

BIOETHICAL GUIDELINES FOR THE STUDY OF CHRONIC PAIN IN ANIMALS: A PARADOX?

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SUMMARY

The study of nociception in animals is a biomedical research field directly implicated with an ethical framework. In this work I will refer to the ethical considerations we must bear in mind when dealing with experimental approaches in animals used for the study of normal -physiological- and abnormal -pathological- mechanisms related to what humans denote as pain. In fact, this implies a paradox for, if we are to comply with international bioethical guidelines, we have to show that our research animals are not subject to suffering or pain during the experimental procedures or as a consequence of them. Therefore, the use of procedures or agents to withdraw suffering or pain would intrinsically cancel the mechanisms which are the object of our study. How can we study pain without causing it? In some way, this implies the transgression of the ethical code of a society claiming to be more modern and civilized and which demands and promotes human well-being; this entails essentially a life without pain.

The analysis of these problems needs several platforms or levels. The first level is the social one, where society plays various roles not only as a defender of animal rights, but also as a victim within itself or related fellow creatures of long-term pain suffering or that associated with terminal diseases. Secondly, an academic platform comprising thinkers of all the related disciplines in this area and, finally, a platform constituted by peer judges and experts dealing exactly with a specific bioethical problem.

In this sense, the concrete proposal here is to incorporate society and make it share responsibility with the afore mentioned platforms, into a collegiate body provided with bioethical decision capacity in relation to the development of projects where nociception research is undertaken.

We are faced with a problem of social shared responsibility between the scientific and general communities, having solutions subject of being improved by means of rational approaches and avoiding any radical positions, regardless of its scientific appearance or antivivisection resemblance.

Key words: Pain, bioethics, chronic nociception, animal models.

RESUMEN

Hoy en día no queda claro, ni es un hecho consciente para amplios sectores sociales, el papel benéfico de las investigaciones

biomédicas realizadas con animales, que han redundado en una mejor calidad de vida en el campo de la salud. Esta falta de claridad se debe, en parte, a la ignorancia y en parte a que algunos sectores que realizan este tipo de investigaciones prefieren mantener anestesiada la conciencia de la opinión pública por razones diversas, una de las cuales es la bioética. Es por esto que cada vez es más imperioso sacar a la luz pública y a los foros académicos estos temas que nos atañen a todos.

Un campo de investigación biomédica directamente implicado con la bioética es el relacionado con el estudio del dolor. En este trabajo me referiré a las consideraciones bioéticas en torno a abordajes experimentales con animales, en los cuales se investigan los mecanismos normales -fisiológicos- y anormales -patológicos- relacionados con lo que el hombre expresa como dolor.

Si nos atenemos a los lineamientos bioéticos internacionales nosotros debemos demostrar que nuestros animales de investigación no sufren dolor durante los procedimientos experimentales o a consecuencia de éstos. Por lo tanto, la utilización de técnicas o fármacos para eliminar el sufrimiento y el dolor cancelaría intrínsecamente los mecanismos objeto de nuestro estudio. Es decir, se establece una paradoja: ¿cómo estudiar el dolor sin producir dolor? Esto de alguna manera implica transgredir el código ético de una sociedad que se pretende hoy más moderna y civilizada, y que en otro sentido, exige y promulga el bienestar humano, lo cual incluye de manera prioritaria una vida sin dolor.

El análisis de estos problemas tiene que realizarse desde distintas plataformas o niveles. El primero de ellos sería el nivel social, esa sociedad que se constituye tanto en defensora de los derechos de los animales, como también en la sociedad que padece en sí misma o en sus prójimos (animales domésticos) la desgracia del dolor de plazos largos o asociado a enfermedades terminales. La plataforma académica estaría constituida por pensadores de todas las disciplinas interesadas, y una constituida por jueces pares y expertos relacionados puntualmente con el problema bioético específico.

En este sentido, la propuesta concreta es incorporar y responsabilizar a la sociedad civil integrada por las plataformas antes mencionadas en un cuerpo colegiado que tome las decisiones bioéticas relacionadas con el desarrollo de proyectos en que se investiga la nocicepción.

Palabras clave: Dolor, bioética, nocicepción crónica, modelos animales.

