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Special feature

Indian lab animal medicine: Getting ready for the global stage

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Abstract

As biomedical research becomes more globalized, India can provide the rest of the world possibly unique insights into the care and use of laboratory animals. Nowhere else is such a rich and deep cultural veneration for life juxtaposed with society and technology modernizing at such astonishing speed. How will our Indian colleagues reconcile these two powerful and seemingly contradictory elements? Just as important, will India's scientific community and regulators regard Western standards of lab animal care as something to adopt in an identical fashion or something to adapt to domestic circumstances? The intent of this address is to explore these fascinating aspects of India today from an outsider's perspective and to consider how all parties may benefit together.

Key words: laboratory animals, LASA, India

Keynote Address

Vice Chancellor Singh, Dean Garg, LASA President Ramachandra, LASA Secretary Qadri, and fellow conference attendees: it is my pleasure to be here today to speak to you. I am grateful for the opportunity to finally visit a country that has fascinated me for a long time. I am honored to participate in this Fourth International Conference of the Laboratory Animal Scientist's Association (India). I am delighted to extend a welcome from the American College of Laboratory Animal Medicine to our lab animal veterinarian colleagues in India. And I am humbled to be asked to deliver the keynote address at such an important conference involving experts in lab animal care from India and around the world.

You may not realize that India and Indians are highlighted in the media in the US almost every day. They also frequently

appear in the news intersecting science and business, a combination that just so happens to be a personal interest of mine. For example, one of the most popular writers in the US today is Atul Gawande, a surgeon at Brigham and Women's Hospital in Boston and an associate professor at Harvard Medical School. Dr. Gawande is a MacArthur Fellow and also a writer for the New Yorker magazine, publishing books and articles on improving healthcare in America. His most recent book, "The Checklist Manifesto – How To Get Things Right", has provided hospitals as well as those in many other industries simple strategies to reduce mistakes and improve quality (Gawande, 2009). Another example involves Ratan Tata, Chairman of Tata Sons Ltd. He recently presented the Harvard Business School (HBS) with a gift of $50 million from Tata-affiliated charities. This is the largest gift ever received by the school from an international donor. It will finance a new academic and residential building to be named Tata Hall for the school's executive education program. And it just so happens that the recently appointed dean of the business school is Nitin Nohria, who has a B. Tech. in Chemical Engineering from the Indian Institute of Technology in Bombay.

Finally, the cover story of last month's edition of Entrepreneur magazine features Amit Chatterjee. A veteran of Silicon Valley high tech, he recently launched Hara, a "green" software company that has had a big impact already in how energy is managed (Wang, 2011). But these and similar news items should be no surprise, given India's historically strong emphasis on education and its recent turn to free-market capitalism. India has the second highest population with over 1.2 billion people, and is the most populous democracy in the world. It is the latter statistic that says much about India's recent progress and its prospects for continued growth. The fact that Indians have a strong voice in how their government is run and how that, in turn, is expected to provide its citizens with opportunity and transparency are in contrast with other large developing countries that still struggle with restrictive, authoritarian rulers.

Just as importantly, Indians are famous for their tendency to improvise. One obvious example is how you drive here. If there are two lanes marked on the highway, there may be four or five lanes of traffic at any given time, depending on the circumstances. This national characteristic and its broader implications were nicely captured in a recent column by Jug Suraiya in the Times of India. Titled "Chaos Is Our Dharma", it began with the statement "It's often said that India is functioning chaos". But the column went on to note that in Indian driving habits and other activities "out of apparent chaos emerges progress." It continued with the observation that "Other societies go by the inflexible exactitude of rules. We, all of us, write our own rule books as we go along. We function by that uniquely Indian concept called 'andaz', approximation. Other cooks use exact recipes; we use inexact, and creative, andaz. A pinch of this and a dash of that. How much precisely? Arre, use your andaz, bhai." (Suraiya, 2011).

