

# Radio-Telemetry

a tool in humane endpoint determination ?

René Remie

International Microsurgical Training Centre, Lelystad, The Netherlands  
Department of Bio-monitoring & Sensoring, University Centre for Pharmacy, Groningen University, The Netherlands  
Solvay Pharmaceuticals BV, LASW, P.O. Box 900, Weesp, The Netherlands

Transmitting data captured by instrumentation and measuring devices to a remote station where it is recorded and analyzed. For example, data from a weather satellite is telemetered to earth

## Agenda

- ◆ What is a humane end-point
- ◆ When to use humane end-points
- ◆ How to use humane end-points
- ◆ Telemetry
  - ✦ Wireless reporting technology
  - ✦ ICH Guidelines (S7A,B)
  - ✦ Current possibilities
- ◆ Some examples
  - ✦ From simple toward complicated
- ◆ Should we implant devices just to assess or revise endpoints?

## What is a humane end-point?

OECD:

- ◆ A humane endpoint can be defined as the earliest indicator in an animal experiment of severe pain, severe distress, suffering, or impending death.

## When to use humane end-points

- ◆ Applicable in any study that leads to pain or death!
  - ✦ Pharmacological research
  - ✦ Toxicology
  - ✦ Cancer studies
  - ✦ Vaccine research and quality control
    - ◆ Pertussis, rabies etc.
  - ✦ Testing of other biologicals
    - ◆ diphtheria, tetanus
  - ✦ Infection models
    - ◆ BSE

Modified from Dag Eide

## How to use humane end-points

- ◆ Biomarkers
  - ✦ urine, blood, histology of early signs
- ◆ Clinical signs
  - ✦ OECD's long list
- ◆ Microchip implant systems
  - ✦ Telemetry: Temp, Blood pressure, heart rate..

Modified from Dag Eide

## Telemetry Systems

Wireless reporting technology

- ◆ Non-implanted Systems
- ◆ Partially-implanted Systems
- ◆ Fully-implanted Systems

## Telemetry Systems

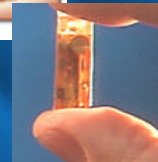
Wireless reporting technology

- ◆ Non-implanted Systems
  - ✦ Surface bio-potentials
  - ✦ GI capsules

## Given M2A Camera and Medtronic ph sensor



- ◆ Given swallow able TV camera for diagnosis of gastric bleeding or determination of gastric emptying and transit
- ◆ Medtronic Bravo ph capsule for measurement of gastric reflux



## Telemetry Systems

Wireless reporting technology

- ◆ Partially-implanted Systems
  - ✦ Back-pack systems (trans-cutaneous connections)
    - ◆ Pressures
    - ◆ Flows (probes and other high current devices)
    - ◆ Bio-potentials

## Telemetry Systems

Wireless reporting technology

- ◆ Fully-implanted Systems
  - ✦ Transponders (powered by external inductance)
    - ◆ Read-only
    - ◆ Programmable
      - + ID
      - + Temperature
  - ✦ Hermetically sealed transducers-radio transmitters including power supply



## Telemetry Systems

Wireless reporting technology

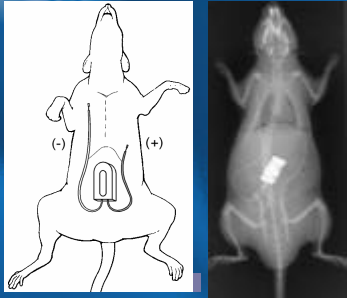
- ◆ Transmitters
  - ✦ Temperature
  - ✦ Activity
  - ✦ Pressures
    - ◆ Blood (arterial & venous)
    - ◆ Ventricular
    - ◆ Ocular
    - ◆ Pleural (indirectly respiratory rate)
    - ◆ Intra-cranial
  - ✦ ECG (heart rate, QT-intervals)
  - ✦ EMG
  - ✦ EEG
  - ✦ Blood flow
  - ✦ Bio-potentials
    - ◆ Coupled to all kind of biosensors (pH, etc)
    - ◆ Bio-impedance cardiography

