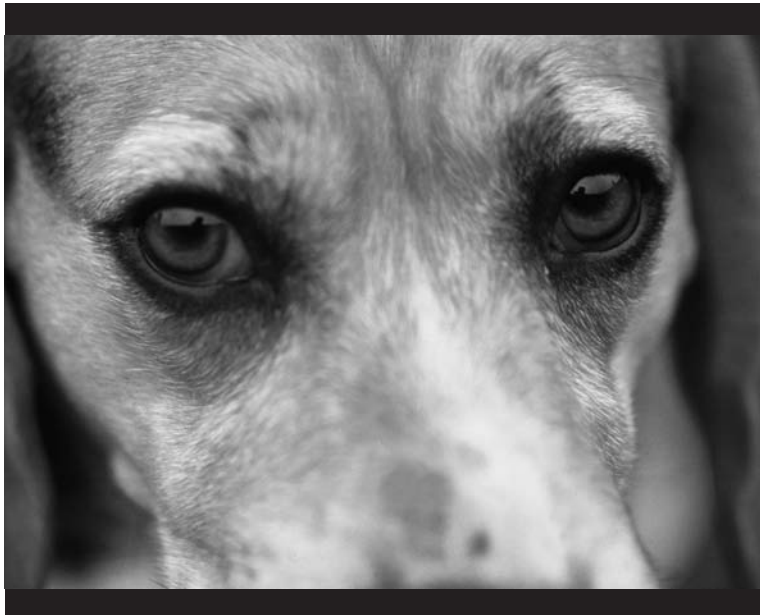

**Animal Aid exposes and campaigns
peacefully against all animal abuse,
and promotes a cruelty-free lifestyle**



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Curiosity Killed the Dog

An Animal Aid report on the use
of animals in Basic Research
A Case Study



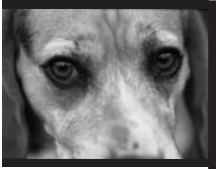
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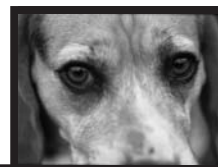


Curiosity Killed the Dog

An Animal Aid report on the use of animals in Basic Research **A Case Study**

Written by André Menache BSc (Hons) BVSc MRCVS FRSH
Scientific Consultant to Animal Aid
Published by Animal Aid, October 2005

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Summary

This special report was prompted by Animal Aid's discovery of a long-running series of terminal experiments on dogs, carried out at a leading UK medical school and funded, in large part, by one of the country's biggest charities – the British Heart Foundation.

Begun 16 years ago and aimed at measuring physiological responses to experimental heart-related procedures, the Leeds Medical School-based project seemed to Animal Aid to be both repugnant (it has involved opening the chests of anaesthetised dogs, cutting their spinal cords, draining and recirculating their blood, and cutting nerves to the brain, gut and diaphragm) and without scientific merit.

We presented a dossier of the team's work to heart specialist and medical researcher, Dr. John J. Pippin,* and asked for his written assessment as to the merits of the work, in terms of human medicine.

Dr Pippin's response was scathing. In fact, he has called for those involved to have their Home Office licences revoked. It is a call that Animal Aid endorses.

In his critique to the Home Office, Dr Pippin declared: 'This work provides an exceptional example of a common practice: the manipulation of animal models for convenience and usefulness, regardless of the effects upon the validity of results obtained. This is not uncommon among those researchers who propose and perform studies to satisfy their scientific curiosity and sustain their careers, without sufficient regard for potential applications to humans.

'Very evident in this collection of papers is the characteristic use of one study to justify the next. In many cases, unanswered (usually unforeseen) questions arising from one study produced the rationale for a later study. In several instances, the team invokes conflicting or erroneous results from previous studies (sometimes their own) to justify another study.'

The larger scandal disfiguring this long-running research project has been the

willingness of the Home Office regulators to sanction an enterprise that, by any objective assessment, fails to demonstrate obvious benefits for human medicine. The same charge of lack of due diligence can be levelled at the British Heart Foundation, a major research charity that, for many years, has directed publicly donated money at the Leeds team.

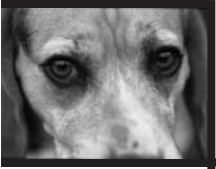
The team's activities are categorised, under the official Home Office formulation, as 'basic' or 'fundamental' research. These are catch-all terms that may or may not *promise* tangible benefits for human or even animal medicine. The regulators are content for the research to be speculative. It need only carry the suggestion that at some future, unspecified date something concretely beneficial might emerge.

Blue skies research is all very well, many people would agree, where public money is not involved and where the research materials are inanimate. But the Leeds team have been working at a publicly funded institution, with additional funds coming from a charity. Furthermore, the object of their attention has been beagle dogs.

While the Leeds Medical School project is a particularly shocking example of basic research using live animals, this report demonstrates that there is a good deal that is fundamentally problematic about this whole area of work.

** John J Pippin MD graduated from the University of Massachusetts Medical School in 1980 and subsequently specialised in nuclear cardiology. Among his academic appointments are faculty positions at Harvard Medical School and the Medical College of Virginia. In addition to his numerous scientific publications, he is the recipient of several prestigious awards for clinical and research excellence.*

In February 2005, he presented evidence at a US Food and Drug Administration hearing on the misleading results of animal tests with respect to the anti-inflammatory drug, Vioxx.



2 Introduction

Basic Research (aka 'Fundamental Research') involves experiments whose primary purpose is an increase in the fund of knowledge available in a particular field of scientific endeavour. Typically, questions are posed and answers sought by means of animal experiments. Such studies, according to a Home Office definition, may be aimed solely at an increase in knowledge, an application of existing knowledge beyond the scope of the investigator, or else, at providing a practical solution to an existing medical or veterinary problem.