All these components have had a hand in making India an economic marvel in recent years. Allow me to review some statistics, extracted from the encyclopedia website Wikipedia (Anonymous, 2011). India's annual economic growth averaged 7.5% over the last several years while hourly wages more than doubled over the last ten years. Since 1985, 431 million Indians have been lifted out of poverty. The Indian economy ranks fourth at $3.6 trillion if purchasing power parity is taken into account. By this metric, India's GDP is expected to overtake Japan's this year and will exceed that of the US in 2045. In 19 years, India's middle class will exceed 580 million persons. Over the next 40 years, India's average annual growth te is forecasted at 8%. This translates to being the world's fastest growing economy during that time. A major category of growth in the private sector is high technology, especially contract software development and customer support. The service sector as a whole now accounts for 54% of GDP, the largest such category in the national economy. Home to seven of the world's top fifteen technology outsourcing companies, India is second only to the US as the most favorable outsourcing destination.

One consequence of this rise of high tech outsourcing touched home after my father-in-law began exploring the internet about 10 years ago. After he made several calls to America Online for assistance, he told me that whenever he called, the support person on the other end of the phone always sounded Indian. I smiled and replied, "George, that's because they're in India!"

But what does all this have to do with the care and use of lab animals in India? One connection is that the earlier initiation of western outsourcing of software programming and high tech support call centers is now being mirrored by western outsourcing of preclinical testing to contract research organizations (CRO's) in India and other developing countries. A conversation I had less than a week ago with the chief scientific officer of an established biopharma company in the Boston area nicely fit with this trend. He had just returned from India after concluding negotiations with a CRO for *in vivo* drug screening and pharmacokinetics services. When I asked him what drew his company there, he answered that such services were offered at less than one-third the cost compared to the same assays performed by CRO's in the US.

Offering dramatically lower prices and comparable scientific expertise, Indian CRO's will continue to attract interest from pharmaceutical and biotechnology companies. And the cost advantage Indian CRO's currently offer will be augmented eventually by comparable quality and equivalent regulatory compliance. All of these factors will drive more drug development off-shore because multinational pharmaceutical companies face ever growing pressure to replenish their new drug pipelines and biotechnology firms need to conserve cash during difficult periods of equity financing.

What about domestic drivers for more medical research and commercialization? One can start with life threatening infectious and other diseases that afflict India, many of which are endemic only to tropical regions and therefore unlikely to be of immediate interest to the west. It will be left to India and other developing countries to develop better vaccines and drugs for these diseases. In addition, a growing middle class and resultant larger tax base means Indian society can afford better medical care, in turn strengthening the domestic pharmaceutical industry. Thus, continued investment is more than justified in India's biomedical research infrastructure, including animal models of disease and *in vivo* product testing where appropriate. It's no surprise that the Indian government has doubled its life science research budget over the last five years (Tole and Vale, 2010). And as evidence of the financial opportunities to investors in this arena, consider Shantha Biotechnics. This is an Indian biotech firm that was purchased for €571 million by Sanofi-Aventis in 2009. Compare that acquisition price with the fact that it was launched with $1.2 million of private equity in 1992, a very nice return indeed (Chakma *et al.,* 2010).

Given this encouraging background, how should India and LASA respond? We in the lab animal care field in the west are eager to help. That should not be limited to visiting India to give a couple of lectures and then returning home – such efforts are inefficient and ephemeral. A more fruitful relationship would be to help train the trainers in proven concepts and techniques for optimizing animal health and welfare without compromising experiments and assays. Sharing instructional material, in print and over the internet, is one logical strategy, especially if content is jointly designed and adapted to local needs.

As an example, at last year's national AALAS meeting, the first virtual reality rodent barrier was debuted at our exhibit booth. It was designed for learning how to navigate through a vivarium and how to perform proper microisolator technique. Modeled as sort of a game, it is intended to instruct animal care staff and researchers how to do things right, and can be viewed anytime from anywhere. The final prototype should be ready for launch later this spring on our website, www.virtualvivarium.com, initially in English and later in Spanish, (Brazilian) Portuguese, and Mandarin Chinese. A parallel version in Hindi shouldn't be difficult to produce if there are interested collaborators from LASA.

