NAS/IOM Committee Meeting on

The Use of Chimpanzees in Biomedical and Behavioral Research

Post-Meeting Comments by

Jarrod Bailey, PhD
Science Director/Consultant
New England Anti-Vivisection Society

June 1, 2011

I would like to thank the committee once again for the opportunity to speak at the meeting on May 26th, and for the members' constructive questions following my remarks.

Many of the members' comments and responses, and some of the points raised by some of the speakers, could only be addressed briefly in the meeting due to time restrictions. I have compiled this concise document in the hope that the further information it contains will be helpful in the committee's continuing deliberations.

1. Reference to publications of Project R&R: Release and Restitution for Chimpanzees in U.S. Laboratories

   I would like to refer the committee to these scientific papers, by myself and various other authors, which have been provided as complete documents to the study organizer, Dr. Bruce Altevogt. They contain very detailed information and references on the use and relevance of chimpanzees in many areas of research, including HIV/AIDS and cancer. I would like to draw the members' attention particularly to the two papers on hepatitis C, which dispute claims put forward by Harold Watson and Kevin Kregel that chimpanzees were crucial historically in hepatitis C research, continue to be necessary in the evaluation of hepatitis C vaccines and the development of monoclonal antibody therapies, and that *in vitro* and clinical approaches are inferior to the use of chimpanzees to study the virus and hepatitis C pathology:

   An Assessment of the Use of Chimpanzees in Hepatitis C Research Past, Present and Future: 1. Validity of the Chimpanzee Model
   Bailey, J. (2010). Alternatives to Laboratory Animals (ATLA), 38(5), 387-418.
   Available: http://tiny.cc/toxu6

   An Assessment of the Use of Chimpanzees in Hepatitis C Research Past, Present and Future: 2. Alternative Replacement Methods
   Bailey, J. (2010). Alternatives to Laboratory Animals (ATLA), 38(6), 471-494.
   Available: http://tiny.cc/5mesu

   Please see also Point 7 below.

2. Historical use of chimpanzees in hepatitis B research

   Drs. Watson and Kregel asserted the past importance of chimpanzee use in hepatitis B research. I would like to impress upon the committee that this importance is disputed. Due to notable differences in HBV pathology between humans and chimpanzees, chimpanzees did not serve as useful models for hepatitis B: rather, chimpanzees were used more simply as "bioreactors" to provide a source of the virus for research.

It is therefore suspect to claim that without chimpanzees there would be no HBV vaccine. It would not have been developed as it was, but a greater concentration on the development of *in vitro* methods of study would probably have paid off—as it has done for hepatitis C. Nevertheless, this argument of historical usefulness is peripheral to the salient question being addressed by the committee: of the need for chimpanzee use now and in the future, given today and tomorrow's state of science and a comparison with what alternative research methods—much advanced since this early work on hepatitis B—can provide.

3. Planned use of chimpanzees in drug safety and efficacy studies

Dr. Watson mentioned that many future drug-testing regimes must involve chimpanzees, as they are the most related species to humans. To my knowledge, there is no scientific proof that the use of chimpanzees is more predictive than using any other method, *in vivo* or *in vitro*, to assess the safety and efficacy of a new drug. Indeed, Professor Caldwell of St. Mary's Hospital Medical School, London observed, "It has been obvious for some time that there is generally no evolutionary basis behind the particular-metabolizing ability of a particular species. Indeed, among rodents and primates, zoologically closely related species exhibit markedly different patterns of metabolism."
Caldwell, J. (1992). Species differences in metabolism and their toxicological significance, *Toxicol. Lett.* **64**, 106.

4. Use of U.S. chimpanzees by other countries

Dr. Watson implied that chimpanzee use must be scientifically necessary, because scientist from countries that have banned or limited it are using chimpanzees in American laboratories.