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INTRODUCTION

The contribution of biomedical research in animals is a subject which either is not completely understood or is not made conscious by wide sectors of the population. However, a quality of life improvement in the field of health has been achieved from it. The former is due sometimes to ignorance and other times because researchers would rather keep dormant public opinion conscience, bioethics being among the various reasons. Therefore, it is imperative to draw light on these subjects so that the general public and academic forums discuss these issues, for they should concern us all.

One of the fields of biomedical research directly implicated within an ethical framework is the study of pain. In this manuscript I will refer to the ethical considerations we must bear in mind when dealing with experimental approaches in animals used for the study of normal –physiological– and abnormal mechanisms –pathological– related to what humans denote as pain.

Why is bioethics necessary in dealing with animals? In order to answer this question a brief historical perspective with a social reference is pertinent. Certain laws and precepts have been formulated ever since we conceive civilisation. One of the most ancient ones is referred in the Deuteronomy which quotes: ‘You shall not muzzle the ox when he threshes the corn’ (2). After a long period of time, in 950 A.D., the South Welsh Prince Aberfraw Howel Dda established the value of the domestic or house cat as well as the fines and punishments for “all those who endangered its life, wounded it or did not care for it properly” (8). We must bear in mind that these visionary laws had an utilitarian as well as a pragmatic foundation, and were not intentioned for the preservation and well being of those species.

WHY MUST ANIMALS BE TAKEN INTO ACCOUNT?

One of the roots of the matter lies in the European anthropocentric view held from the Sixteenth to the Eighteenth centuries. At that time, imperial expansions materialized as overseas colonies with policies that subordinated conquered lands. In this context, the “natives from beyond the sea” were considered as inferior beings. This pathetic fact is patent in the defense that the clergyman Bartolomé de Las Casas makes on behalf of the American natives in the presence of Sepúlveda and other Spanish hierarchs in 1550 (3, 6). Not to mention the treatment received by thousands of African slaves sold to America in conditions similar to those of beasts of burden. These historical facts provide a scalar reference to the treatment considerations bestowed on animals, which were seen from a subordinate

perspective to European culture and in the strictest utilitarian sense.

THE EVERLASTING PROBLEM OF CONSCIOUSNESS

This manner of approaching the problem is derived from the concept of cognitive consciousness bestowed by the dominant social groups to themselves, other ethnic groups and, indeed, to animals. Nowadays, it has been undoubtedly demonstrated by Griffin (5) and Dennett (1) among others, that the animal evolutive scale underlies a similar evolution of cognitive consciousness. In a limited way, cognitive consciousness is referred to as the capacity of all organisms endowed with a nervous system for self-acknowledgement. This ability is related, on the one hand, to attention and memory processes among others, and on the other, to propositive interaction with its surroundings: social and geographical. These concepts pose that a group of animals, more precisely that of non-human primates (bonobos, chimpanzees, orangutans, gorillas) and possibly cetaceous experience pain in a similar manner and within the same concept or interpretation that humans give to it. In some way or another, all animals provided of a Nervous System and in accordance to its place in the evolutive scale, will respond to a noxious stimulus. The higher the position in the phylogenetic scale, the more complex and elaborate such response will be.

Consequently, man is now conscious that animals are endowed with consciousness (animal conscience). This statement brings living beings closer, making animals, under the eyes of society, its fellow creatures and extending its protective cloak not only to its fellow men, but also to animals providing them with legal, moral and ethical protection.

THE PARADOX

If we are to comply with international bioethical guidelines, we have to show that our research animals are not subject to suffering or pain during the experimental procedures or as a consequence of them. Therefore, the use of procedures or agents to withdraw suffering or pain would intrinsically cancel the mechanisms which are the object of our study. How can we study pain without causing it? This implies in some way, the transgression of the ethical code of a society claiming to be more modern and civilized which demands and promotes human well being, this entails essentially a life without pain. At this point I feel the need of punctuating some concepts in relation to pain and nociception.

Pain has been defined as an alarm mechanism that prevents an organism from suffering a real or potential harm entailed of a disagreeable emotional or sensorial content (7). Generally, pain is associated with a recognizable source as the origin of the harm, having a known topography, magnitude, and temporality, which together, with the perception characteristics, has been defined as *qualia*. That is, the sensorial quality of pain, verbally reported by human beings. The animal counterpart of the former concept is called nociception. In this case, what is being assessed is a set of responses –motor, endocrine, emotional, and finally behavioural– associated with the level of physiological development as well as with the affective cognitive level of the species in study. This entails problems with regard to the translation and interpretation of the concepts of sensation and perception between animals and man.

