.

The key to the acceleration of the validation of replacement methods can be found in the existence of significant financial support for the different institutions concerned, but the crucial factor remains the pooling of data. An international cooperation mechanism is emerging, the International Cooperation on Alternative Test Methods (ICATM). It brings together the Interagency Coordination Committee on Validation of Alternative Methods (the American ICCVAM), ECVAM and their Canadian and Japanese equivalents.

Particularly everyone (industrialists and governments) responsible for providing the public with synthetic molecules is awaiting the results of these cooperation efforts, needing to be assured of the validity of the control methods without prejudice to their *in vivo* or *in vitro* nature.

3.7) LIMITATIONS OF IN SILICO METHODS

Based on the interpretation of large data bases using IT (Information Technology) strategies, the methods named *in silico* by obvious analogy with *in vivo*, are largely employed during screening operations of molecules for therapeutic purposes. The analysis strategies take into account the known relationships between molecular structures

⁶⁰ *Alternatives to animal experimentation in basic research*, ALTEX (2004) 21, sup 1:3-31



and their pharmacological properties. They allow considerable savings of time and finances compared to the classical screening operations conducted on laboratory animals. Independent of the ethics concerning the protection of laboratory animals, these two arguments have rapidly convinced the pharmaceutical industry. The screening process for therapeutic molecules is made easier by the fact that the synthesis proposals presented to the chemists are based on anterior knowledge of properties observed in natural molecular systems or in artificial molecular lines that will serve as reference for the screening of new molecules.

In the field of toxicology, the level of uncertainty is higher. Earlier data is lacking especially for the synthesis of molecules based only on physicochemical data. In this context the toxicological evaluation of molecules produced by nanotechnology could possibly be questioned. Briefly, the strength of the *in silico* methods is interconnected with that of their databases. It could be jeopardized in the absence of reliable references which is not crucial in pharmacology but is likely to be in toxicology, particularly in industrial toxicology or even ecotoxicology.

In addition, there is an intrinsic limitation to the prospects of developing *in silico* methods :
"The computation of the number of possible conformations and interactions of a simple three-dimensional protein exceeds the capacity of the most powerful computers; as a matter of fact, it is one of the most complex questions in contemporary biology. This complexity, based on the enormous amount of possible interactions of simple elements, is even increased by the appearance of emerging properties resulting from the combination on a grand scale of elementary functions. For the moment it is difficult to understand the nature of these numerous

interactions, essential for health or disease, without a more advanced biophysical understanding of the rules of self-assembly of organic molecules, of their quantitative interactions and of their control mechanisms based on the laws of molecular recognition which are not yet completely understood". Elias ZERHOUNI, professor at the Johns Hopkins university, director of the National Institute of Health (2002-2008), associate professor at the 'Collège de France' (College of France), chair Innovation Technology, inaugural lecture, January 21st 2011.

4) SYNTHETIC OR COMBINATORIAL APPROACHES

Observing the difficulties encountered and the delay in the development and validation of methods capable of replacing animal models, recommendations were made for the creation of structures in order to encourage and organize multidisciplinary cooperation projects. In Europe, at least three independent institutions are thus bringing together researchers from universities and from several industrial sectors : AXLR 8 (for 'Accelerating the transition to a toxicity pathway-based paradigm for chemical safety assessment through internationally coordinated research and technology development'), ECOPA (European Consensus-Platform for Alternatives) and IVTIP (In Vitro Testing Industrial Platform, created and supported by the services of the European Community). Their objective is to replace or at least reduce the number of animals used in toxicology through coordination of research and the dissemination of future methods. Based on disciplines such as bioinformatics or genomics, the latter are to be used within the framework of integrated systems using data obtained *in vivo*, *in vitro* and *in silico*, from invertebrates or from vertebrates including mammals and humans⁶¹.

⁶¹) www.axlr8.eu/eu-funded-3rs-research



In the United States, the EPA (Environmental Protection Agency) and the NCCT (National Center for Computational Toxicology), member of NIEHS (National Institute of Environmental Health Sciences), in collaboration with the USEPA (US Environment Protection Agency), the NIH (National Institute of Health) and the FDA (Food and Drug Administration) developed an equivalent program since 2009 : the Comp Tox (for Computational Toxicology Research Program)⁶².