## Tiny animal telemetry devices

- ◆ Mouse
  - ✦ Transgenic
- ◆ Hamster
- ◆ Neonatal rat
- ◆ Exotic
- ◆ Fish
- ◆ Grasshopper
- ◆ Sparrow



### Rat ECG Device Placement

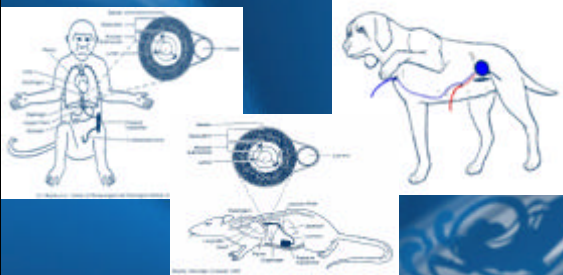


### Rat BP and ECG Device Placement

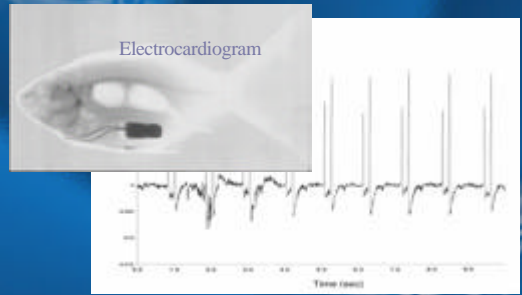


### Telemetry for Intra pleural pressure

- ◆ Primates, canines and rodents

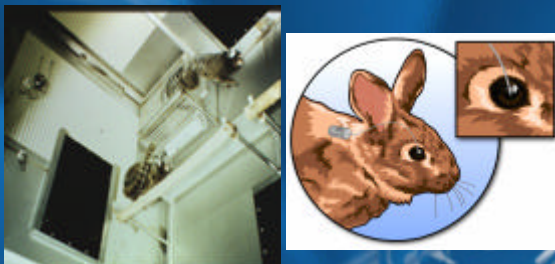


### Telemetry for Fish (*Carassius auratus*)

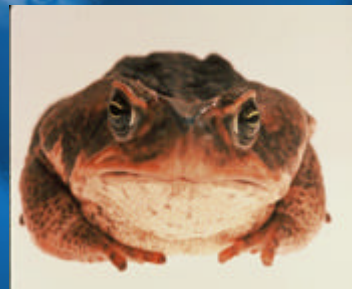


### Telemetry for Intra-Ocular Pressure

Marmosets, Rhesus, and Rabbits



### Telemetry for Amphibians

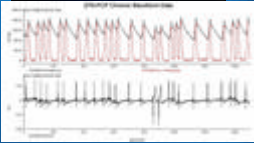


## Multiple channel devices



### D70-PCTP

- Provides measurement of 2 pressures, ECG, temperature and activity in large animals (dogs, primates, etc.)
- Measurement of systemic and intra-pleural pressure
- Measurement of systemic and LV pressure

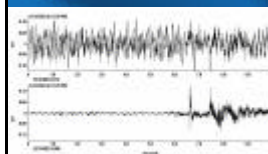


## EEG in the mouse



### F20-EET transmitter

- 2 biopotentials, temperature, activity in mice
- Small transmitter size
- Applications in sleep, seizure, and EMG studies



## Refinement by Radio-telemetry

- Handling and Restraint
  - Increase Blood Pressure and Heart Rate
  - Increase Body Temperature
  - Increase Rectal Temperature
  - Increase Norepinephrine
  - Increase Epinephrine
  - Decrease Oxygen consumption
- Anesthesia has its effect on the animal and the results

## Equine BP measurement... 1714



- First scientific measure of equine arterial pressure
- Brass tube inserted into horse artery measured pressure ...and killed horse

## Refinement by Radio-telemetry

- Minimizes stress
- Automates measurements
- More humane
- Provides accurate and predictive data