Another useful way for us to help is by hosting lab animal veterinarians and animal husbandry program managers. I understand that the Indian government provides funding for such persons to spend time in the US to learn advanced tools and techniques in lab animal care. We launched something similar last fall, a Latin America training fellowship in lab animal science, in collaboration with the International Council for Laboratory Animal Science (ICLAS). The Americas Regional Committee of ICLAS solicits applications and selects three awardees, each of whom spend three months embedded in our department. We provide airfare, housing, and a small stipend, and also arrange for training fellows to visit other major academic and industry programs in the Boston area. They are also required to develop a personal research or development project that will be implemented upon their return, and we stay in touch after they leave. It is our hope that we can teach the teachers, who will take back to their countries lessons learned with us. We also expect to learn from them – more on that in a minute. Our first two training fellows were from Uruguay and Brazil, and our third will be arriving next month from Costa Rica. While three months flies by, it appears to be enough time to absorb the basics and to prepare for the more important steps of sorting and implementing when the training fellows return home. A similar initiative involving Indians coming to the US would be well worth the expense and should be encouraged.

What we expect to learn from our Latin America training fellows is identical to what I hope we in the west would learn from our colleagues in India. And they fall into three categories.

First, you have species of animals that we will never see in the west. India is one of seventeen "megadiverse" countries as designated by Conservation International, home to an estimated 7.6% of all mammalian, 12.6% of all avian, 6.2% of all reptilian, 4.4% of all amphibian, and 11.7% of all fish species (Gadgil, undated). As your wildlife biologists learn more about the physiology, anatomy, and behavior of these native animals, presumably through conservation initiatives, please ask them to be on the look-out for novel traits that could be of value as animal models of human disease. In other words, what innate characteristics may these animals possess that can be applied to investigations in immunology and vaccines, cancer, diabetes, heart disease, neurodegeneration, etc.?

Consider that India is home to many species of bats. And bats are natural and often asymptomatic reservoirs of viruses fatal to humans. And this doesn't just apply to rabies but has been also demonstrated for Hendra, Nipah, SARS, and Ebola viruses (Calisher *et al.,* 2006). If bats are permissive yet clinically robust hosts for human pathogens such as these, what does that suggest about their immune systems? Do they harbor clues to viral resistance or viral clearance that could lead to better vaccines or post-exposure therapies? Much remains to be discovered, and perhaps bats native to India can be informative in this regard.

The second category of lessons sought from India is how lab animal care is adapted to developing country circumstances. Feel encouraged embracing evidence-based "andaz" rather than western standards that are usually instituted as "rules". When we say in the US that we have a "standard" way of doing things, this implies that everyone

should always follow the prescribed method and never deviate. When such "standards" in lab animal care are also quantified, such as the required minimum size of cages or minimum frequency of husbandry tasks, we call them as "engineering standards" because they are easily measured and implied to be absolute. But it is important to distinguish how the word "standard" is used in western English versus elsewhere. In their book, "Understanding A3 Thinking – A Critical Component of Toyota's PDCA Management System", the authors point out that "in Toyota, the meaning and intent of the word 'standard' is closer to another definition, a 'basis for comparison'. In other words, it is more of a scientific definition as used in experimental research. A standard is necessary to determine whether an improvement has been achieved" in a manufacturing process (Sobek and Smalley, 2008). It is not a rule that never should be violated. The authors end this discussion by quoting a Japanese proverb, "Only a fool knows just one way of doing things". Therefore, use logic and the scientific method to prove or disprove the value of alternative methods of achieving a desired objective when it involves lab animal care. Several husbandry changes we've adopted or are considering will serve as examples.

For decades, it was believed that washing cages had to include at least one stage of at least 82 ºC (180 ºF) wash water because this temperature was printed in multiple editions of the Guide for the Care and Use of Laboratory Animals ("The Guide"). The Guide is published by the US National Academies of Science (National Research Council, 2010). It is the dominant reference publication on this subject in the US and also has regulatory standing if one receives research funding from the US government. It also serves as the primary guidance document by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC). In addition, the US Animal Welfare Act also uses 82ºC as a standard for adequately sanitizing cages for applicable species (US Code of Federal Regulations, 2008). But on more careful reading of those documents, one discovers that lower water temperatures are allowed if one can demonstrate by other means that cages are sufficiently clean. For the past six years, we have washed rodent barrier cages in cold water and without detergent because those cages are sterilized in an autoclave after washing and before they're returned to the vivarium. So the temperature of wash water is immaterial as long as cages come out clean. For larger species and metal caging, we also wash with water not always reaching 82ºC and confirm sufficient sanitation by testing washed surfaces for microbial residue. This approach saves energy, provides a more comfortable work environment for cage wash staff, and has been deemed acceptable at our last two AAALAC site visits.