In 2009, with a slightly broader perspective, the 'Agence Française de Sécurité des Produits de Santé' (AFSSAPS) (French Agency for the Safety of Health Products) created the 'Groupement d'Intérêt Scientifique' (GIS) (Scientific Interest Group), FRANCOPA whose objective is to encourage the development of alternative methods allowing the reduction or elimination of recourse to laboratory animals especially in the development, evaluation and monitoring of health products and chemical substances. FRANCOPA brings together the ministerial institutions : the Ministry of Research, AFSSAPS, INERIS ('Institut National de l'Environnement et des RISques' (National Institute for Environmental Protection and Industrial Risks)), ANSES ('Agence Nationale de Sécurité Environnementale et Sanitaire', ex-ANSSET (National Agency for Environmental and Health Safety); research institutions : INSERM, CNRS, representatives of the industrial sectors concerned : UIC ('Union des Industries Chimiques' (Chemical Industry Association)), FEBEA ('Fédération des entreprises de la beauté' (Federation of Beauty Companies)), LEEM ('les Entreprises du Médicament' (Pharmaceutical Companies)), the SPTC ('Société de Pharmaco-Toxicologie Cellulaire' (Society of Cellular Pharmaco-Toxicology)) and two animal protection associations : OPAL ('Recherche Expérimentale et Protection de l'Animal de Laboratoire'

(Experimental Research and Protection of Laboratory Animals)) and the 'Fondation Française des Droits de l'Animal, Éthique et Science' (LFDA) (French League for Animal Rights, Ethics and Science) [35]. In this way, our country joins the other European countries with national platforms who meet in the European ECOPA platform (European Consensus Platform on 3 R Alternatives to Animal Experimentation)⁶³.

It is obvious that the resources committed today in the development in toxicology of methods of the combinatorial type, should in the future result in a certain number of tests that could significantly reduce the use of laboratory animals in pharmacology. A first stage could involve studies of the metabolism whose principles should easily allow electronic simulations.

5) CONCLUSIONS

The complexity of organisms cannot be modeled by the simple addition of basic biological systems. The highly integrative nature of life has compelled the disciplines of general biology and the biomedical disciplines in particular, to use, in a reasonable and limited way, when necessary, models of a complexity level similar to that of humans : the laboratory animal.

Today, fundamental research, whether physiological, immunological or genetical is more focused on the cellular and molecular approaches. Nevertheless, they cannot but resort to laboratory animals when they wish to integrate the results obtained *in vitro* at the level of the complete organism. The same applies to research on the knowledge of physiopathological mechanisms, the foundation of medical and surgical therapeutics.

In toxicology and safety of health products or in pharmacology, the *in vitro* or *in silico* approaches help to achieve - besides the

⁶² www.oecd.library.org

⁶³ www.ecopa.eu



gratification of showing greater respect for the life and well-being of animals - important savings in time and costs. The spontaneous development and the regulatory introduction of the use of these methods are currently challenged by the shortcomings of the proposals stemming from their research and by the cumbersome nature of their validation procedures.

The very limited scope of *in vitro* and *in silico* methods and economic as well as ethical reasons have compelled the international scientific community and public authorities to

make important human and financial efforts in order to develop, as a result of progress in bioinformatics, the so-called combinatorial methods. The objectives of these methods are to analyze and synthesize earlier data bases in relation with more recent results acquired by the entire range of *in vitro*, *in vivo* and *in silico* experimental methods. Each of these approaches remains essential because each of them contributes, from its specific perspective, to the synthetic knowledge of the phenomena of life at the level of the whole organism, whether human or animal.



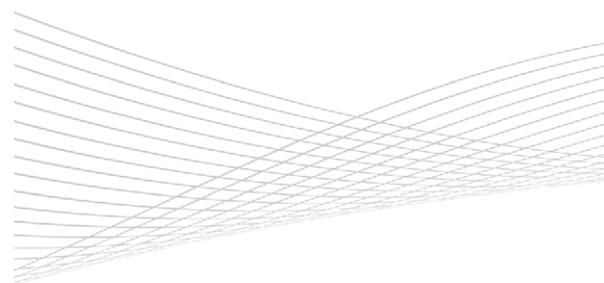


CHAPTER 3

PRACTICE OF ANIMAL EXPERIMENTATION. BASES FOR AN ACADEMIC APPROACH

From chapters I and II, four general principles emerge which could constitute the basis for the approach adopted by our academy. They are :

- to reaffirm a vital prerequisite : recourse to animal experimentation is essential to the progress of knowledge and of medicine in the current scientific situation;
- to regard laboratory animals with respect due to their sentient nature and the phylogenetic origin they have in common with human beings;
- to acknowledge that in biology in general and in biomedicine in particular, the experimental approach should use the whole range of methodological possibilities it has created without prejudice in an objective manner;
- to establish the conditions for a social dialogue based on knowledge and mutual respect.



1) FIRST BASIS : RECOURSE TO ANIMAL EXPERIMENTATION IS INDISPENSABLE

The arguments and conclusions of the second chapter establish the inevitable nature of the necessity to resort to animal models in biomedical disciplines at the present day and probably for a long time to come.

At present, the in vitro and in silico methods are restricted to fundamental approaches, of a molecular or cellular nature, to certain aspects of toxicology and to the initial selection of molecules in pharmacology. They can only partly replace the animal models (chapter II § 3). Moreover, when applied, the in vitro methods do not prevent the euthanasia of a certain number of animals. They respect, sometimes with difficulty, the scientific criterion of the



reproducibility of results and remain handicapped by considerable delays in their regulatory ratification (Chapter II § 3. 6). The practical applications of the in silico methods on the other hand, are currently restricted to the pharmacological and toxicological selection of molecules and in the future to the important yet partial involvement in the combinatorial approaches (Chapter II, § 4).

