Good welfare – good scientific output: Refining husbandry and procedures for primates in the laboratory

Hannah M. Buchanan-Smith & Lou Tasker

University of Stirling, Scotland

Janet Kelly

Covance, UK
Why primates?

Total: 4,688 procedures in 2010, and 66% in toxicology

Same principles

Figure 4: Procedures using non-human primates, 1995-2010

Source: Home Office. *Statistics of Scientific Procedures on Living Animals Great Britain*
Refinement is about animal welfare: “Any approach which avoids or minimises the actual or potential pain, distress and other adverse effects experienced at any time during the life of the animals involved, and which enhances their well-being” Buchanan-Smith et al., 2005
Promoting good welfare

- Social housing
- Appropriate weaning age
- Large, complex enclosures
- Socialisation with humans
- Positive reinforcement training
Laboratory Environment

- Rearing Environment
- Study Protocol
- Designated Establishment
- Transport

- Family separation
- Socialisation and PRT
- Enrichment
- Rearing practices
- Prenatal stress
- Restraint
- Dosing
- Sampling
- Capture
- Journey
- Handling
- Health screening
- Behavioural restriction
- Complex enclosures
- Husbandry inc. socialisation
In vivo model in regulatory toxicology

Battery of measures

Evaluate effects and signs of toxicity

Repeated measures

ECG
BP

Cardiovascular
Respiratory
Central nervous system
Ocular
Renal
Gastro-intestinal
Hepatic

Clinical pathology
Haematology & Clinical Chemistry
General health
Body weight change

Organ weights
Gross Pathology
Histopathology
Overlapping measures – toxicity and welfare

Physical
coat & body condition, body weight fluctuation
longevity, growth rate, susceptibility to disease, reproduction and infant care, individual nutritional requirements, wound healing, post-mortem indicators.

Clinical
heart rate, blood pressure, haematology, biochemistry, body temperature, cortisol, immunological functions.

Behavioural
repertoire & activity budgets (including grooming, sleeping, play, social and aggressive behaviours, facial expressions and vocalizations).

JWGR (2009)
The link between good welfare & good scientific output

Good welfare
- Normal and stable
- Acclimatised (NRC 1996; Weed & Raber 2005)

Good scientific output
- Valid – the right measure!
- Reliable & Repeatable (precision, consistency, absence of confounding factors & unplanned variation)

The link
- Compromised welfare affects behaviour, physiology and immunology
- unreliable conclusions?
- unwanted variation in scientific output?
Repeatability - Acclimatisation

Rhesus macaques, 6 mo acclimatisation (n=6m, 6f)

Week 1 after arrival - habituation to:
• Body-touching and hand-feeding (every day),
• 10 min chair restraint (twice a week),
• Water gavage (twice a week)
• Blood sampling and ECG recordings (every month)

Is 6 month acclimatisation period sufficient?

– Cardiac parameters
– Haematology
– Biochemistry

Hassimoto et al 2004
Repeatability - Acclimatisation

Telemetered male rhesus macaques – Doyle et al, 2008

Hassimoto et al 2004
**Repeatability - Acclimatisation**

<table>
<thead>
<tr>
<th>Blood parameter</th>
<th>Change over 6 mo</th>
<th>Mean value</th>
<th>SD</th>
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<tbody>
<tr>
<td>WBC</td>
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<td>RBC</td>
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Key:
- **Males & females differ**
- **Males & females decrease**
- **Males & females increase**

Hassimoto et al 2004
RESTRAINT – a welfare problem, a science quality problem

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td>Line et al 1991; <strong>Schnell</strong> &amp; Wood 1993; Hassimoto &amp; Herada 2003; Jenkins et al 2008; Kelly et al in prep</td>
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<tr>
<td>Readability/Quality of ECG trace</td>
<td>↓</td>
<td><strong>Kelly et al in prep</strong></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td>Golub and Anderson 1986; <strong>Schnell</strong> and Wood 1993; Schmelting et al 2008; Hassimoto &amp; Herada 2003</td>
</tr>
<tr>
<td>Respiration rate</td>
<td></td>
<td>Berendt &amp; Williams 1971</td>
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<tr>
<td>Blood – biochemistry*</td>
<td>↑, ↓</td>
<td>Landi et al 1990; Hassimomo et al 2004</td>
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* Individual parameters vary
Telemetry

• Reduces research animal stress from restraint, and improves quality of data.
• Interplay 2Rs (Reduction and Refinement) and opposing effects within Refinement.
• May be +ve Refinement, +ve Reduction.

• Not feasible for all research animals
  o Surgery
  o Expense
  o Time
## Changing Restraint - to improve welfare and science

<table>
<thead>
<tr>
<th>Refinement</th>
<th>Parameter change</th>
<th>Author</th>
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</table>
| Socialisation with care staff | Fearful behaviour towards care staff  
                           | Blood pressure                     | Clay et al 2009                  |
|                           |                                                       | Tasker et al in prep              |
| Restraint technique       | HR  
                           | Trace quality                     | Kelly et al in prep               |
| Habitation to restraint   | Blood pressure  
                           | Variation                         | Schmelting et al 2008             |
|                           |                                                       | Tasker et al in prep              |
| Training (PRT)            | Fearful behaviour & stress-related behaviours  
                           | Self-injurious behaviour          | Clay et al 2009                   |
|                           |                                                       | Plasma cortisol                   | Bassett et al 2003                |
|                           |                                                       |                                 | Baker et al 2003                  |
|                           |                                                       |                                 | Reinhardt 1992                    |
|                           |                                                       |                                 | Bentson et al 2003; Koban et al 2005 |
|                           | Cooperation                                          | Reinhardt & Cowley 1992          |
Bass et al (2009)

• Assessment of the potential for cardiotoxicity, including arrhythmias, is paramount to assure appropriate monitoring for human safety.

• Sensitivity of identifying cardiac risk (arrhythmias and ventricular repolarization as seen in test article-related changes in the QT and QTc intervals) is significantly improved in non-restrained versus restrained cynomolgus macaques.
Conclusions

Improved positive socialisation with humans, and improved restraint impacts on:

Physical health
Closer to normal, stable - baseline measures

Behaviour
• Fear responses to care staff, during handling & CV data collection

Cardiovascular (HR & BP)
• Lower baseline values
  - Greater accuracy to quantify drug-induced changes
• Fewer trace artefacts e.g. movement, vocalisation, tension
  - Cleaner traces, easier to determine arrhythmias
• Faster data collection
• Better repeatability (less variation). 5 x BP measures

Enhanced socialisation ➔ better welfare ➔ better scientific output + improved restraint & PRT
Acknowledgments

Meeting organisers and many helpful colleagues

Providers of images

Funders
BBSRC
Covance Laboratories Ltd, Harrogate
Just launched: http://marmosetcare.com/

An interactive site with information on how best to care for common marmosets in captivity – for private owners, researchers, zoo and laboratory professionals.