## ICH Guidelines

The International Conference on Harmonization: Guideline on Safety Pharmacology Studies Evaluation for Human Pharmaceuticals (S7A) states that:

*'in conducting in vivo studies it is preferable to use unanesthetized animals' and that 'data from unrestrained animals that may be chronically instrumented for telemetry or other suitable instrumentation methods for conscious animals...are preferred'.*

The preparation and use of conscious instrumented animals is explicitly regulated under the Animal Welfare Act (CFR 9) and its international equivalents, United States Public Health Service Policy on Care and Use of Laboratory Animals (USPHS), the Guide for the Care and Use of Laboratory Animals (ILAR Guide), and numerous professional 'white papers'. There are potentially significant consequences for both scientists and institutions for non-compliance.

## From simple to complicated

- ◆ KISS
  - † Easy applicable
    - ◆ No surgical intervention
    - ◆ No anesthesia
  - † Reliable
  - † Cost effective

## From simple to complicated

- ◆ Non-implanted Systems
  - † Surface bio-potentials ☹
  - † GI capsules ☺
- ◆ Transponders (powered by external inductance)
  - † ID
  - † Temperature
    - ◆ Hartinger et al.2001 ☹
      - ◆ Rabies vaccine control test, temp. drop too late to be of use
    - ◆ Kort et al. 1998 ☺

### Kort et al. Lab Ani. (1998) 32, 260-269

Table 1 Mean body temperatures of rats during the course of experiment, either recorded by transponder or rectally

Rats	Transponder (n = 34)		Transponder (n = 44)	
	Subcutaneous	Intraperitoneal	Subcutaneous	Intraperitoneal
Mean T1	36.6 ± 0.22	37.1 ± 0.20		
Mean T2	36.7 ± 0.23	37.0 ± 0.20		
Mean T3	36.7 ± 0.24	36.8 ± 0.20		
Shift T1-T2	-0.12 ± 0.04	-0.01 ± 0.04		
Shift T1-T3	-0.07 ± 0.05	-0.25 ± 0.06		
SD <sub>paired</sub> T1-T2	0.15	0.16		
SD <sub>paired</sub> T1-T3	0.21	0.28		

T1 = first recording of the body temperature by transponder  
 T2 = second recording of the body temperature by transponder  
 T3 = body temperature established rectally  
 Shift T1-T2 = mean difference between T1 and T2  
 Shift T1-T3 = mean difference between T1 and T3  
 SD<sub>paired</sub> see M&M Statistics

Klebsiella pneumoniae, intratracheal inoculation  
 T < 36°C → median survival time 24 h. (two out of three animals)

### Kort et al. Lab Ani. (1998) 32, 260-269

Table 2 Mean body temperatures of mice during the course of experiment, either recorded by transponder or rectally

Rats	Transponder (n = 43)		Transponder (n = 55)	
	Subcutaneous	Intraperitoneal	Subcutaneous	Intraperitoneal
Mean T1	37.2 ± 0.42	36.7 ± 0.19		
Mean T2	37.4 ± 0.43	36.9 ± 0.18		
Mean T3	36.9 ± 0.46	37.2 ± 0.21		
Shift T1-T2	-0.23 ± 0.06	+0.22 ± 0.07		
Shift T1-T3	+0.23 ± 0.11	+0.55 ± 0.13		
SD <sub>paired</sub> T1-T2	0.29	0.36		
SD <sub>paired</sub> T1-T3	0.49	0.70		

T1 = first recording of the body temperature by transponder  
 T2 = second recording of the body temperature by transponder  
 T3 = body temperature established rectally  
 Shift T1-T2 = mean difference between T1 and T2  
 Shift T1-T3 = mean difference between T1 and T3  
 SD<sub>paired</sub> see M&M Statistics

## From simple to complicated

- ◆ Partially-implanted Systems ☹
  - † Back-pack systems (trans-cutaneous connections)
    - ◆ Pressures
    - ◆ Flow probes (and other high current devices)
    - ◆ Bio-potentials
- ◆ Are going to be replaced by fully implantable devices in the near future