For lack of experimenting on humans, the use of animal models today is the only method able to reflect in a synthetic manner, the complexity of an organism's reactions. For this reason, for more than a century, in vivo methods are being successfully employed in the entire range of biomedical disciplines, either preceding or succeeding in vitro methods (Chapter I § 2.2).

Of course, the condition is that each model is used rationally, with full awareness of its limitations and within a well-defined regulatory and ethical framework (Chapter II § 1 and § 2).

2) SECOND BASIS : SENTIENCE AND THEIR BIOLOGICAL PROXIMITY TO HUMANS IMPLY THAT ANIMALS SHOULD BE RESPECTED

In the field of animal experimentation, the respect for the sentient nature and the phylogenetic proximity of animals can be approached on two basic levels. As a priority, the objective is to eliminate pain, the extreme manifestation of sentience, from the experimental protocols. Then, next to pain, the rational use of animals and their well-treatment should aspire to restrict their use and to ensure a physical and mental state that can be considered a state of well-being during their entire lifespan as a model. These approaches have been proposed since 1985 by Michael A.FOX in his book « The care for animal experimentation. An evolutionary and ethical perspective »⁶⁴. They influence to a large

extent the legislation and ethical approach of the scientific community towards animals.

2.1) PAIN CONTROL

The fact that the animal is recognized as a sentient being has generally been integrated into the French law on the protection of nature in 1976, since this was the first time this notion was introduced in a text of our legislative system. It would obviously be a big mistake to assume that researchers needed the enactment of this law to adopt this notion. At the beginning of the 19th century, physiologists certainly carried out experiments in a situation where truly effective anesthetic methods were non-existent neither in human nor in veterinary medicine. This is probably the reason why one of their first areas of interest was sentience and the role of the sensitive nervous system. The fact that the animal is a sentient being did not escape Charles BELL (1774-1842) and François MAGENDIE. Their names also remain attached to the role of peripheral sensitive and motor nerve roots, the first established knowledge in physiology of the nervous system.

As soon as they became available, anesthetics were also used in experimentation, except for those few fields where they could interfere with the outcome of the experiment by rendering useless the studied responses, when these are modified or abolished by the anesthetic. In those situations, experimenters have researched and adopted palliative solutions of which probably the best example can be found in the fields of neurophysiology of pain and pharmacology of antalgics which both require the provocation of controlled pain in the laboratory animal, most often limited to its perception threshold. For the ethics committees, pain risk assessment during the presentation of the experimental project remains one of their major activities together with the recommendations and surveillance of the application of analgesic procedures⁶⁵.

⁶⁴ FOX Michael « The care for animal experimentation. An evolutionary and ethical perspective » University of California Press. Los Angeles. 1985

⁶⁵ http://www.aclam.org/Content/files/files/Public/Active/position_pain-rodent-rabbit.pdf



2.2) NEXT TO SUPPRESSION OF PAIN, LIMITING THE RECOURSE TO LIVE ANIMALS AND ENSURING THEIR WELL-TREATMENT FORM THE BASES OF AN ETHICAL APPROACH

As already reported (chapter I §2.2.3) two initiatives from the research community form the current basis of the ethical approaches - well beyond the simple prevention of pain - towards laboratory animals: the "3R" rules and the concept of ethics committees. This ethical approach of animal experimentation is currently demanded by virtually all scientific publications.

2.2.1) the three «R»'s

Concerned with the improvement of the condition of animals, two English scientists, William RUSSELL (zoologist 1925-2006) and Rex BURCH (microbiologist 1926-1996) have decreed the principle known as the "rule of the 3R's", its theory was later adopted in the national and European regulations (Chapter I § 2.4) [12]. The three letters "R" are the initials of "Replacement", "Reduction", and "Refinement".

"Replacement" means that living and/or conscious animals should be substituted by insensitive preparations. This term establishes the principle of the replacement methods which aim to replace animals of high systematic position either by animals from a lower scale of zoological complexity or by of organ, tissue or isolated cell preparations (Chapter II § 3).

"Reduction" concerns the downsizing of the numbers used in an experiment. This principle, which seemed to be easy to apply, in reality involves the pursuit of a delicate statistical compromise. The increase of the number of animals is sometimes necessary or even indispensable in order to ensure the significance and preserve the statistical relevance of the results which, if these objectives are not achieved, defeats the usefulness of an

experiment. The concern for the necessity to reduce the number of animals encouraged the development of new toxicity evaluation methods (Chapter II § 3.3).