The 27 instances of this since 2005 must be taken in context, representing as it does only an estimated 4 or 5% of chimpanzee studies during this time. Further, a significant proportion—if not all—of these studies appear to be collaborative, with the foreign component a minor one. These international collaborations must be investigated further so that any use of chimpanzees may be scientifically critiqued. In itself, this point does not demonstrate the scientific necessity of chimpanzee research, nor the necessary or widespread demand on U.S. chimpanzees by scientists outside of the country.

5. Chimpanzee contributions to new hepatitis C drugs

Dr. Watson suggested chimpanzees had been instrumental in the continued development of a proposed new drug for hepatitis C, SPC3649. I would like to make the following points:

- In vitro experiments as well as human clinical trial studies of SPC3649 were completed or in progress *before* the chimpanzee study began, making it unclear why the chimpanzee study was conducted at all.

- While temporary reduction of viremia has been observed overall in the four chimps used in the study, these results do not support a consistent clinical response to the drug. In many measured categories, there are non-trivial differences between the two chimpanzees in the same dose groups, as well as between the two different dose groups.

- While a key finding was the "long-lasting suppression" of the hepatitis C virus, the amount of virus began to rise after the treatment and reached pre-treatment levels in 3 out of the 4 chimpanzees by the end of the study.

- Only one in four liver biopsy sets from the chimps showed a substantial temporary improvement.

- It is troubling that the properties and functions of miR-122 are not fully understood. We do know that it is implicated in cholesterol regulation and lipid metabolism, and has been associated with resistance to liver cancer. Because chimps are generally resistant to liver cancer, miR-122 studies in chimpanzees do not seem appropriate to clarify whether repression of miR-122 might lead to increased incidences of liver cancer in humans.

6. <u>Citation analysis/efficacy study of chimpanzee research</u>

Dr. Harlow asked for further details of the random chimpanzee studies used in this analysis, over and above the details of the cited and citing papers listed in the provided study:

Chimpanzee Research: An Examination of Its Contribution to Biomedical Knowledge and Efficacy in Combating Human Diseases
Bailey, J., Balcombe, J. & Capaldo, T. (2007). Project R&R.
Available: http://www.releasechimps.org/pdfs/chimp-efficacy-paper-main.pdf

In particular, those studies that had not been cited at all, or had not been cited with relevance to human biomedical progress, were requested. I have attached a table containing all relevant

data on the entire sample of 95 papers that was compiled during the writing of the paper, but which was not included in the final draft for brevity (see Appendix).

7. Points raised by Dr. Kregel's remarks

Dr. Kregel asserted that *in vitro* clinical, and other non-chimpanzee methods of hepatitis C research couldn't replace chimpanzee experiments.

All approaches have limitations and caveats. One of the committee's responsibilities is to determine if the chimpanzee can provide human-relevant essential data that the other methods are unable to provide. The two papers cited in Point 1 above go into considerable detail in this respect, outlining the breadth of important data such approaches have provided. Briefly, I would ask the committee to consider the following:

- The relative research interest of chimpanzee use in HCV research has declined by approximately 60% over the past three decades, while the use of alternatives has increased 80-fold over the same period.

- HCV pathology in chimpanzees and humans is very different. For example: there is a much lower rate of chronic infection in chimps due to greater viral clearance; immune responses to HCV differ; resultant liver fibrosis and cirrhosis are milder in chimps and hepatocellular carcinoma is rare.

- The claimed contributions of chimpanzee use to HCV understanding are exaggerated. Chimps were not required to characterize high-titer human serum samples used in the process of identifying HCV; they were not necessary in the development of infectious HCV clones, and in any case these were not integral to the development of virus-like particles (VLPs), pseudoparticles (HCVpp), and full life-cycle infectious cellular clones (HCVcc); and they were not essential to demonstrate that HCV infection does not elicit protective immunity.

- *In vitro* HCV research methods: permit the investigation of the entire viral life cycle; facilitate reverse genetics analyses to elucidate HCV genomics, proteomics, and interactions with and roles of host factors; permit the study of the humoral immune response and neutralising antibodies to aid vaccine development; help with

identification of therapeutic targets and the screening and testing of antiviral compounds.