In reality, claims of relevance to human medicine will always be made by those involved in basic research. This is to give weight to their application for funding and for a Home Office licence.

Basic research is normally subdivided into *toxicological* and *non-toxicological* procedures. The latter (non-toxicity tests) may include *efficacy studies* (where a procedure is designed with the aim of achieving a particular desired effect), *metabolism* (bodily function), *nutritional evaluation* (food studies), etc. In addition, basic studies may be categorised according to the *body system* in question, e.g. respiratory, cardiovascular, nervous, digestive, reproductive.

3 Legislation covering basic research

All animal experiments are 'regulated' by the Home Office, under the 1986 Animals (Scientific Procedures) Act.

While current law makes it difficult to avoid animal testing during the safety evaluation phase of new pharmaceutical products, scientists conducting basic research have no legal requirement to use animals. It is left to the individual scientist to judge what is worth studying, and whether or not to

use animals. In order to perform an animal experiment (referred to as a 'procedure'), a researcher must obtain a personal, as well as a project, licence. The proposed research programme will be scrutinised by a professional body (the Home Office Inspectorate), 'composed of medical and veterinary graduates with higher professional and academic qualifications and experience of clinical practice and quality research' (1).

4 The scope of basic research in the UK

According to official Home Office figures, there has been a steady *increase* in the number of animals used in basic research over the last 10 years, from 24% of the total number of procedures in 1993, to 30% in 2003 (the *total* number of procedures in 1993 and 2003 was the same i.e. 2.8 million).

5 Categories of basic research

Of the various fields of basic research, the largest single category in 2003 was the immune system (nearly half a million procedures), involving several different species of animal. The next largest category was the nervous system, followed by the cardiovascular, respiratory and digestive systems.



6 Examples of basic research I

Experiment 1

Ten five-week-old kittens had the eyelids of one eye sewn together and kept closed for ten days. In five of the kittens, the sewn eye was then opened, while the healthy eye was surgically manipulated to make it squint. Fourteen days later, the kittens were anaesthetised and had part of their skulls removed in order to expose the brain area that is responsible for vision. Behavioural and optical imaging experiments were subsequently performed.

There is no mention in the article of whether the kittens were allowed to recover from the experiment or whether they were euthanased.

The authors do not provide any clear conclusion. Instead, they explain why their study appears to contradict that of other researchers, and also why the results could differ when the experiment is performed in monkeys.

Comment:

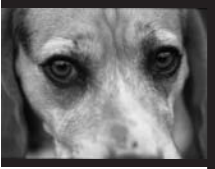
This is yet another minor variation on a category of research called 'monocular deprivation', often used to study the human condition known as amblyopia ('lazy eye'). Cats were used in this experiment even though their eyes lack a macula and fovea – two areas of critical importance in the human eye. A Harvard trained pediatric ophthalmologist commented on this type of research in 1990 in an affidavit (next column) presented in an Israeli court of law. This document, together with several other sworn statements made by eye specialists, all concurred on the lack of applicability of these experiments to the human condition.

'I do not believe that straining to find out new ways of depriving cats of visual input has added, or will add, to our knowledge about the connections of the eye to the visual cortex in cats... even if it adds a little to our knowledge of visual connections in cats, the applicability of this knowledge to human amblyopia is essentially nil. Clinical research, done with children who are actually suffering from amblyopia, would seem to be the only way to find out more about how to treat this important condition which affects about two per cent of the population.'

Affidavit by Robert Petersen MD, The Children's Hospital, Boston USA

Source: Correlated binocular activity guides recovery from monocular deprivation.

Nature 2002; Vol. 416: 430-433.
Kind P, Mitchell D, Ahmed B, Blakemore C, Bonhoeffer T, Sengpiel F.
University laboratory of physiology, Parks Road, Oxford.
Funding: Wellcome Trust, Medical Research Council (UK), Max-Planck-Gesellschaft, Canadian Institutes of Health Research, Oxford McDonnell Centre for Cognitive Neuroscience.



Examples of basic research 2

Experiment 2

Sixty-two ferrets, of whom 39 were albino, were used in this study. Their ages ranged from ten weeks to 24 months.

Eight of the ferrets were anaesthetised and had a radioactive compound injected directly into their left eye. In conjunction with general anaesthesia, a neuromuscular blocking agent was used – the use of such drugs giving cause for special concern, because the paralysis they produce may mask signs of pain.

Other animals were anaesthetised and surgical slits made in the skull through which to insert several electrodes into the brain. In another six albino and six non-albino ferrets, a fluorescent compound was injected directly into the brain. Again, these procedures were made under a combination of anaesthesia and paralysis. The skull wounds were covered and the ferrets allowed to recover from the anaesthetic. Seven more albino animals were anaesthetised and received deep brain injections. These animals were allowed to recover and then euthanased 2-7 days later.

The authors conclude that 'the results presented here on anaesthetised, paralysed pigmented ferrets are similar to previous studies'.

Comment:

The experiment was directed at the discovery of scientific data for its own sake – a crumb amongst the millions of other crumbs of basic research that are discoverable, but totally inapplicable to human or animal health.

Source: Relay of visual information to the lateral geniculate nucleus and the visual cortex in albino ferrets

The Journal of Comparative Neurology 2003, vol 461: 217-235.

Akerman J, Tolhurst D, Morgan J, Baker G, Thompson I.

University Laboratory of Physiology, Oxford.

Funding: Medical Research Council (UK), Wellcome Trust, McDonnell-Pew

Foundation.



7 The peer review process of approving animal research

Peer review, with respect to basic research, is a twin process – it occurs *prior* to an animal experiment taking place and, *once again*, *subsequent* to the data being obtained from the animal research.