"Refinement" refers to any reduction in the severity of procedures by avoiding or reducing pain, discomfort and any other category of distress, or to an improvement in the animal's well-being. This principle often is a factor for improving the quality of the experiment because the reactions that are induced by pain or stress, which might interfere with the outcome of the experiment, are removed. "Refinement" therefore also includes any measure that might improve the quality and the performance of the experiment (for example due to the choice of methods (Chapter II § 3.2).

2.2.2) «Enrichment»

In parallel with the « *Refinement* » approach, the introduction in the 1980s of the ethological « *Enrichment* » concept should also be reported. This concept aims to improve, through environmental enrichment, the well-treatment of the animals and as a consequence their well-being. The results of this approach are still under discussion both with regards to the adaptation of the environmental enrichment methods to the species concerned and to their possible interference with the outcome of the experiments⁶⁶.

2.2.3) Relationship between benefits for humans / distress for animals

The three principles of W.RUSSELL and R.BURCH which establish the « alternative » approach today are broadened with the introduction of the relationship comparing the expected benefits for the health of human beings with the distress suffered by the animal. This obviously non-mathematical relationship introduced by the Anglo-Saxon authors remains a subject for formal study and a deciding factor in the

⁶⁶ BAUMANS V. *Science based assessment of animal welfare: laboratory animal*. Rev. Sc. Tech. Off. Int. Epiz. (2005) 24(2), 503-514



decision of an ethics committee or other authority assigned by the legislator to ratify an experimental protocol.

2.2.4) The ethics committees

We have to thank a Canadian initiative (1969) for the creation of committees in charge of reviewing and formulating an advisory opinion on experimental projects (Chapter I § 4.2.4). This approach progressively spread throughout the world, reaching France at the beginning of the 1990s, first in the pharmaceutical industry and the laboratories of the Defense Ministry, later, in the early 2000s in the large public research institutions. The evolution of these committees occurred in two stages.

Initially and, in the absence of any official or regulatory policy, spontaneous initiatives were inspired by the Anglo-Saxons' methods and elaborated by a working group of GIRCOR ('Groupe Interprofessionnel de Réflexion et de Communication sur la Recherche' (Interprofessional Group for consideration and Communication on Research), GRICE ('Groupe de Réflexion Interprofessionnel sur les Comités d'Éthique appliquée à l'animal de laboratoire' (Interprofessional Group for consideration on the Ethics Committees for laboratory animals)) in order to challenge and optimize their experiments.

Realizing the necessity to codify the activities of these spontaneous committees, the principle of which was laid down in article R-214-122 of the 'Code rural', the ministries in charge of respectively Agriculture and Research created the 'Comité National de Réflexion éthique sur l'Expérimentation Animale' (CNREEA) (French national committee for consideration of ethics in animal experimentation), whose specific mission was the drawing up of a national charter. The members of this committee belong to the ministries involved, are experts in human and veterinary medicine, members of animal

protection associations as well as personalities qualified in philosophy, sociology and legal sciences. The complete National Charter, edited by the CNREEA and adopted on June 23rd 2009 by the two ministries is presented below.

It gives indeed a precise idea of the bases and practical methods for an ethical approach towards laboratory animals. It welcomed more than fifty ethics committees amongst its members and very soon another fifty committees joined them. As a result, in 2012, approximately a hundred ethics committees in France, ratified through their membership to the national charter, assumed the advisory role stipulated by the European legislation 2010/63/EU which has now been implemented by French legislation.

THE NATIONAL CHARTER ON THE ETHICS OF ANIMAL EXPERIMENTATION

Article 1 : Respect for the animal

The ethics of animal experimentation is based on the duty that Man has to respect animals as living and sensitive beings.

Article 2 : Individual responsibility

Any use of an animal for experimentation engages the moral responsibility of each person involved.

Article 3 : Responsibility of institutions

The institutions are morally responsible for experiments carried out on animals in their establishments.

Article 4 : Skills

This responsibility involves, at all levels of intervention, an ethical training and regulatory scientific and technical skills proper to the species used and regularly updated.

Specialized skills from experts in physiology, ethology or medicine should be sought whenever necessary for the animals concerned.

Article 5 : General Principles

Careful consideration of a sound scientific,



ethical and societal basis justifying the use of the animal must precede any experimental procedure.

The use of methods and techniques aiming at eliminating or reducing to an absolute minimum the suffering of animals must be considered systematically. The development and promotion of such methods must be encouraged.

Optimization of living conditions, accommodation and care of the animals used must be permanent and continued throughout the animal's life.

The recommendation of an ethical committee must be requested before conducting any experiment on animals.

Article 6 : Ethical procedure

The use of animals for any experimental procedure must be preceded by careful consideration of:

- the usefulness of the planned experiment with respect to studies performed by others;
- the pertinence of the chosen methods and the probability of them yielding tangible results;
- the lack of alternative methods to achieve the same goal;
- the adequacy between the animal models planned and the scientific objectives;
- the extent of animal suffering relative to the expected benefit from the results;
- the biological and cognitive characteristics of the species concerned;
- the need to ensure that the choice of species, in the case of non-domesticated animals, does not threaten biodiversity;
- limiting to a minimum the number of animals required;
- the choice of living conditions, accommodation, care and use of animals, such that their physiological and behavioral needs are respected as much as possible.