- Full life cycle infectious cellular clones (HCVcc) are being much improved: multiple cell lines can be used to increase replication and viral titers; intra- and intergenotypic chimeras with other HCV isolates are improving efficiency; and dedicated systems for other strains are showing promise.

- Studying pathological events early in HCV infection is not the preserve of the chimpanzee. Informative studies have been performed with sufferers of needle stick injuries, and prospective investigations with new admissions to young offenders institutes, for example.

8. Bioterrorism research

   There exists much speculation surrounding the need for chimpanzees for future research, as may be needed, into new microbial agents for bioterrorism.

   This is entirely speculative with no scientific foundation. In common with all other claimed requirements for chimpanzee research, these should be critically assessed for any need for chimpanzee data that other methods could not provide. Given that scientific methods have logic and consistency to them, based on available data regarding all of the major disease categories I have investigated, the probability that suddenly at some point in the future *only* a chimpanzee will be able to provide a valid model for the investigation of some bioterrorism agent must be considered a miniscule possibility at best. Given this low probability, the scientific merit of the substantial economic waste of limited research dollars to house and maintain chimpanzees in U.S. laboratories for this small "just in case" scenario is not merely an economic and ethical question but a scientific one as well: is it prudent to absorb critical amounts of funding that could otherwise be appropriated to other avenues of research needed and most likely productive in the here and now?

In summary: I would like to reiterate that, given the ethical and economic costs of chimpanzee research, the onus should be on those who wish to use chimpanzees to prove beyond doubt that chimpanzee research provides data that:

- Cannot be obtained in any other way

- Is relevant to, and predictive of, human biology and response
- Is essential (or at least likely to be essential) to tangible human medical progress

Finally, the involvement of chimpanzees in any area of research or testing does not demonstrate their crucial involvement. Data from chimpanzee experiments may be interesting, but this does not mean it is useful or necessary.

I hope that this information is helpful, and I would be happy to attend to any further questions the committee might have; to present further information at future meetings on specific areas requested by the committee; or, to sit as a member or as a non-voting advisor.

Jarrod Bailey, Ph.D.

Appendix

Table 1: 95 randomly selected chimpanzee studies and 27 citing medical papers

	Chimpanzee studies				Citing medical papers		
	Author(s)	Year	Journal	Cited	Author(s)	Year	Journal
1	Anderson *et al.*	1997	*Clinical Immunology and Immunopathology* **84**, 73–84	1			
2	Anderson *et al.*	2004	*Proceedings of the Royal Society of London — Series B: Biological Sciences* **271**, Suppl. 6, 468–470	0			
3	Baker *et al.*	2000	*American Journal of Primatology* **51**, 161–175	0			
4	Bard	1998	*Developmental Neuropsychology* **14**, 471–494	1			
5	Bering *et al.*	2000	*Developmental Psychobiology* **36**, 218–232	4			
6	Bertoni *et al.*	1998	*Journal of Immunology* **161**, 4447–4455	2	Khanna *et al.*	1999	*Immunological Reviews* **170**, 49–64
7	Bigger *et al.*	2001	*Journal of Virology* **75**, 7059–7066	10	Feld & Hoofnagle	2005	*Nature* **436**, 967–972
7	Bigger *et al.*	2001	*Journal of Virology* **75**, 7059–7066	10	Kim & Wang	2003	*Carcinogenesis* **24**, 363–369
8	Black *et al.*	1997	*AIDS Research & Human Retroviruses* **13**, 1273–1282	1			
9	Bloomsmith *et al.*	2003	*Animal Welfare* **12**, 359–368	0			
10	Bloomsmith *et al.*	2003	*Applied Animal Behaviour* **84**, 235–250	0			
11	Boudet *et al.*	1996	*AIDS Research & Human Retroviruses* **12**, 1671–1679	0			
12	Boysen & Berntson	1995	*Journal of Experimental Psychology: Behavioural Processes* **21**, 82–86	19			
13	Brahimi *et al.*	2001	*Infection & Immunity* **69**, 3845–3852	2			
14	Brams *et al.*	2001	*International Immunopharmacology* **1**, 277–294	6	Gescuck & Davis	2002	*Current Opinion in Rheumatology* **14**, 515–521
14	Brams *et al.*	2001	*International Immunopharmacology* **1**, 277–294	6	Tong & Stone	2003	*Cancer Gene Therapy* **10**, 1–13
15	Bukh *et al.*	2002	*Proceedings of the National Academy of Sciences* **99**, 14,416–14,421	3			
16	Butovskaia *et al.*	1995	*Fiziologicheskii Zhurnal Imeni I.M. Sechenova* **81**, 89–94	0			
17	Buxhoeveden & Casanova	2000	*Laterality* **5**, 315–330	2			
18	Cacchione & Krist	2004	*Journal of Comparative Psychology* **118**, 140–148	0			
19	Call & Tomasello	1998	*Journal of Computer Psychology* **112**, 192–206	8			