The initial peer review is undertaken by Home Office officials and by a local ethical review committee – the latter, at the institution where the research takes place. The task of these two bodies is to examine the research proposal and decide whether to approve it. Assuming the proposal *is* approved, a subsequent review process will be undertaken by an editorial board, *after* the study has been carried out. At this point, the results of the completed research are assessed with respect to publication in a scientific journal.

Based on the above, one might be tempted to conclude that all animal research is conducted and monitored to very high welfare standards. Alas, this is not the case. Leaked documents and undercover video footage have revealed horrific animal suffering and researcher incompetence, which Home Office inspectors failed to detect (2).

8 Critique of the peer review process

It follows that the peer review process that takes place within the research institution, as well as the subsequent Home Office 'cost-benefit analysis' aimed at quantifying animal suffering, should both be open to public scrutiny. In practice, however, this is rarely, if ever, the case. Institutional ethical committees do not contain public representatives, and certainly would not host a scientist with an opposing view.

Leading medical journalists, including the editor of the *British Medical Journal*, have gone on record as saying that '*Peer review is a very flawed practice... and prone to abuse and bias. Much of the time it doesn't pick up errors*' (3). It can also be observed that the peer review community is an elite group who, researchers will acknowledge in private, are not above looking favourably upon a colleague, on the one hand – and being unhelpful to a researcher with whom they have had a scientific or personal dispute.

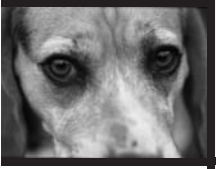
9 Citation analysis

There are certainly more objective ways of assessing animal research than the current peer review system.

One such method is '*citation analysis*' – the process whereby the impact or 'quality' of a piece of science is assessed by counting the number of times other scientists mention it in their work (4). This is particularly suited to animal experimentation in basic research, since the justification for such animal studies invariably points to human benefit.

A recently published study on applications of biomedical research involving animal models makes a compelling case for using citation analysis in the peer review process. The authors of this study investigated the frequency of citations of the animal research in clinical (human) publications. The outcome was unambiguous.

Less than 10 per cent of all citations in the clinical publications contained references to the animal research. More significantly, only in two publications could a direct correlation between the results from animal experiments and observations in humans be noted. However, even in these two cases, the hypotheses that had been verified successfully in the animal experiment failed to yield any clinical advance (5).



10 Conclusion

The acquisition of knowledge for its own sake does not justify inflicting pain and suffering on sentient creatures.

The animal research described above and in the case history is, in our view, not about science or helping human beings through rational research. It is about the search for grants, academic prestige and career development.

The Home Office (Animals Scientific Procedures Division) must clearly take a large share of the blame for reinforcing deficient systems of vetting and

oversight, and thereby allowing repetitive research of unproven scientific merit to gain its seal of approval. Indeed, the Home Office has gone on record as saying that peer review and support of animal research by a reputable funding body *'cannot be taken to guarantee the relevance, importance, or scientific validity of any individual experiment or publication'* (6).

Finally, the charitable organisations that fund animal research urgently need to review their grant-awarding criteria.

References

- (1) Home Office letter to Animal Aid, dated 10 August, 2005.
- (2) Animal experiments: bad ethics, bad science, page 5 (www.animalaid.org.uk)
- (3) 'A question of ethics' – The Guardian, 30 June, 2005.
- (4) freespace.virgin.net/john.hewitt1/pg_gloss.htm
- (5) Lindl T et al. ALTEX 18, 171-178, 2001.
- (6) Home Office letter to Animal Aid, dated 30 August, 2005.



Appendix I: A case study of basic research involving the cardiovascular system

Evaluation of Animal Research at Leeds Medical School
Prepared by John J. Pippin, MD, FACC
Research Consultant, PCRM

01. The effect of stimulation of the atrial receptors on plasma renin activity in the dog. *Journal of Physiology* 1988;398:411-21.

Left atrial balloon distension to stimulate atrial receptors produced reflex decreased plasma renin level and increased urine output. This effect was blocked by cervical vagosympathetic nerve trunk cooling, which the research team concluded meant that the afferent limb of this reflex involves myelinated vagal fibers.

02. The effect of stimulation of left atrial receptors on coronary blood flow in anaesthetized dogs. *Journal of Physiology* 1989;408:45-56.

Left atrial balloon distension, while simultaneously blocking normal reflex tachycardia, results in decreased coronary blood flow. This response was abolished by cooling the cervical vagosympathetic trunk or giving bretylium. The research team concluded that the afferent limb of this reflex response involves myelinated vagal fibers, and the efferent limb involves cardiac sympathetic pathways.

03. The effect of distension of the urinary bladder on activity in efferent vagal fibers in anaesthetized dogs. *Quarterly Journal of Experimental Physiology* 1989;74:493-501.

Bladder distension was produced by volume infusion. In 8 dogs, 11 efferent vagus fibers were identified which responded to changes in carotid artery pressure. These fibers also responded to bladder distension by causing reflex decrease in vagus nerve activity. It was also found that the bladder distension-mediated decrease in vagus activity was affected by the level of carotid sinus pressure.

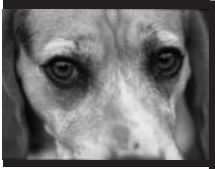
04. Efferent limb of the atrial receptor reflex decrease in plasma renin activity in anaesthetized dogs. *Quarterly Journal of Experimental Physiology* 1989;74:503-9.

Left atrial balloon distension produced decreased plasma renin activity and increased urine output. Tachycardia and natriuresis were blocked. The reflex plasma renin decrease was abolished by renal denervation. The team concluded that the efferent limb of this reflex involves the renal nerves.