## From simple to complicated

- ◆ Fully-implanted Systems ☹☺
  - † Hermetically sealed transducers-radio transmitters including power supply

## Possible parameters for humane endpoints

- Temperature
- Activity
- Pressures
  - + Blood (arterial & venous)
  - + Ventricular
  - + Ocular
  - + Pleural (indirectly respiratory rate)
  - + Intra-cranial
- ECG (heart rate, QT-intervals)
- EMG
- EEG
- Blood flow
- Bio-potentials
  - + Coupled to all kind of biosensors (pH, etc)
  - + Bio-impedance cardiography

## Joint Working Group on Refinement, Ethical justification

The Working Group considered whether animals should be implanted with devices specifically for assessing and revising end-points, or whether this should only be an incidental benefit of instrumentation that is a necessary part of the project. It was concluded that, on a case-by-case basis, any adverse effects associated with implantation purely for monitoring purposes should be considered against the potential to refine the endpoint and the predicted level and duration of suffering that this will prevent (see Kort *et al.* 1999). Animals should not be implanted with telemetry devices that are scientifically unnecessary to the study unless it is certain that they will benefit, and the balance of harms and benefits will need to be fully and critically considered in each case by the scientists as well as by the relevant ethics or animal care and use committees.

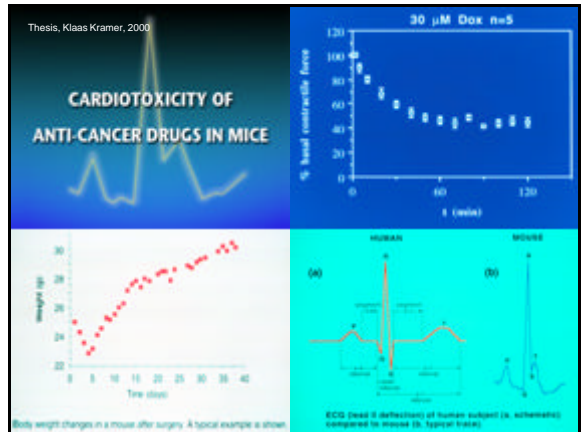
## Joint Working Group on Refinement, Ethical justification

### Recommendations:

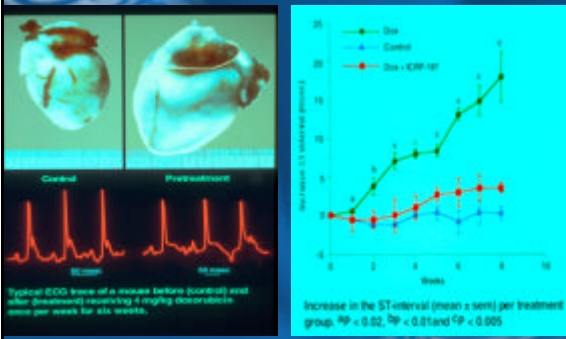
- Think beyond using telemetry solely to obtain the scientific data that you require, use it to assess and monitor animal well-being and to refine procedure: and husbandry wherever possible.
- If telemetry is used in toxicology or disease studies, regularly review the data to see whether there are any indicators that would enable humane endpoints to be further refined.

Thesis, Klaas Kramer, 2000

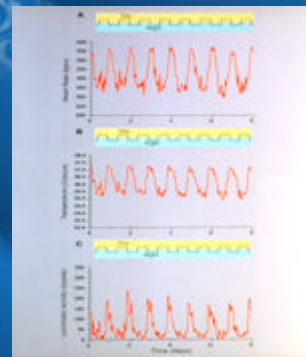
### CARDIOTOXICITY OF ANTI-CANCER DRUGS IN MICE



## ST-interval measures telemetrically



## Circadian rhythm



In case time and the chairman allows  
Other recent techniques

- ◆ Remote sensing
  - † Biophotonic imaging
    - ◆ Acousto-optical tomography (AOT)
    - ◆ Photo-acoustic tomography (PAT)
  - † MRI