Article 7 : The role of the ethical committees

Each ethical committee serves to ensure discussion and consideration of issues.

It gives recommendations on the use of animals in research projects submitted to it, referring to the principles stated in this Charter.

These recommendations are justified and can include additional recommendations.

Each ethical committee contributes to the promotion of the ethical principles laid out in this Charter.

Article 8 : Composition of ethical committees

Each ethical committee brings together multidisciplinary skills, to issue competent advices. Civil society (lay members) and veterinary medicine are represented.

Article 9 : Professional conduct of the ethical committees

Any ethical committee must be independent, impartial and must guarantee confidentiality of documents submitted to it. It must take into account the advice or recommendations of the Comité National de Réflexion éthique sur l'Expérimentation animale.

2.2.5) The death of the laboratory animal

With regards to euthanasia, two ethical problems can be identified, besides its techniques which are properly codified by regulations.

- The decision to shorten the suffering of an animal during the experiment is the subject of thorough considerations by the scientific community; it concerns a strictly organized monitoring approach in order to prevent an animal from crossing a threshold of distress described by the Anglo-Saxons as « end point », and which has been translated into French as « point limite » or « point critique »^{67 68};
- the simultaneous euthanasia of large groups of rodents or dogs after a long stay in the animal facility (chronic toxicology) often is a traumatic experience for the biotechnician or animal caretaker. The leaders of research teams who have ignored this feeling of distress for a long time are currently investigating measures to prevent it (Chapter III § 4.1).

⁶⁷ DEMERS G., GRIFFIN G., DE VROEY G. HAYWOOD J.R. ZURLO J. et M. BEDARD. Harmonization of animal care and use guidance, Science, 312, 700-701, 5 mai 2006.

⁶⁸ www.ccac.ca/Document/Normes/Lignes_directrices/points_Limites.pdf



2.2.6) Rehabilitation or «Re-homing» the laboratory animal

Since a few years animal protection associations abroad, and now also in France, are proposing an alternative to euthanasia at the end of an experiment. With the approval of the scientific institutions, animal protection associations such as GRAAL ('Groupement de Réflexion et d'Action pour l'Animal' (Association of reflection and action for animals) are taking care of dogs, cats, primates, more rarely rodents, or other less conventional species⁶⁹. These associations are responsible for re-housing the animals in private homes or zoos on condition that their future well-treatment is guaranteed. The animals they entrust should be healthy, show no after effects and present behavioral traits that suggest easy adaptation to their future physical and social environment.

3) THIRD BASIS : RATIONALITY, OBJECTIVITY AND DIVERSITY DICTATE THE EXPERIMENTAL APPROACH

The principle of any experimental approach is founded on the rationality of 4 successive stages of reasoning : a critical analysis of the state of affairs or the original observation of a phenomenon, hypothesis, experimentation and deduction. It is through this kind of reasoning that Louis PASTEUR (1822-1895) was able to refute the theory of spontaneous generation or Claude BERNARD (1813-1878) to develop the fundamental principle of the constancy of the internal environment. For that matter, the latter brilliantly formalized the experimental approach with regards to physiological research.

Progress in the world of biomedical research can indeed only be achieved through regular sequencing of these four steps. The accuracy of deduction is built on the quality and reliability of the experiment. If the ultimate

object of the study can be directly engaged in the experimental process, the critical mind of the researcher only needs to focus on the environmental conditions and the reliability of the measurements. In research directly or indirectly targeting human health, an intermediate problem intervenes, that of the model, because experiments on human beings are very often impossible (Chapter I, § 1.2).

The dual structural and phylogenetic relationship linking humans and animals (Chapter I, § 1.3) always compels biologists and doctors to resort to animal models. Researchers, conscious of the limitations of this type of models (Chapter I § 1.4), build their choice based on a complex set of arguments combining scientific performance, respect of ethics and regulations with practical requirements : prior experience with the model, availability, experience in the treatment of the species being considered and economic considerations.

The issue of choice is important. Since it is the key to the reliability of the outcome and of its interpretation, it often puts at risk the career of the researcher, if not the future of his team or laboratory. Those in charge of institutions that coordinate and finance research rarely forgive an error of judgment in the choice of models used. The large diversity of models shown to have been used by the laureates of the Nobel Prize in physiology or medicine from 1901 to 2011 (Chapter I § 2.2,) illustrates the complexity of this choice, which for some people appears to be limited to the anonymous and popular « guinea-pig ».