05. The effect of distension of the urinary bladder on activity in efferent renal fibres in anaesthetized dogs. *Journal of Physiology* 1989;409:357-69.

Bladder distension was produced by volume infusion. In 11 dogs, 26 efferent vagal fibers were identified which responded to changes in carotid artery pressure. These fibers also responded to bladder distension by increasing renal nerve activity. In 6 other dogs, 13 efferent fibers showed a graded response to bladder distension, which was proportional to intravesical pressure and inversely proportional to carotid artery pressure.

**Appendix I: A case study of basic research
involving the cardiovascular system**



Appendix I: A case study of basic research involving the cardiovascular system

06. The effect of stimulation of the atrial receptors on plasma cortisol level in the dog. *Journal of Physiology* 1989;413:299-313.

Left atrial balloon distension produced reflex decrease in plasma cortisol levels, and increased urine output. Cooling of the cervical vagosympathetic trunk abolished these responses, suggesting that the afferent limb of this reflex involves the vagal nerves. Hypophysectomy abolished the plasma cortisol decrease, but not the diuretic response, suggesting that the efferent limb of this reflex requires the pituitary gland.

07. The effects of ventricular end-diastolic and systolic pressures on action potential and duration in anaesthetized dogs. *Journal of Physiology* 1992;457:75-91.

Performed on open-chest dogs with blockade of autonomic influences on the heart. Elevation of left ventricular peak systolic pressure, while keeping end-diastolic pressure constant, shortened the monophasic cardiac action potential. Elevation of end-diastolic pressure, while keeping peak systolic pressure constant, lengthened the monophasic cardiac action potential. Changes in myocardial segment lengths were compared to ventricular pressures, and suggested that the changes in action potential were related to contraction-excitation feedback.

08. Reflex responses to stimulation of mechanoreceptors in the left ventricle and coronary arteries in anaesthetized dogs. *Journal of Physiology* 1993;472:769-83.

This study was done to identify the mechanism for reflex vasodilation in response to increased aortic root pressure in dogs (demonstrated in other dog research). Cannulations, variable perfusions, and pressure and flow measurements involved the aortic root, left ventricular apex, left atrium, carotid sinuses, and hindlimb arteries. A series of experiments using variable aortic, ventricular and combined pressures suggested that the reflex increased vasodilation due to increased aortic root pressure is from stimulation of coronary artery baroreceptors.

09. Afferent discharges from coronary arterial and ventricular receptors in anaesthetized dogs. *Journal of Physiology* 1993;472:785-99.

This study came directly from the previous study, and was designed to determine if there was a contribution from left ventricular receptors to aortic root pressure-mediated reflex vasodilation. Simultaneous aortic root, left ventricular, coronary arterial and vagus nerve instrumentation, measurements, and changes in pressure were used to assess differential effects and vagal responses. Vagal afferent fibers were classified as myelinated (10) or non-myelinated (11), based upon conduction velocities. Non-myelinated fibers showed variable responses to aortic and ventricular pressure changes, and to drug infusions. Myelinated fibers showed a more consistent and graded response to pressure changes, and were more sensitive to coronary arterial than to left ventricular pressure changes. The team concluded that reflex vasodilation was likely mediated by myelinated vagal afferent fibers, which were likely attached to coronary arterial mechanoreceptors.

10. Reflex vascular responses from aortic arch, carotid sinus and coronary baroreceptors in the anaesthetized dog. *Experimental Physiology* 1996;81:397-408.

Reflex vascular responses to independently altered pressures in aortic, coronary and carotid baroreceptors were measured. Increased pressures produced vasodilation in all cases, more prominently in coronary and carotid baroreceptors. The time for post-vasodilation recovery of vascular resistance was longest for the coronary artery. The reason(s) for this difference was unknown.



11. Delayed sympathetic efferent responses to coronary baroreceptor unloading in anaesthetized dogs. Journal of Physiology 1996;497(part 1):261-9.

This study was to determine whether distension of subdiaphragmatic veins produces reflex vasoconstriction and interacts with the carotid baroreflex. An extensive perfusion circuit was devised to control carotid and thoracic aortic pressures, splanchnic and limb blood flows, and cardiopulmonary blood flows. Elevated splanchnic pressures produced increased carotid baroreflex responses and vasoconstriction in splanchnic and limb vascular territories. These responses were not affected by cutting vagal or phrenic nerves, but were prevented by cutting peripheral nerves supplying the affected regions.

12. Reflex vascular responses to abdominal venous distension in the anesthetized dog. American Journal of Physiology 1996;271(3 part 2):H1049-56.

This study came directly from study #10, and was designed to identify the location of the reflex determinant which results in slower post-vasodilation recovery of vascular resistance after coronary artery pressure changes, compared to carotid artery pressure changes. An extensive perfusion circuit was devised to control aortic root, aortic arch, coronary artery and carotid artery perfusion and pressure. Rapid coronary artery afferent responses to increased and decreased pressures excluded prolonged activation of these afferents as the mechanism. Increased coronary artery pressure produced a reflex decrease in either renal or lumbar sympathetic nerve activity, which recovered slowly after coronary pressure decreased. The team concluded that the delayed recovery of coronary arterial resistance post-vasodilation was due to delayed recovery of the efferent limb of the reflex, mediated by either renal or lumbar sympathetic nerves.

13. Vascular responses to stimulation of carotid, aortic and coronary artery baroreceptors with pulsatile and non-pulsatile pressures in anaesthetized dogs. Experimental Physiology 1996;81: 969-81.