Ultrasound-mediated imaging techniques

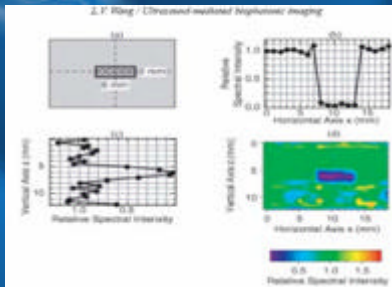
J. P. Wang / Ultrasound-mediated biophotonic imaging

Table 1

Motivation for acousto-optical tomography (AOT) and photo-acoustic tomography (PAT). For comparison purposes, we chose optical coherence tomography (OCT) and diffuse optical tomography (DOT) as the pure optical imaging modalities and ultrasonography (US) as the pure ultrasound imaging modality.

Properties	Modalities			AOT/PAT
	OCT	DOT	US	
Contrast	Good	Excellent	Poor for early cancers	Excellent (= DOT)
Resolution	Excellent (~10 μm)	Poor (~5 mm)	Excellent & scalable (~150 μm)	Excellent (= US)
Imaging depth	Poor (~1 mm)	Excellent (~5 cm)	Good & scalable (~3 cm)	Good & scalable (= US)
Speckle artifacts	Strong	None	Strong	None
Scattering coefficient	(~100/cm)	(~100/cm)	(~0.5/cm)	

Biophotonic imaging



Biophotonic imaging

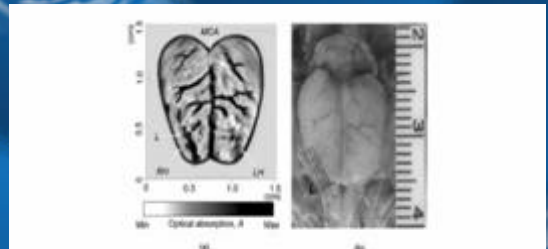
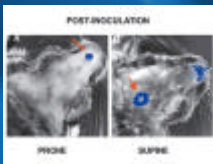


Fig. 9. a. Non-invasive PAT image of a supratentorial lesion (3 mm × 4 mm, in the right cortex cortex-artery thrombosis) on a rat's cranium acquired with the skin and skull intact. RH, right cerebral hemisphere; LH, left cerebral hemisphere; and L, lesion. The blood vessels distributed on both sides of the middle cerebral artery (MCA) are imaged clearly. The matrix size of the image was 1000 (horizontal) × 1000 (vertical), showing a 1.5 cm × 1.5 cm region. b. Open-skull photograph of the rat cranium surface acquired after the PAT experiment.

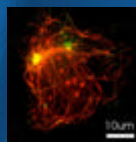
Biophotonic imaging of nontypeable *H. influenzae* during experimental otitis media

[http://www.microbial-pathogenesis.org/H\\_influenzae\\_86028/index.php?contents.php&file.html&bodya.php?article\\_id=40&Example\\_Session=da5dd494977e67558489676e83b4b2](http://www.microbial-pathogenesis.org/H_influenzae_86028/index.php?contents.php&file.html&bodya.php?article_id=40&Example_Session=da5dd494977e67558489676e83b4b2)

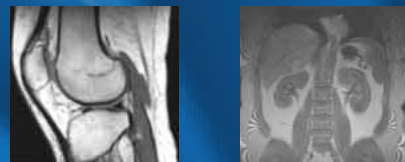


"...biophotonics [is becoming] a field that will drive the discovery of new principles of cellular and molecular biology."

- 2004, *Nature Reviews Molecular and Cellular Biology*



Magnetic resonance imaging (MRI)



## Take home messages

- ◆ Radio-telemetry is a valuable tool
- ◆ Spin-off from the experimental approach
  - + Determine indicators up front
  - + Constantly look for possible refinement in the data
- ◆ No complex surgical intervention for humane endpoints per se
  - + Balance of benefits
- ◆ Transponders can help!
- ◆ Use remote sensing techniques
  - + Biophotonicimaging
  - + MRI