The *in vitro* and *in silico* methods, widely used in cellular and molecular biology may seem to be a priori completely satisfactory substitutes for Man from an ethical point of view and particularly tempting from an economic and practical point of view. Unfortunately, the highly integrative nature of life limits the

⁶⁹ www.graal-défenseanimale.org.



possibilities of these models as soon as they are being studied in the context of issues targeting the entire organism, whether human or animal (Chapter II § 5). With regards to the effects of aggressive agents or modulators, data obtained *in vitro* can only be guiding factors for formulating hypotheses concerning the global organism. The regulatory mechanisms at the different levels of the organism may either amplify or nullify the phenomena observed at a cellular or molecular level.

The importance of these hypotheses derived from *in vitro* experiments or *in silico* approaches depends on their relative specificity. They reduce the span of the *in vivo* investigations, thus limiting the number of animals used and increasing the effectiveness of the human and financial resources committed to achieving the targeted health issue. As a result, a constant flow can be observed in all disciplines pursuing human and animal health, very often within the same research team, between primary *in vitro* experiments and the *in vivo* confirmation methods. As a matter of fact, it is just as important to revert to *in vitro* in order to clarify the results obtained *in vivo*. This helps to explain and understand the origin of the phenomena observed *in vivo*, in order to identify increasingly targeted approaches for these methods.

To further improve the aspects of effectiveness and ethics, bioinformatics proposes to facilitate and optimize the dialogue between *in vitro* and *in vivo*. Encouraged by the success of the so-called *in silico* methods, used for the electronic selection of molecules with pharmacological or toxic properties, the scientific community and public authorities are investing considerable human resources in the approaches combining the entire system of available methods in order to accelerate progress in biomedical disciplines

and at the same time noticeably reducing the use of experiments on live animals (Chapter II § 4). This takes us far from the naivety of those who, sometimes in good faith, believe that, at the beginning of this 21st century, only the molecular and cellular levels need to be studied with or without the use of electronic resources, in order to solve all problems relating to human and animal health without resorting to animal models.

4) FOURTH BASIS : TOWARDS CONCILIATION ON THE DEBATE REGARDING ANIMAL EXPERIMENTATION THROUGH DIALOGUE AND MUTUAL RESPECT

As discussed previously, the controversy on animal experimentation cannot be solved by rational argumentation (Chapter I § 4.1 and 4.2). Some people are convinced that it is only based on objective facts (recognition, or not, of the necessity to resort to animal models). It is in actual fact based on a conflict. The subjective image that each individual developed with regard to animals is opposed to the principles of rationality and experimentation aiming to gain knowledge. In the absence of a solution based only on rationality, the controversy could nevertheless be partially appeased if both parties show some mutual respect, built on dialogue and obligations that have been freely agreed upon.

4.1) COMMUNICATION, ONE OF THE DUTIES OF THE RESEARCHER

The fact that he/she is in some way appointed by the community to develop knowledge and to improve human health, should urge the researcher to reflect on how his fellow citizens perceive his activities. This means that he should take into account not only the sensitivity of the animals he uses but also that of his contemporaries who indirectly witness his scientific activities.



To this end, he should clearly and without condescension inform on his objectives and his resources, in short, he should communicate both with the neutral public that is not engaged in animal protection, and with the specialized analysts. The major reproach addressed to researchers and research institutions is the inadequacy of communication (Chapter I § 3.1).

Recourse to laboratory animals should be a totally transparent process. This is achieved by means of national and international statistics or through the ethics committees. However, at the individual level as well, that of the researcher or the research institute, this transparency should become a code of conduct. The pretext of secrecy should be overcome, if necessary using certain adequate precautions to give an honest presentation of the methods used.

Another inquiry addressed by the public to researchers, in particular those who use primate models, concerns the respect for biodiversity and potential damage to wildlife. Communication on this issue from researchers and research institution also is insufficient. Providing the public with information on the European or national regulatory provisions in this field and presenting the know-how of today on the primate breeding centers should be sufficient to reassure their contemporaries on this issue.

In parallel with the lack of communication on the part of researchers towards the public, it can be observed that there also is insufficient communication within the research institutions themselves. The relationship established between animal technicians and the animals they are looking after and for which they are responsible, is not always experienced as it should be. Because of a lack of accurate information or sufficient explanations, this category of staff, who are recruited because of their interest in animals and who are often attached to them, sometimes has difficulties

enduring their professional practice, especially the practice of euthanasia at the end of the experiment. Extreme situations like this can be observed with experiments on chronic toxicology conducted in dogs but may equally be found with euthanasia of rodents. The attitude of experimenters should take into account this distress, especially in their communication with the staff in charge of animal care.

4.2) THE DUTIES OF SOCIETY

The media, who generally express themselves in the name of society, should respond to the first step to be made by the researcher, by taking an objective position balancing the information provided by the research institutions with those issued by the so-called « antivivisectionist » associations. To this end, prior to publication, they should ensure the veracity of the facts that are brought forward by both parties.