One current approach to the bioethical problem within this context was issued by the ethical committee of the International Association for the Study of Pain (IASP). This commission published, in 1983 (10), the ethical guidelines for the experimental pain research in conscious animals (the term conscious referred in this manuscript implies solely that the animal is awake) consisting of 7 points, which I transcribe here:

1. It is essential that the intended experiments on pain in conscious animals be reviewed beforehand by scientists and lay-persons. The potential benefit of such experiments to our understanding of pain mechanisms and pain therapy needs to be shown. The investigator should be aware of the ethical need for a continuing justification of his investigations.
2. If possible, the investigator should try the pain stimulus on himself; this principle applies for most non-invasive stimuli causing acute pain.
3. To make possible the evaluation of the levels of pain, the investigator should give a careful assessment of the animal's deviation from normal behaviour. To this end, physiological and behavioural parameters should be measured. The outcome of this assessment should be included in the manuscript.
4. In studies of acute or chronic pain in animals, measures should be taken to provide a reasonable assurance that the animal is exposed to the minimal pain necessary for the purposes of the experiment.
5. An animal presumably experiencing chronic pain should be treated for relief of pain, or should be allowed to self-administer analgesic agents or procedures, as long as this will not interfere with the aim of the investigation.
6. Studies of pain in animals paralysed with a neuromuscular blocking agent should not be performed without a general anaesthetic or an appropriate surgical procedure that eliminates sensory awareness.
7. The duration of the experiment must be as short as possible and the number of animals involved must be kept to a minimum.

These guidelines definitely solve some questions with regard to the procedure and the management of experiments correlating nociception and conscious animals. The afore mentioned paradox is clearly evident in point number 5, which refers to chronic pain. It seems that people with a good conscience are reluctant to inflict pain for a long period of time or lacking of causal control. This fits well in the Baconian, cited by Jay Gould (4), scheme of attracted idols (understood by Bacon as: “active biases wherewith the mind is preoccupate”), that is, those persons showing prejudices imposed from the outside or, as Jay Gould remarks in his article on the wars of science (4), “our lamentable tendency to taxonomize complex situations as dichotomies or conflicting opposites”. In our case, this means acute *vs.* chronic pain, physiological *vs.* pathological, in brief, science against science. In other words, we tend to tear apart a concept and work only with the bits and pieces that we are able to handle and forget about the rest. As Bacon concludes: “we reject demonstration or syllogism, for that it proceeds confusedly; and lets Nature escape our hands”. This situation drives us to propose alternative routes to confront the paradoxes propounded by ourselves.

If we return to the matter of human pain, there are various entities coursing with pain but lacking a direct relation, causal or temporal, to inflicted damage. This kind of pain is known as pathological or neuropathic, in the sense that it has lost its alarm function, that is, we encounter a painful sensation but no real or potential damage. Some examples of the former are present in nervous deafferentation, central pain, post-herpetic neuralgia, and painful phantom limb, just to mention a few (7).

New and specific therapies have been developed to treat pain in humans due to systematic and dedicated biomedical research. But when dealing with the mechanisms underlying neuropathic pain new invasive methods should be designed, methods that are not ethical when utilized in humans. Therefore, animals should be used instead in this type of research.

The need of inflicting pain or suffering to animals entails relentlessly serious ethical restrictions in the experimental design. The rules and guidelines -personal, institutional, national and international- alert us all the time in trying to reduce animal suffering to a “minimum necessary”. This principle must be present at every level of the experimental design, as well as while running the experiment. There are some practical guidelines propounded by Zeltser and Seltzer (9) in

order to define this minimum:

1. Use the lowest number of experimental groups needed to make your point.
2. Use the lowest possible number of control groups.
3. Reduce the number of animals per group to the lowest possible needed to establish statistical significance.
4. Pilot experiments may sometimes yield minor and statistically non-significant differences between experimental and control groups. In scientific disciplines other than pain research, experimenters may proceed with a second run of the experiment based on a number of animals sufficiently larger to guarantee statistical significance. In neuropathic pain research, however, this strategy should be questioned by the investigator. An identical replication of the study would probably yield no larger differences between the experimental groups. Increasing the number of cases in the group would reduce variance and would merely enable the establishment of statistical significance but would not increase intergroup differences. We should ask ourselves in such cases if, from an ethical point of view, small intergroup differences justify a larger scale study.
5. In some scientific fields, in addition to the first run, studies include a replication experiment which is welcomed as a rigorous attempt to support the reported findings, especially if the study came up with novel and important results. However, in neuropathic pain research, replications might be reduced in scale to show that the trend of the results of the original study reappears in the replication run.
6. Likewise, researchers in neuropathic pain should be allowed to use archival baseline control data, particularly when the data bank has been pooled in the same laboratory, using the same animal species, age, sex, and environmental conditions, and preferably by the same experimenters.
7. Because the field of animal models for neuropathic pain is still quite young, modellers should first consider investing in animal models that replicate the main syndromes of neuropathic pain in humans, i.e., those affecting the majority of patients and not rare cases.
8. Animal models of neuropathic pain must demonstrate that the animals suffer from pain of comparable intensity to the human syndrome, yet the level of pain must never be debilitating. Extreme suffering in animals may include a combination of drastic weight loss; profuse vocalization while walking or at rest; abnormal social interaction with cage mates as reflected by reduced sexual behaviour, neglect of pups, extreme aggression to cage mates, or muricidal behavior; or extreme aggression on handling by humans.

To these considerations, Zeltser and Seltzer (9) have added a factor taking into account the phylogenetic

scale. They consider that investigators must seriously question the use of dogs, primates and dolphins as subjects in neuropathic pain models. Especially when the evidence in pilot experiments provides no significant differences between higher or lower animals in the phylogenetic scale.

With regard to point 7 in these second group of guidelines, establishing that animal models of neuropathic pain must be used to elucidate “main” syndromes rather than rare cases. In my opinion this should not be a validation criterion. To clarify the former let us refer again to humans, particularly cases of central pain, where the syndrome courses with self-mutilation. These are singular cases from a statistical point of view but very relevant with regard to the underlying physiopathology.

DISCUSSION

With the arrival of modern techniques, such as functional imaging in brain, *in situ* neurochemistry, and behavioural sciences, the study in the field of pain has undergone a complete transformation. The identification of brain structures and the functional linkage among them has been established. For the first time, the cerebral activation related to cognitive–affective functions has been literally visualized. This is slippery terrain that was under the academic jurisdiction of psychology, but nowadays lies overtly in the field of experimental integrative physiology, not only human but animal as well. These facts have led to a design of experimental animal research where time (chronicity) represents a crucial factor in the study as is the case in neuropathic pain models or in the so-called pathological pain models. To face these new experimental challenges in the field of pain, we have the opportunity to review and to bring up-to-date the bioethics pertaining this field.

The analysis of these problems needs several platforms or levels. The first level is the social one, where society plays various roles not only as a defender of animal rights, but also as a victim within itself or related fellow creatures of long-term pain suffering or that associated with terminal diseases. Secondly, the academic platform comprising thinkers of all the related disciplines in this area and, finally, a third platform constituted by peer judges and experts dealing exactly with a specific bioethical problem.

In this sense, the concrete proposal on my part is to incorporate society and make it share responsibility with the afore mentioned platforms, into a collegiate body provided with bioethical decision-making capacity in relation to the development of projects where nociception research is undertaken.

Therefore, the design of animal experimental models must be developed in order to validate the following points:

- a) The animal model used must present a reasonable resemblance to the phenomenon encountered in humans.
- b) The model must provide the intrinsic mechanisms for the understanding of the phenomenon.
- c) Experiments must be carried out within the bioethical norms and criteria established for experimental pain research and complying with similar parameters as those described in this manuscript.

Finally, we are faced with a problem of social shared responsibility between the scientific and general communities, having solutions subject of being improved by means of rational approaches and avoiding any radical positions, regardless of its scientific appearance or antivivisection resemblance.

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RESPUESTAS DE LA SECCION AVANCES EN LA PSIQUIATRIA Autoevaluación	
1.	C
2.	B
3.	A
4.	E
5.	E
6.	B
7.	E
8.	B
9.	C
10.	D
11.	D
12.	C
13.	E
14.	C