Cited = the number of subsequent papers in which the article was cited.

Table 1: continued

	Chimpanzee studies				Citing medical papers		
	Author(s)	Year	Journal	Cited	Author(s)	Year	Journal
20	Cervenakova *et al.*	2003	*Electrophoresis* **24**, 853–859	1	Brown	2005	*Vox Sanguinis* **89**, 63–70
21	Cianelli & Fouts	1998	*Human Evolution* **13**, 147–159	0			
22	Cong *et al.*	2000	*Virology* **274**, 343–355	0			
23	Conley *et al.*	1996	*Journal of Virology* **70**, 6751–6758	10	Armbruster *et al.*	2004	*Journal of Antimicrobial Chemotherapy* **54**, 915–920
23	Conley *et al.*	1996	*Journal of Virology* **70**, 6751–6758	10	Armbruster *et al.*	2002	*AIDS* **16**, 227–233
23	Conley *et al.*	1996	*Journal of Virology* **70**, 6751–6758	10	Hone *et al.*	2002	*Journal of Human Virology* **5**, 17–23
23	Conley *et al.*	1996	*Journal of Virology* **70**, 6751–6758	10	Sleasman & Goodenow	2003	*Journal of Allergy and Clinical Immunology* **111**, 582–592
23	Conley *et al.*	1996	*Journal of Virology* **70**, 6751–58	10	Yang *et al.*	1998	*Journal of AIDS & Human Retrovirology* **17**, 27–34
24	Cook *et al.*	1997	*Journal of Pharmacology & Experimental Therapeutics* **2**, 677–689	0			
25	Crowe *et al.*	1999	*Virus Research* **59**, 13–22	1	Kneyber & Kimpen	2002	*Paediatric Infectious Diseases* **21**, 685–696
26	Dash *et al.*	2001	*Journal of Medical Virology* **65**, 276–281	0			
27	Digilio *et al.*	1997	*Journal of Virology* **71**, 3684–92	0			
28	Egger *et al.*	2002	*Journal of Virology* **76**, 5974–84	5			
29	Elkington *et al.*	2004	*European Journal of Immunology* **34**, 3216–3226	0			
30	Esumi *et al.*	2002	*Vaccine* **20**, 3095–3103	0			
31	Fernandez-Carriba *et al.*	2002	*Brain Research Bulletin* **57**, 561–564	1			
32	Fu *et al.*	2001	*Journal of Virology* **75**, 73–82	0			
33	Fujii *et al.*	1997	*Neuroscience Letters* **227**, 21–24	0			
34	Fujita	1997	*Perception & Psychophysics* **59**, 284–292	1			
35	Gearing *et al.*	1996	*Neurobiology of Aging* **17**, 903–908	0			
36	Goh *et al.*	1998	*Nature Medicine* **4**, 65–71	10	Gallo	2002	*Immunological Reviews* **185**, 236–265
37	Grob *et al.*	1997	*Nature Medicine* **3**, 665–670	2	Bardsley-Elliot & Perry	2000	*Paediatric Drugs* **2**, 373–407

Cited = the number of subsequent papers in which the article was cited.