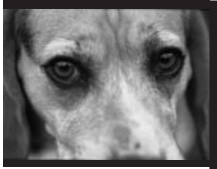
Deriving from several previous studies, this was designed to investigate the ranges of pressures required to elicit various baroreceptor reflex vascular responses, and the influences of pulsatile v. non-pulsatile flow. An extensive perfusion circuit was devised to control perfusion and pressure for the 3 baroreceptor regions investigated. Cardiopulmonary bypass and induced ventricular fibrillation were used to prevent contamination of coronary artery baroreceptor pressure. Data analysis was limited to those dogs which demonstrated specific minimum pressure responses. Reflex responses were obtained at lower coronary perfusion pressures than carotid artery or aortic arch perfusion pressures. Carotid responses, but not coronary or aortic responses, were influenced by pulsatile v. non-pulsatile flow.

14. Mechanisms responsible for changes in abdominal vascular volume during sympathetic nerve stimulation in anaesthetized dogs. Experimental Physiology 1997;82:925-34.

This study was designed to determine whether sympathetic-mediated decreased abdominal blood flow is due to decreased blood volume or vasoconstriction. Abdominal perfusion was controlled for either volume or pressure, and was drained at constant pressure via the IVC. Various experiments demonstrated predominantly vasoconstrictive influence, which was inversely related to the magnitude of sympathetic stimulation. The passive component increased after splenic pedicle ligation, which was interpreted to show that passive volume changes were important after splenic pedicle ligation (!?).

15. Reflex vascular responses to alterations in abdominal arterial pressure and flow in anaesthetized dogs. Experimental Physiology 1997;82:995-1005.

This study was designed to determine if there are abdominal vascular baroreceptors in the dog. Abdominal circulation was isolated, maintained by aortic perfusion, and drained



Appendix I: A case study of basic research involving the cardiovascular system

from the IVC to a reservoir. Perfusion pressure responses were larger at higher carotid sinus pressures. Responses were unaffected by cutting vagus, phrenic and splanchnic nerves, but were abolished by cutting the spinal cord at T12. The team concluded that there is evidence for abdominal baroreceptors, with the afferent pathway involving the spinal cord.

16. Structure and in vitro function of human subcutaneous small arteries in mild heart failure. *American Journal of Physiology* 1998;274(5 part 1):C1298-305.

This study compared morphology, tension generation and response to ramipril for small subcutaneous arteries among patients with mild heart failure and healthy controls. Compared to normal controls and placebo-treated mild heart failure patients, the ramipril-treated patients' arterial segments showed enhanced vasoconstrictor responses to both norepinephrine and angiotensin II. The team concluded that this enhanced response may identify upregulation of receptor-mediated events.

17. Blood mobilization from the liver of the anaesthetized dog. *Experimental Physiology* 1998;83:513-22.

This study was designed to evaluate the contribution of the liver to overall abdominal vascular capacitance and compliance in the dog. The liver was vascularly isolated, perfused through the hepatic artery and portal vein, and drained at constant pressure from the hepatic veins. Results indicated that the dog's liver (like the spleen in other experiments) has a major capacitance role and is highly compliant. The team suggested that if this is also true for humans, the liver would be the most important controllable blood reservoir in the body.

18. Reflex vascular responses in the anaesthetized dog to large rapid changes in carotid sinus pressure. *American Journal of Physiology* 1998;275(4 part 2):H1169-77.

This study examined reflex vascular responses to large rapid increases and decreases in carotid sinus pressure. An extensive perfusion circuit was devised to control perfusion and pressure in the carotid sinus, thoracic aorta, abdominal circulation and a hindlimb. Results showed that reflex-mediated vasodilation occurred more rapidly and more completely than vasoconstriction. The team concluded that if similar findings occurred in humans in response to alternating gravitational forces, there may be a predisposition to syncope.

19. Reflex control of splanchnic blood volume in anaesthetized dogs. *Journal of Physiology* 1998;513(part 1):263-72.

Various vascular isolation techniques were used to control perfusion and pressure within splenic, hepatic and caudal circulations. These regions were drained through the IVC, portal and femoral veins. Variation of carotid sinus pressure showed greater volume changes during constant pressure perfusion than during constant volume perfusion. The liver's capacitance role greatly exceeded that of the splanchnic circulation, but large passive changes in splanchnic flow occurred in response to flow changes.

20. Absence of early resetting of coronary baroreceptors in anaesthetized dogs. *Journal of Physiology* 1998;513(part 2):543-9.

This study was designed to determine whether coronary baroreceptors reset differently from carotid and aortic arch baroreceptors, after sustained distension at low and high pressures. An extensive perfusion circuit was devised to control perfusion and pressure in the carotid, aortic arch and coronary artery baroreceptors. Results indicated rapid resetting of carotid baroreceptors, but delayed resetting of coronary baroreceptors.



21. Reflex responses from the main pulmonary artery and bifurcation in anaesthetized dogs. *Experimental Physiology* 2000;85:411-20.

Open-chest dogs with cardiopulmonary bypass and blockade of secondary modulation of responses from other reflexes. Proximal aspects of the pulmonary circulation were vascularly isolated, perfused through the left PA, and drained through the right PA to maintain desired PA pressure. Results showed that pulmonary baroreceptor stimulation produces proportional pressor and hyperventilatory responses. Greater vascular responses were obtained at lower PA pressures when negative thoracic pressure was introduced, *indicating that the response would likely be greater in a closed-chest animal.*

22. Absence of reflex vascular responses from the intrapulmonary circulation in anaesthetized dogs. *Experimental Physiology* 2000;85:421-30.