Secondly, neither media nor justice should show any lenience towards the use of violence. If not to acknowledge their competence, their good faith or their ethical attitude, anyone working within a legal framework, such as researchers, deserves a minimum of respect from their fellow citizens. This respect should be expressed by guaranteed security and by continued support from the media in case of proven violence. Whatever romanticism journalists might openly or discretely attribute to « commando actions » of a few « antivivisectionists », they should be reminded that this is the expression of a minority wishing to impose its opinions by force with sometimes disastrous consequences for the « liberated » animals being placed in new naïvely improvised living conditions.

It is indeed the duty of public authorities and the media to clearly play respectively an educational and a popularizing role. They should remind animal protectors and so-called « antivivisectionist » associations of the



contradiction existing between the demands for health, longevity or the systematization of the precautionary principle and the cessation of animal experimentation. They should be made to realize the inescapable truth : except for one fraction of toxicology, animal experimentation still is indispensable for progress in biological and medical disciplines.

The animal protection associations who entertain moderate viewpoints (Chapter III § 3.3) or the patient associations who support biomedical research, who are even more concerned than the public at large, should have the liberty to publicly and clearly pronounce themselves, each from their own angle, against the violent actions and extreme rhetoric of the radical so-called « anti-vivisectionist » associations.

Finally, children and adolescents who are particularly sensitive in this matter, should be taught respect for animals with diligence and with accuracy, without indulging in anthropomorphic complacency. This should be the duty of the entire educational body, and especially, at the level of secondary schools and colleges, of the teachers of natural and life sciences, on condition that they themselves receive quality training on this issue.

4.3) FAVORING MUTUAL LISTENING

When creating the 'Commission Nationale de l'Expérimentation Animale' (National Committee for Animal Experimentation), the legislator, concerned with conciliation and dialogue, has included the participation of representatives from the recognized animal protection associations. The regular participation of these associations has since proven to be constructive. Although they do not conceal their ultimate objective which is the abolishment of animal experimentation, their arguments and immediate objectives have remained moderate. It would be appropriate if the sincerity of their moderation could be confirmed in their public statements.

The same climate of dialogue and mutual respect

has been observed during the debates that resulted in the collective publication of the national charter on the ethics of animal experimentation and which are ongoing within the 'Comité National de Réflexion sur l'Éthique en Expérimentation Animale' (French national committee for consideration of ethics in animal experimentation).

Since the dialogue has now broadened to including representatives of civil society, it is entirely appropriate that these should participate in the debates of the two national institutions, the 'Commission Nationale de l'Expérimentation Animale' (National Committee for Animal Experimentation) and the 'Comité National de Réflexion sur l'Éthique en Expérimentation Animale' (French national committee for consideration of ethics in animal experimentation). The presence of discussion partners such as the members of the 'Conseil Économique et Social' (Economic and Social Council), the members of patient associations or consumer organizations would deepen the discussions and would offer a broader and more objective foundation for the proposals of both national institutions.

Less official, equally productive but needing to dispel the objections from either side, are visits to laboratories for small groups of people concerned with the controversy. These allow a direct dialogue which is extremely beneficial for creating a climate of conciliation. There is the obvious condition that the researchers give the visitors a sincere welcome and that the beneficiaries of the visits in turn are willing to testify of their visit within their associations as well as in public.

Finally, it is regrettable to have to note that, during the few public debates on animal experimentation, the attitudes and arguments of so-called communication definitely encouraged the climate of confrontation the organizers sought but certainly not that of objective information to the public or of reciprocal listening.





CONCLUSION

RECOMMENDATION OF THE FRENCH VETERINARY ACADEMY ON ANIMAL EXPERIMENTATION, ITS ROLE IN RESEARCH AND ITS PERCEPTION IN SOCIETY.

THE FRENCH VETERINARY ACADEMY

Observing that resorting to the use of animals for scientific research purposes is disputed by a certain number of our fellow citizens :

- some adhering to philosophical beliefs that places Man on strictly the same level as the entire group of other animal species;
- others showing spontaneous compassion towards animals, expressed with regards to any situation in which the latter are or risk being ill-treated ;
- lastly those, sometimes scientists themselves, disputing the validity of animal models as a reliable source of knowledge in human and veterinary pathology.