Here's another example of thinking beyond the confines of conventional husbandry practices. Western standards dictate that rodent cages should be changed no less frequently than every two weeks. For a static cage housing 4-5 mice, changing is often required at least a couple times a week, and so the standard is followed. A ventilated microisolator cage housing 4-5 mice eliminates much of the ammonia from the cage and so it usually can go two weeks without needing a change. But what if a cage houses only one or two mice? Does that cage actually require changing at the same maximum two week interval? We conducted a pilot study a couple of years ago and found that 30% of our mouse cages could go longer than two weeks without needing changing, based on ammonia levels and general appearance inside the cage (Brandolini, *et al.,* 2009). Considering that we now have 29,000 mouse cages in daily use, changing cages only when they need it rather adhering to a rigid schedule would yield major savings in labor and supplies, and free up staff to perform more necessary tasks. We continue to evaluate these findings and think about how a more rational system of cage changing may be implemented universally.

Finally, vivarium design always devotes space for storing bags of feed and bedding because this is always included in the "standard" list of physical features a vivarium should possess. But this occupies valuable space that, if not truly essential, could be used for more worthy needs, such as housing more animals to conduct more research. We examined our feed and bedding supply process and discovered two things.

The first discovery came from our practice of assigning cage-front staff responsibility for ordering feed and bedding based on their respective rooms' needs, bringing up the bags from the receiving dock, and unloading them in the feed and bedding storage room. But then we looked at how retail stores such as supermarkets stock their shelves, and remembered it's not the store but the vendors that estimate how many products to deliver and then often stock the shelves themselves. When we calculated the cost of labor involved when our staff performed these tasks, it exceeded $150,000 a year. And that did not include the actual purchase costs for those items. We want our workers to be experts in lab animal care, not experts in ordering supplies and stocking shelves. So we have launched a pilot experiment with our primary feed vendor to see how it works if they deliver feed to the vivarium and drop it off not to the feed storage room but to drop-off points deeper within the barrier, allowing our staff to walk shorter distances to get what they need for the animals when they need it. After the pilot is completed, we will compare notes with the vendor. If this new system seems to have worked to both party's satisfaction, they can propose a separate price for delivery and stocking in addition to selling us their product. We can then determine if the price is attractive and also avoid the need for temporary feed storage space.

The second discovery we made about our feed and bedding supply program is how we did not need a separate room for storing bedding either. If bags of bedding are delivered frequently enough, and if there is enough space in the clean side of cage wash where bags are opened for dispensing bedding into cages, why do we need an intermediate location

for stacking bedding bags and then unstacking them and hauling them to cage wash? In one of our barrier facilities, we now have what is possibly the first situation for any large program in the US in which clean cage wash is also the same room as (temporary) bedding storage. Two days supply of bags are stacked right next to the bedding dispenser and stored nowhere else. I know what you're thinking – what if there is a disruption in delivery or a sudden and unexpected demand for more bedding, after which we quickly run out? My current hypothesis is that sufficient bedding can be obtained from our four other barrier facilities to get us through any shortages until more supplies arrive. If we learn otherwise, then we go back to the drawing board and conduct additional pilots. In the meantime, the former feed and bedding storage room in this one facility has been converted into much needed office space.

But how will flexible husbandry practices like these are regarded by others not as creative in their thinking? There is good news in this respect. The newest edition of the Guide was just released and is replete with changes that embrace performance standards over engineering standards (National Research Council, 2010). This jargon may sound arcane but it has major implications for the future of lab animal care. If you have an equal or better way of maintaining animal welfare or employee safety than a conventional approach, and have the hard data to prove it, there is growing recognition and even encouragement that you're free to use your way rather than be confined to others' standards. And as research funding in the US becomes tighter, more of us over there will be forced to identify and eliminate waste in everything we do to keep our costs competitive for our scientist customers and institution employers.

