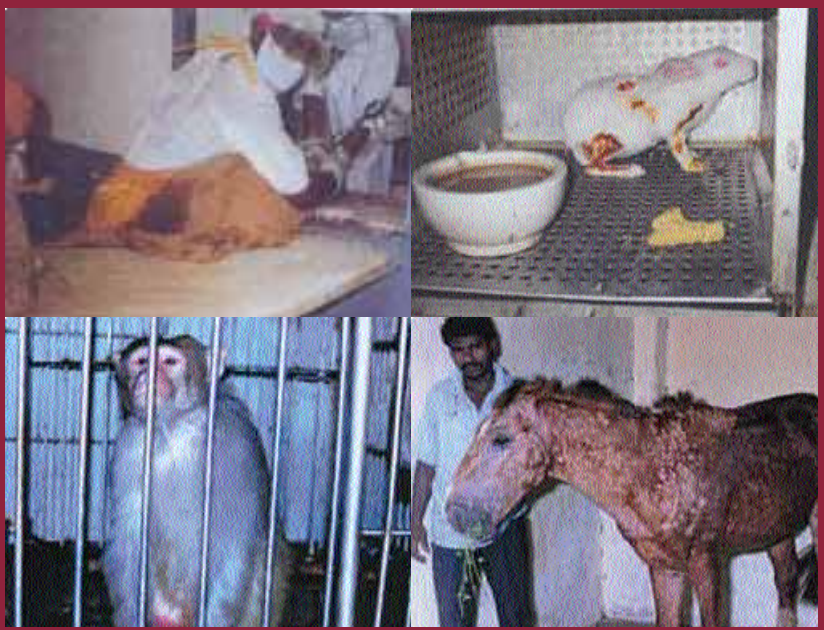
Animal Defenders International • National Anti-Vivisection Society

Animal Experimentation in India



Unfettered science:
How lack of accountability and control has led to
animal abuse and poor science

"The greatness of a nation and its moral progress can be judged by the way its animals are treated. Vivisection is the blackest of all the black crimes that man is at present committing against God and His fair creation. It ill becomes us to invoke in our daily prayers the blessings of God, the Compassionate, if we in turn will not practise elementary compassion towards our fellow creatures."

And, *"I abhor vivisection with my whole soul. All the scientific discoveries stained with the innocent blood I count as of no consequence."*

Mahatma Gandhi

Thanks

With thanks to Maneka Gandhi and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) of India for their report on the use of animals in laboratories, which has been used for this critique of the state of scientific and medical research in India.

Animal Defenders International and the National Anti-Vivisection Society UK fully support and encourage the efforts of the members of India's CPCSEA to enforce standards and controls over the use of animals in laboratories in India, and their recommendation that facilities and practices in India's research laboratories be brought up to international standards of good laboratory practice, good animal welfare, and good science.

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There are extreme examples of bad animal husbandry and laboratory practice in CPCSEA's study.

However, other aspects of the findings represent common problems in the world's laboratories – such as this small, bare monkey cage at the All India Institute of Medical Sciences (AIIMS).

Introduction

Animal Defenders International (ADI) and the National Anti-Vivisection Society UK (NAVS), have been presented with a substantial dossier of animal suffering by Maneka Gandhi, former chair of India's Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

In this report, ADI/NAVS discuss the evidence gathered by the CPCSEAduring the course of their inspections of 467 laboratories in India, which paints a horrifying picture of the state of research inside India's animal experimentation facilities: substandard and unhygienic conditions, sick and dying animals and appalling animal suffering, as well as poor science.

In addition we have reviewed the international scientific literature for research papers from India, and provided a critique of this work; we have also examined CPCSEA's evidence in light of legal controls and laboratory practice in other countries.

We find that there are key faults in the governance of the animal research industry in India: there is no proper critical review of proposals to use animals in experiments; there are no management structures in place to deliver full accountability and legal compliance; no adherence to animal welfare policies; no requirement to seek to use the sophisticated non-animal techniques which are now available, prior to making the decision to use animals.

Our conclusion is that literally years of scientific research in India has been invalidated by poor scientific procedure, poor laboratory practice and lack of appropriate animal care.

A number of laboratories mentioned in CPCSEA's report were selected for examination here:-

All India Institute of Medical Sciences (AIIMS), New Delhi
Bengal Chemicals, Kolkata
Bombay Veterinary College, Parel, Mumbai
Delhi University, College of Pharmacy
Haffkine Biopharmaceutical Corporation Ltd., Pune
Indian Institute of Science, Bangalore
Indian Veterinary Research Institute, Izatnagar
Jai Research Foundation, Ahmedabad
Jawaharlal Nehru University, New Delhi
Kakatiya University, Warangal
King Institute of Preventive Medicine, Chennai
Marathawada University, College of Veterinary Sciences
Maulana Azad Medical College, New Delhi
National Institute of Virology, Pune
Patel Chest Institute, University of Delhi
Vaccine Institute, Vadodara
Vins Bioproducts Ltd., Hyderabad

Dr S. Chinny Krishna, Vice Chair of the Animal Welfare Board and CPCSEAnominee notes: *"....out of the 467 laboratories which have so far been inspected by various nominees, it has been found that more than 400 of such laboratories do not have even basic facilities for proper housing of animals which are under their charge*[i]*."*

The CPCSEAwas formed in 1964, but soon lapsed into inactivity. In February 1991 the CPCSEAwas re-constituted under an industry chair, Dr A.S. Paintal, Director General of the Indian Council for Medical Research. However, the Committee again apparently failed to address any of the very clear problems within India's animal experimentation community. In February 1996 a new CPCSEAwas constituted, chaired by Maneka Gandhi (at that time a Member of Parliament). The revitalised CPCSEAintroduced a raft of regulations in an attempt to regulate the

introduction

industry and commenced an inspection programme to assess science and animal welfare conditions in nearly 500 laboratories[1].