Open-chest dogs with cardiopulmonary bypass and blockade of reflexogenic mechanisms not being measured in the study. Left lung vascular territory was isolated, and was perfused through the left PA and drained through the left pulmonary veins. Pressures were controlled to the carotid, aortic and coronary baroreceptors, and to the heart chambers. Results indicated that the lung was innervated, but changes in pulmonary arterial or venous pressure did not produce changes in systemic or limb vascular resistances. Different dogs showed different results in responses to pulmonary pressure changes and effects upon phrenic nerve activity.

23. Reflex effects of independent stimulation of coronary and left ventricular mechanoreceptors in anaesthetized dogs. *Journal of Physiology* 2000;528:349-58.

This study was designed to examine reflex responses to independently controlled stimulation of ventricular and coronary artery mechanoreceptors. Manipulations performed included mechanical ventilation, cardiopulmonary bypass, balloon occlusion of LV outflow to prevent coronary perfusion, LV apical cannulation to regulate LV volume, carotid and aortic root cannulation to regulate pressures. Results indicated that coronary baroreceptors were important for cardiovascular hemodynamic control, with minimal if any contribution from ventricular mechanoreceptors. The authors note that this is contrary to previous dog studies which showed significant reflex responses attributed to ventricular mechanoreceptors.

24. Reflex vascular responses to independent changes in left ventricular end-diastolic and peak systolic pressures and inotropic state in anaesthetized dogs. *Journal of Physiology* 2001;532 (part 2):549-61.

This study was designed to examine the nature and physiological role of ventricular mechanoreceptor-mediated reflex vasodilation in the dog. Manipulations included mechanical ventilation, cardiopulmonary bypass, isolation of ventricular pressures from the coronary arteries and aorta by a LV outflow tract balloon, and cannulation of the LV apex, carotid and coronary arteries, aortic root and abdominal aorta. Increased carotid or coronary pressure produced vasodilation, which was unaffected by inotropic stimulation or changes in ventricular peak systolic pressure, and was influenced in a small but proportional manner by increases in end-diastolic pressure. The team concluded that the only effective ventricular determinant of reflex responses was increased filling volume, and that the influence was so small as to be unimportant under normal conditions.

25. Responses to stimulation of coronary and carotid baroreceptors and the coronary chemoreflex at different ventricular distending pressures in anaesthetized dogs. *Experimental Physiology* 2001;86:381-90.

This study was done because most previous work involving the effects of ventricular mechanoreceptors was flawed due to inadequate localization of stimuli to specific



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reflexogenic areas (authors' words). Manipulations included mechanical ventilation, cardiopulmonary bypass, aortic valve balloon obstruction, and cannulation of the LV apex, carotid and coronary arteries, and aorta. Results showed that ventricular mechanoreceptor stimulation, either alone or in conjunction with changes in other reflexogenic areas, has minimal effect on reflex responses.

26. Influence of dietary salt intake on the response of isolated perfused mesenteric veins of the dog to vasoactive agents. *American Journal of Hypertension* 2003;16:6-10.

This study was designed to examine the influence of dietary salt intake upon the vasoconstrictor response of capacitance vessels in the dog. Lengths of mesenteric vein were studied *ex vivo*, after feeding dogs low, intermediate and high salt diets. Vascular responses to cumulative doses of norepinephrine and acetylcholine were determined. Results demonstrated greater vasoconstrictive response to both drugs in dogs fed high salt diets, and it was suggested that this may explain the hypertensive effects of dietary salt in humans.

27. Phasic negative intrathoracic pressures enhance the vascular responses to stimulation of pulmonary arterial baroreceptors in closed-chest anaesthetized dogs. *Journal of Physiology* 2004;555(part 3):815-24.

This study came from the study (# 21) which showed greater responses to pulmonary baroreceptor reflexes in the presence of negative intrathoracic pressure, suggesting that a closed-chest model may be more accurate. Manipulations included mechanical ventilation, cardiopulmonary bypass, isolation of pulmonary perfusion, and cannulation of the carotid and coronary arteries, aortic arch and abdominal aorta. Using apparently arbitrary definitions of threshold pressures, set points and rates of change, the effects of phasic intrathoracic pressures upon the stimulus-response curve of PA baroreceptors was examined. Results showed displacement of the stimulus-response curve to lower pressures during phasic (presumably physiological) intrathoracic pressures.

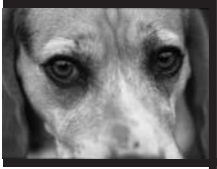
28. Pulmonary arterial distension and vagal afferent nerve activity in anaesthetized dogs. *Journal of Physiology* 2004;555(part 3):805-14.

This study was a variation of the above study (# 27), designed to examine afferent activity from pulmonary baroreceptors under conditions of simulated physiological changes in intrathoracic pressure. Manipulations included mechanical ventilation, cardiopulmonary bypass, isolation of pulmonary perfusion, pulsatile pulmonary perfusion to simulate physiological blood flow, monitoring of vagus nerve impulses, and use of open and closed-chest measurements. Results showed that pulmonary baroreceptor activity was triggered at lower perfusion pressures in closed-chest dogs with phasic negative intrathoracic pressure.