There is one caveat for those of you who work in a Good Laboratory Practices environment, especially as a CRO. Tread cautiously here because most western sponsors come from rigid, SOP-driven cultures. You will have to be either nimble in eliminating waste and lowering your costs where it won't show up on a sponsor's audit or successfully appeal to their rational side (and their checkbook).

In any event, I'll tell you a story that underscores Indian attitudes about avoiding unnecessary costs. Last October, I visited the new headquarters of the Harvard China Fund in Shanghai, strategically located in the heart of the financial district and around the corner from many luxury retail stores. While there, I learned that HBS had installed executive education classrooms next to the Fund's offices and had great success in attracting Chinese businessmen and women to courses conducted there by HBS faculty. It is no surprise after decades of Communist rule that many Chinese executives lack knowledge about the subtleties of finance and other capitalist subjects, and these courses are in great demand. The Harvard brand name doesn't hurt either. By contrast, I was told that when HBS tried to launch the same courses in India, they failed. Courses were considered by Indian business managers to be too expensive and not helpful enough to justify the price. The lesson learned by HBS, somewhat to their surprise, was that Indians clearly wanted something cheaper and of greater value, and wouldn't pay more for less.

On a similar theme, the Financial Times columnist Gillian Tett recently wrote about "reverse innovation", a term coined by Professor Vijay Govindarajan of the Tuck School of Business at Dartmouth College. He observed that executives at multinational corporations are seeking ways to introduce innovations from developing countries can be exported to western markets. Ms. Tett quotes a chief technology officer of a US multinational as saying, "In the west we assume that innovation is there to make products more powerful, flashier, faster – but in emerging markets, innovation is about commoditisation, about cutting costs" (Tett, 2011).

Consequently, I look forward to learning about innovations you develop that also will reduce costs for us in the west. What andaz for lab animal care will arise from India that we can adopt?

The third category of lessons to be learned from India involves your broad and deep reverence for life of all kinds. India's cultural tradition dates back to 8,000 BCE and has a continuously recorded history for over 2,500 years. India today has a dramatically different attitude towards animals than in the west. In your country, animals are valuable to individual families, not for companionship, but for prosperity and even survival. In addition, the sacred standing of particular species in many of your religious beliefs is something we don't apply in the west.

This sacrosanct status afforded animals likely causes major problems for you who care for research animal subjects to which bad things may be intentionally done. It causes us the same problems, both in terms of society's unease and our personal discomfort. But these problems should be troublesome personally and otherwise. That's because using animals for research or testing that involves pain and distress shouldn't be a casual experience for anyone. If it is, you're in the wrong field.

But here's my request to you. In western culture, based on centuries-old Judeo-Christian-Muslim beliefs, we maintain mostly a dominion-based attitude toward animals. Even with the recent phenomenon in the US of considering some animals as members of one's immediate family, we still aim to be (hopefully benevolent) stewards or overlords when it comes to our relationship with animals. One consequence of this attitude, from my amateur sociologist perspective, is that when it involves lab animals, we occasionally tolerate mistakes that to the animal are catastrophic. If a water bottle or an automatic watering valve leaks by accident, killing the mice inside the cage, it's certainly a regrettable episode, especially to the scientist or sponsor who has invested much time and effort in the study and especially if that mouse was

the only one of its kind with respect to genotype, stage of the experiment, or recipient of precious test article. However, we may not take such episodes seriously enough to insist on a zero-defects approach, especially for the sake of the mice themselves. Instead, we try to find the cause (such as bad equipment, poorly trained or overworked staff, or maybe even a mouse that is especially sensitive to hypothermia) or think we already know the cause without any further investigation, and assume or hope we're right. What if such an attitude was applied to airplane maintenance or elevator installations? Society certainly wouldn't tolerate such a cavalier approach in those situations involving human lives. So is there something in the Indian ethos for respecting life at a higher plane that can help us in the west find a better framework for honoring the animals to which we provide care, so that everything rather than merely something is done to avoid unintended losses and the additional expense of doing so are recognized as necessary?

In conclusion, India is on an exciting path but has much more to accomplish. We in the west are ready and willing to assist. India can become a leader in lab animal care and use by leveraging its native species, leveraging its adaptive culture, and leveraging its unique moral beliefs.

Thank you for your time and attention. It has been a privilege to deliver this keynote address and I wish you all a successful meeting

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