CONSIDERING

- that in human and animal medicine, society makes increasing demands requiring considerable efforts from research ;
- that animal experimentation has played and still plays a decisive role in the acquisition of biological knowledge and in its contribution towards progress in medicine ;
- that experimentation in humans can only be considered in a limited number of situations strictly defined by the principles of bioethics, such as clinical trials which are essential for the evaluation of new treatments, and that consequently, recourse to laboratory animals remains inevitable, in particular for the evaluation of the safety and efficacy of any therapeutic innovation ;



- that since the European directive of 1986 pertaining to the use of animals for scientific purposes, supplemented in France in 1992 with the report of Minister Hubert Curien, respect for animals during the performance of animal experimentation has undeniably progressed, especially due to specific legislation, the training of staff, the setting of standards for animal facilities and the *a priori* review of experimental protocols by the ethics committees member of a national charter. The inadequacies observed in the communication of researchers and their management caused the public to more than often ignore these advances ;
- that progress in in vitro alternative or replacement methods on cells or cell-lines or in silico through bioinformatics simulations notably contribute to reducing the number or animals used for scientific purposes ;
- but that these approaches are directed to molecular or sub-cellular levels and that it should be possible to re-evaluate the conclusions of their outcome at the level of the integral organism ;
- that the replacement methods in toxicology and in biosafety can only be ratified after a circumspect and slow procedure because of the underlying public health and legal challenges ; to-date it is impossible to consider total replacement, even in toxicology;

REAFFIRMING⁷⁰

- the irreplaceable role of animal models in the research on fundamental and medical life sciences ; research which in future would limit itself, were it only based on in vitro and in silico models thus ignoring the complexity of biological processes at the level of the organism.

RECOMMENDS

- that the efforts that are already well under way towards an optimized, rational and respectful use of animal life should continue in scrupulous compliance with national laws and European guidelines and that they should continuously improve themselves through interactive exchanges between all the elements under consideration regarding the practices and ethics of the use of laboratory animals : official national institutions, ethics committees, professional organizations, Life Science academies;
- that the dialogue, put into practice for some years, of the two official institutions, the 'Commission nationale de l'Expérimentation animale' (national Committee for animal Experimentation) and the 'Comité National de Réflexion sur l'éthique en Expérimentation Animale' (national committee for consideration of ethics in animal experimentation), with certain animal protection associations, should be opened up more widely, involving representatives of civil society, patient and consumer associations, members of the economic and social council and that it should be led with determination to allow biological and medical research to continue in a climate of conciliation, answering the demands of society and taking into account the evolution of the concept on the relationship between humans and animals.

This recommendation, adopted by the academic Assembly during its meeting of June 21st 2012, is the conclusion of the report « *Scientific Research and Animal Experimentation. State of affairs* », of the « Human-Animal Relationships » Commission of the French Veterinary Academy.

⁷⁰ Avis de l'Académie Vétérinaire de France sur la proposition de loi relative "au recours à la vivisection et à l'utilisation des animaux domestiques en laboratoires" déposé par M. le Député Flory.
Avis adopté par l'Académie Vétérinaire de France le 10 mai 2007



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SUMMARY

In its report «**Scientific research and animal experimentation. State of affairs**» the «Human-Animal Relationships» Commission of the French Veterinary Academy provides clear and useful insight in a debate that tends to oppose human health and animal protection.

Biomedical research is a must in our society and, until now, animal experimentation is the major source for progress in medicine and biology. The opposition is based on ignorance and defiance. The public at large is little concerned and considers its demand for a rapid solution to health problems as a priority.

The recent spectacular progress in molecular biology has revealed the high degree of complexity of living organisms and, more than ever, made the recourse to cellular and animal models indispensable. The combinatorial approach based on the bioinformatic treatment of the entire system of *in vivo*, *in vitro* and/or *in silico* data, is becoming the model for the future.

The academic attitude is based on a postulate and three avenues for action:

- in the present scientific situation, recourse to animal models is indispensable;
- the ethical procedures that have presently been defined should be widely promoted and strictly applied;
- rationale should continue to guide the choice of experimental methods;
- all opportunities for a dialogue should be explored with the intent to appease social controversy.



RÉSUMÉ

Dans son rapport « **Recherche scientifique et expérimentation animale. Etat de la question** » la Commission « Relations Homme - Animaux » de l'Académie Vétérinaire de France apporte un éclairage précis et utile dans un débat qui tend à opposer santé et protection animale.

La recherche biomédicale est un impératif de notre société et l'expérimentation animale est jusqu'à présent la principale source de progrès en médecine et biologie. L'opposition s'appuie sur l'ignorance et la défiance. Le grand public est peu concerné et souhaite en priorité une résolution rapide des problèmes de santé.

Les progrès récents spectaculaires de la biologie moléculaire ont révélé le haut degré de complexité des organismes vivants et rendu plus que jamais indispensable le recours aux modèles cellulaires et animaux. L'approche combinatoire fondée sur le traitement bioinformatique de l'ensemble des données *in vivo*, *in vitro* et/ou *in silico* s'impose comme le modèle d'avenir.

L'attitude académique se fonde sur un postulat et trois voies d'action :

- le recours aux modèles animaux est indispensable dans l'état actuel de la science ;
- les dispositions à visées éthiques actuellement définies doivent être largement diffusées et rigoureusement mises en jeu ;
- le choix des méthodes expérimentales doit demeurer de l'ordre du rationnel ;
- toutes les opportunités de dialogue doivent être explorées dans un souci d'apaisement de la controverse sociétale.