Table 1: continued

	Chimpanzee studies				Citing medical papers		
	Author(s)	Year	Journal	Cited	Author(s)	Year	Journal
38	Hellekant & Danilova	1996	*Food Chemistry* **56**, 323–328	1			
39	Hellekant *et al.*	1997	*Physiology Behaviour* **61**, 829–841	2			
40	Herndon & Tigges	2001	*Computational Medicine* **51**, 60–69	0			
41	Hook *et al.*	2002	*Applied Animal Behaviour Sciences* **76**, 165–176	0			
42	Hopkins & Bard	2000	*Developmental Psychobiology* **36**, 292–300	1			
43	Hopkins & Russell	2004	*Neuropsychologia* **42**, 990–996	0			
44	Huguenel *et al.*	1997	*American Journal of Respiratory & Critical Care Medicine* **155**, 1206–1210	6	Suzuki *et al.*	2001	*Chest* **120**, 730–733
44	Huguenel *et al.*	1997	*American Journal of Respiratory & Critical Care Medicine* **155**, 1206–1210	6	Turner *et al.*	1999	*JAMA* **281**, 1797–1804
45	Imura	2003	*Animal Cognition* **6**, 253–258	0			
46	Ishikawa *et al.*	1997	*Journal of Toxicological Sciences* **22**, 207–217	0			
47	Jensvold *et al.*	2001	*Journal of Applied Animal Welfare Science* **4**, 53–69	0			
48	Kojima *et al.*	2003	*Primates* **44**, 225–230	0			
49	Leavens *et al.*	2001	*American Journal of Primatology* **55**, 1–14	2			
50	Marzke *et al.*	1999	*American Journal of Physical Anthropology* **110**, 163–178	0			
51	Mast *et al.*	1998	*Hepatology* **27**, 857–861	13	Obriadina *et al.*	2002	*Journal of Gastroenterology & Hepatology* **17**, 360–364
51	Mast *et al.*	1998	*Hepatology* **27**, 857–861	13	Regev & Schiff	1999	*Current Opinion in Gastroenterology* **15**, 234–239
51	Mast *et al.*	1998	*Hepatology* **27**, 857–861	13	Worm & Wirnsberger	2004	*Drugs* **64**, 1517–1531
52	Morris *et al.*	1996	*Journal of Parasitology* **82**, 444–448	0			
53	Nakano *et al.*	2003	*Journal of Parasitology* **89**, 439–443	0			
54	Negishi *et al.*	2004	*Experimental Animal* **53**, 391–394	0			
55	Nehete *et al.*	1995	*AIDS* **9**, 567–572	1			
56	Nerrienet *et al.*	2004	*Journal of General Virology* **85**, 25–29	0			

Cited = the number of subsequent papers in which the article was cited.