Critique of the research work

01. By way of overview, this team's research involves a single area of physiological expertise and a single animal preparation. It has successfully mined those attributes to carry out largely repetitive and unproductive animal studies, using their own and others' previous findings (often incorrect, as noted by the team in the justifications for some studies) to carry on with minor variations upon very few central themes. By doing so, they have published scientific articles for over 16 years, without apparent correlation with, or influence upon, similar areas of human physiology or medicine. This body of work amounts, in my view, to a startling example of the pursuit of disconnected scientific knowledge with no clear human benefits, and to the detriment of dogs.
02. Twenty-seven of 28 published papers reported studies in anaesthetized dogs, and other than variations in the extent of instrumentation and manipulation, this was a single animal preparation. I am not aware of other such long basic science research projects using such a narrow focus.
03. The team mined the research area related to atrial and ventricular receptors and responses for several years, then switched to evaluation of vascular baroreceptors for several more years, then switched to evaluation of pulmonary baroreceptors for the most recent several years. The nature of their research was very similar in all three closely related areas, enabling them to do the same basic research with small variations for a very long time, and without conspicuous human benefit.
04. Very evident in this collection of papers is the characteristic use of one study to justify the next. In many cases, unanswered (usually unforeseen) questions arising from one study produced the rationale for a later study. In several instances, the team invoke conflicting or erroneous results from previous studies (sometimes their own) to justify another study.
05. In many of the reports, the team draw conclusions from study results in the absence of any apparent study hypothesis. This suggests that they may have developed their hypotheses from the results of these studies.
06. In many cases, the team do not suggest how study results may relate to human physiology or disease.
07. In several studies, the team report variable physiological responses among animals subjected to the same experimental conditions, or appear to select animals with specific responses for data analysis. Are they excluding animals who don't produce predetermined responses, or who have uninterpretable results? In either case, this likely invalidates the study results and conclusions.
08. I do not see evidence that the team correlate their study results with similar investigations in humans. Even when they suggest how specific findings may be important for humans (such as with gravitational changes, blood volume regulation or salt loading), the team do not correlate with relevant findings from human studies or provide data to suggest similar mechanisms.
09. Virtually all of the team's studies could be classified as irrelevant to human disease and medicine, even if they weren't biologically and mechanistically unsupportable.

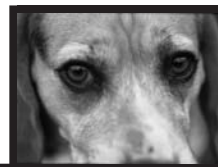


This is because the neural and biomechanical mechanisms they examined in dogs have been known for many years in humans.

10. There is an extreme degree of manipulation of the team's dog model to create non-physiological conditions of convenience favoring their investigations. Their basic dog model is anaesthetized, mechanically ventilated, extensively cannulated, and rendered useless by artificial isolation of the circulations to be studied. Aside from the well-documented effects of such stresses upon research animals' physiological and biochemical responses, such manipulations completely remove the animal model from the influences of an intact and interactive biological system.

When a major argument for such animal research is the need for 'an intact biological system', the extensive modifications of anatomy, physiology, perfusion, respiration, intrathoracic pressure, sympathetic innervation and many other characteristics of that intact system make these study results non-physiological and lacking relevance... even for dogs, let alone humans. Just one example is the team's own recognition that the open-chest dog model used in many of their studies produces different baroreceptor responses than a closed-chest model, and is thus not valid.

11. The extent of manipulation of this dog model is truly ingenious and technically challenging. Such manipulations include not only all those mentioned above (#10), but also variable and non-physiological patterns of perfusion to isolated vascular territories, artificial and contrived patterns of vascular drainage to maintain pressures within a vascular territory, the use of external reservoirs to recirculate blood, cutting of the spinal cord and various nerves (vagus, renal, phrenic, splanchnic and peripheral), simulated pulsatile flow and respiratory intrathoracic pressure changes, *ex vivo* measurements of vascular responses, balloon occlusions of pulmonary veins and LV outflow tract, LV apical cannulation, blockade of reflexogenic mechanisms which may influence those being studied, and sustained ventricular fibrillation to eliminate influence on coronary artery baroreceptors.
12. In one study (#13) designed to evaluate various baroreceptor responses, the animal model was a VF dog maintained on life support for the purpose of the study. Even under these conditions, data analysis was limited to dogs with specific desired responses. Under what circumstances could this animal model, or any of the extensively compromised animals used in these studies, produce results worthy of consideration? How can we imagine there may be some association with human responses, when the responses are not even applicable to the species being studied?
13. This work provides an exceptional example of a common practice: the manipulation of animal models for convenience and usefulness, regardless of the effects upon the validity of results obtained. This is not uncommon among those researchers who propose and perform studies to satisfy their scientific curiosity and sustain their careers, without sufficient regard for potential applications to humans.



Appendix 2: Curriculum Vitae

Personal Information

Name: John J. Pippin, M.D., F.A.C.C.
Home Address: 6716 Gold Dust Trail
Dallas, Texas 75252-5915
(972) 407-9396
jjpippin@sbcglobal.net
Date of birth: January 7, 1950
Place of birth: Brookline, Massachusetts

Education

1971 A.B. (European History), Harvard College
Cambridge, Massachusetts
1980 M.D., University of Massachusetts Medical School
Worcester, Massachusetts

Postdoctoral Training

Internship and Residency

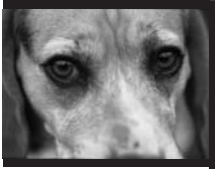
1980-81 Intern in Medicine
New England Deaconess Hospital, Boston, Massachusetts
1981-83 Resident in Medicine
New England Deaconess Hospital, Boston, Massachusetts
1983-84 Chief Medical Resident
New England Deaconess Hospital, Boston, Massachusetts

Fellowships

1984-86 Fellow in Cardiovascular Disease
New England Deaconess Hospital, Boston, Massachusetts
1986-87 Research Fellow in Nuclear Cardiology
University of Texas Southwestern Medical Center and
Parkland Memorial Hospital, Dallas, Texas

Licensures and Certifications

1981 Massachusetts License, Registration No. 48194
1983 American Board of Internal Medicine, Certification No. 92336
1987 ABIM Certification, Cardiovascular Disease
1987 Virginia License, Registration No. 41616
1990 Authorized User of Radiopharmaceuticals
(Nuclear Regulatory Commission Certification)
1991 Oklahoma License, Registration No. 17837