Table 1: continued

	Chimpanzee studies				Citing medical papers		
	Author(s)	Year	Journal	Cited	Author(s)	Year	Journal
57	Newman *et al.*	2001	*Clinical Immunology* **98**, 164–174	2	Hepburn *et al.*	2003	*Rheumatology* **42**, 54–61
57	Newman *et al.*	2001	*Clinical Immunology* **98**, 164–174	2	Matthews *et al.*	2003	*Journal of Viral Hepatitis* **3**, 794–803
58	Obriadina *et al.*	2002	*Journal of Gastroenterology & Hepatology* **17**, 360–364	1			
59	Ogata *et al.*	1999	*Hepatology* **30**, 779–786	5	Koff	2002	*Digestive Diseases & Sciences* **47**, 1183–1194
59	Ogata *et al.*	1999	*Hepatology* **30**, 779–786	5	McMahon *et al.*	2005	*Annals of Internal Medicine* **142**, 333–341
60	Olikowsky *et al.*	1997	*Immunology* **91**, 104–108	4			
61	Ondoa *et al.*	2003	*Journal of Medical Virology* **69**, 297–305	0			
62	Palagi *et al.*	2004	*American Journal of Primatology* **62**, 15–30	1			
63	Pancholi *et al.*	2001	*Hepatology* **33**, 448–454	5	Karayiannis	2003	*Journal of Antimicrobial Chemotherapy* **51**, 761–785
63	Pancholi *et al.*	2001	*Hepatology* **33**, 448–454	5	Moore & Hill	2004	*Immunological Review* **199**, 126–143
64	Parr *et al.*	2000	*Journal of Comparative Psychology* **114**, 47–60	2			
65	Parr	2004	*Animal Cognition* **7**, 171–178	0			
66	Pecher & Finn	1996	*Proceedings of the National Academy of Sciences, USA* **93**, 1699–1704	1			
67	Riska *et al.*	1999	*Drug Metabolism and Disposition* **27**, 1434–1447	0			
68	Robert-Guroff *et al.*	1998	*Journal of Virology* **72**, 10,275–10,280	6			
69	Rodman *et al.*	1999	*Human Immunology* **60**, 631–639	0			
70	Rollier *et al.*	2003	*Hepatology* **38**, 851–858	0			
71	Rollier *et al.*	2004	*Journal of Virology* **78**, 187–196	2			
72	Saito *et al.*	2003	*Primates* **44**, 171–176	0			
74	Shanafelt *et al.*	2000	*Nature Biotechnology* **18**, 1197–1202	0			
75	Sherwood *et al.*	2003	*Anatomical Research: Discoveries in Molecular Cell Evolutionary Biology* **271**, 276–285	2			
76	Shoukry *et al.*	2004	*Journal of Immunology* **172**, 483–492	1			

Cited = the number of subsequent papers in which the article was cited.

Table 1: continued

	Chimpanzee studies				Citing medical papers		
	Author(s)	Year	Journal	Cited	Author(s)	Year	Journal
77	Smith *et al.*	2001	*Journal of Anatomy* **198**, 77–82	0			
78	Smithwick & Young	1997	*Tissue Cell* **29**, 383–412	0			
79	Soos *et al.*	2003	*Clinical Immunology* **109**, 188–196	0			
80	Steiner *et al.*	1999	*Journal of Urology* **162**, 1454–1461	2			
81	Stern & Larson	2001	*American Journal of Physical Anthropology* **115**, 253–268	0			
82	Takahashi *et al.*	1997	*Pharmacometrics* **54**, 327–334	0			
83	Tanaka	1996	*Journal of Comparative Psychology* **110**, 323–335	0			
84	Timenetsky & Barile	1998	*Laboratory Animal Science* **48**, 463–468	0			
85	Tocheri *et al.*	2003	*American Journal of Physical Anthropology* **122**, 101–112	0			
86	Tomonaga	1995	*Perceptual & Motor Skills* **80**, 35–42	0			
87	Tsarev *et al.*	1995	*Journal of Infectious Diseases* **172**, 31–37	2			
88	Uddin *et al.*	2004	*Proceedings of the National Academy of Sciences, USA* **101**, 2957–2962	2			
89	Uller	2004	*Animal Cognition* **7**, 154–161	1			
90	Vahter *et al.*	1995	*Toxicology and Applied Pharmacology* **133**, 262–268	2			
91	Videan & McGrew	2002	*American Journal of Physical Anthropology* **118**, 184–190	2			
92	Wang *et al.*	1996	*Journal of Infectious Diseases* **173**, 808–821	8	Hussy *et al.*	1997	*Journal of Hepatology* **26**, 1179–1186
92	Wang *et al.*	1996	*Journal of Infectious Diseases* **173**, 808–821	8	Nakano *et al.*	1999	*Journal of Hepatology* **30**, 1014–1022
93	Wood	2002	*American Journal of Occupational Therapy* **56**, 160–170	0			
94	Yu *et al.*	2003	*Clinical and Diagnostic Laboratory Immunology* **10**, 579–586	1			
95	Zhang & Vyas	1995	*Drug Metabolism and Disposition* **23**, 1104–1109	0			

Cited = the number of subsequent papers in which the article was cited.