1997 Nuclear Cardiology Certification
Certification Board of Nuclear Cardiology

1998 Texas License, Registration No. K4984

Academic Appointments

1980-83 Clinical Fellow in Medicine
Harvard Medical School, Boston, Massachusetts

1983-86 Instructor in Medicine
Harvard Medical School, Boston, Massachusetts

1987-91 Assistant Professor of Medicine and Radiology
Medical College of Virginia, Richmond, Virginia

1993-97 Clinical Associate Professor of Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma (Tulsa campus)

Administrative Appointments (Clinical and Research)

1987-91 Director, Cardiovascular Stress Laboratories
Medical College of Virginia, Richmond, Virginia

1987-91 Co-Director, Nuclear Cardiology
Medical College of Virginia, Richmond, Virginia

1989-91 Director, Cardiology Fellowship Program
Medical College of Virginia, Richmond, Virginia

1989-91 Research Peer Review Committee
American Heart Association, Virginia Affiliate

1991-97 Medical Director, Nuclear Cardiology
Hillcrest Medical Center, Tulsa, Oklahoma

1994-97 Founding Director, Cardiovascular Assessment Center
William H. Bell Heart & Lung Institute
Hillcrest Medical Center, Tulsa, Oklahoma

1995-97 Founding Director, James D. Harvey Center for
Cardiovascular Research
William H. Bell Heart & Lung Institute
Hillcrest Medical Center, Tulsa, Oklahoma

1995-97 Chairman, Institutional Review Board
Hillcrest Medical Center, Tulsa, Oklahoma

1995-97 Member, Institutional Review Board
University of Oklahoma Health Sciences Center
Tulsa, Oklahoma

1998-2004 Founding Director, Cardiovascular Medicine Department
Cooper Clinic, Dallas, Texas

2003-04 Founding Director, Medical Imaging Division
Cooper Clinic, Dallas, Texas



Administrative Appointments (Non-clinical)

1989-91	Coursemaster, M II Cardiovascular Medicine Medical College of Virginia, Richmond, Virginia
1989-91	Internal Medicine Intern Selection Committee Medical College of Virginia, Richmond, Virginia
1991-97	Medical Director, Tulsa Run, Tulsa, Oklahoma
1992-94	Infection Control Committee Hillcrest Medical Center, Tulsa, Oklahoma
1992-96	Patient Advisory (Bioethics) Committee Hillcrest Medical Center, Tulsa, Oklahoma
1994-96	Member, Physician Advisory Committee Hillcrest Medical Center, Tulsa, Oklahoma
1994-96	Member, Board of Directors Partnership Health Organization Hillcrest Medical Center/Physician PHO

Hospital Staff Appointments

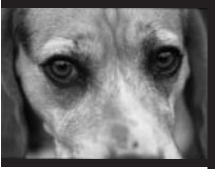
1980-86	New England Deaconess Hospital, Boston, Massachusetts
1987-91	Medical College of Virginia Hospital, Richmond, Virginia
1987-91	McGuire Veterans Administration Medical Center Richmond, Virginia
1991-97	Hillcrest Medical Center, Tulsa, Oklahoma
1991-97	St. John Medical Center, Tulsa, Oklahoma
1994-97	St. Francis Hospital, Tulsa, Oklahoma

Professional Memberships

American College of Cardiology, Fellow
Texas Chapter, American College of Cardiology
American Society of Nuclear Cardiology, Founding Fellow
Texas Medical Association
Dallas County Medical Society
American Society of Hypertension

Awards and Honours

1967	National Merit Semifinalist
1979	Alpha Omega Alpha Medical Honor Society University of Massachusetts Medical School
1981	James L. Tullis Award, New England Deaconess Hospital Boston, Massachusetts



Appendix 2: Curriculum Vitae

1985	Invited Speaker and Panelist American College of Cardiology Extramural Conference New York, New York
1986-91	Clinician-Scientist Award American Heart Association
1989	Invited Speaker, Society of Nuclear Medicine Mideastern Chapter Annual Conference Charlottesville, Virginia
1989	Cardiology Professor of the Year (Fellows' Award) Medical College of Virginia, Richmond, Virginia
1990	Cardiology Professor of the Year (Fellows' Award) Medical College of Virginia, Richmond, Virginia
1990	Cardiology Professor of the Year (Students' Award) Medical College of Virginia, Richmond, Virginia
1996	Invited Speaker and Panelist NIH National Human Subjects Protection Workshop Oklahoma City, Oklahoma
1997	Invited Speaker and Panelist Society of Nuclear Medicine Southwestern Chapter Annual Conference New Orleans, Louisiana
1997- current	Who's Who in Medicine and Healthcare Who's Who in Science and Engineering Who's Who in America Who's Who in the World



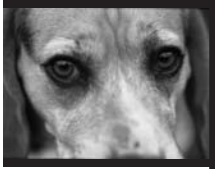
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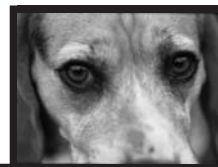
Published Articles

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2. **Pippin JJ**. Breast cancer: screening modalities, results and recommendations. Worcester Medical News, July 8, 1979:10-2.
3. **Pippin JJ**. Breast cancer: the benefits and risks of mammography and breast self-examination. Worcester Medical News, September 10, 1979:16-9.
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1. **Pippin JJ**, Devers SM, Whitehead RY, Buckner DJ, Weilbacher DC, Kettles MA: The ST hump sign: a reliable indicator for false positive electrocardiographic response during treadmill exercise testing.
2. **Pippin JJ**, Devers SM, Henderson YL, Zavala E III, Buckner DJ. Comparison of peak exercise and immediate postexercise blood pressures during treadmill exercise testing: results and clinical implications.

Revised: September 2005 (jjp)