This report is a shocking indictment of animal experimentation in India, but also an indictment of the international research community which is prepared to publish papers from laboratories with such poor practices, and has failed to take action to address the clear welfare problems which have compromised the entire scientific output of a whole country.

Who decides our future?

There is a vociferous lobby within the international scientific community committed to resist accountability and control. This is most notably demonstrated in the fields of genetic modification (GM) and animal experimentation where there is, understandably, enormous public concern and a demand for restrictions, regulation, accountability, and public access to information. A story in the 'British Medical Journal'about CPCSEA's attempts to control animal experimentation in India illustrates the typical response from the scientific community: *"Scientists accuse animal rights activists of stifling research[2]."*

In May 2002, British Prime Minister Tony Blair addressed The Royal Society in a speech entitled 'Science Matters. He stated: *"The idea of making this speech has been in my mind for some time. The final prompt for it came, curiously enough, when I was in Bangalore in January. I met a group of academics, who were also in business in the biotech field. They said to me bluntly: Europe has gone soft on science; we are going to leapfrog you and you will miss out. They regarded the debate on GM here and elsewhere in Europe as utterly astonishing. They saw us as completely overrun by protestors and pressure groups who used emotion to drive out reason. And they didn't think we had the political will to stand up for proper science[3]."*

There is little evidence of this, indeed as Mr Blair himself noted: *"By any measure, our record is outstanding. With 1% of the world's population, we fund 4.5% of the world's science, produce 8% of the scientific papers and receive 9% of the citations[3]."*

Considering the risks posed to humans, other animals, and the environment by unfettered scientific and medical research, this was an extraordinary statement for a Prime Minister to make. Already, new diseases have been created in laboratories through cross-species transmission. Many doctors are concerned about the risks posed to the human population from pig viruses, should animal to human transplantation programmes continue. Concerns about biodiversity and environmental damage from genetically engineered plants, animals and viruses are issues not only for the scientists creating these products, but for farmers, and the whole community.

It is vital that decisions about the direction of science are made within the context of full public awareness and consent – this is not something to be left to those with a vested interest in maintaining their freedom to do whatever they wish.

Unfortunately, there is tendency to sweep aside critical views of the scientific community as simply 'anti-science'. This is as wrong as thinking that unfettered research will automatically lead to progress and good science. **The evidence presented here from India reveals dramatically the failure of self-regulation in terms of animal protection, it also shows that uncontrolled and unaccountable science is ultimately bad science.**

Animal Defenders International and National Anti-Vivisection Society UK are not anti-science, we are against animal experiments. We are in favour of well thought-out, intelligent and properly designed science which is ethically based and works within the context of human society. The majority of research does not use animals anyway, and we believe that science and medical research would be better served if it concentrated on our own species, rather than using the results of experiments on other species.

This report on the state of India's animal research industry brings shame on India's scientific community, and raises important questions about the role of the international research community, science journals, and international funding bodies (including governments).

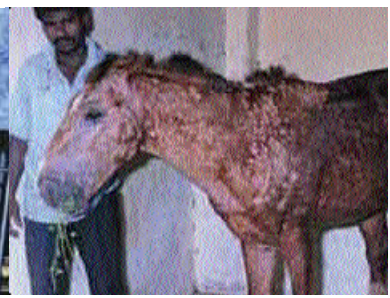
1. S. Chinny Krishna, Not a Maneka creation – History of the CPCSEA, Manushi, no 132, 2002
2. BMJ, p1192 vol. 325, 23.11.02
3. www.number-10.gov.uk/output/Page1715.asp

summary of findings

Haffkine Corp., Mumbai: Conscious sheep held down whilst a hole is drilled into the skull – vaccine production.

Kakatiya University, Warangal: Rabbit under experimentation, showing multiple injuries.

National Institute of Virology, Pune: Monkey in a filthy, barren cage; the room had no light fittings, nor cooling fans.



King Institute, Chennai: Pony suffering from a severe skin infection (subsequently rehabilitated by the CPCSEA).

Summary of findings

The findings of India's Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) show a deplorable standard of animal care in the majority of facilities inspected. Such appaling conditions have not only caused inexcusable levels of animal suffering, but have also undermined any pretensions that the research was conducted scientifically, and that the results were reliable. The findings include:-

- **Use of animals without health orgenetic background knowledge (including strays – street dogs).**
- **Animals living in filthy, unhygienic conditions.**
- **Experiments being performed in similarunhygienic conditions.**
- **Sick and injured animals left unattended, and animals denied post-operative care. This included animals which had been blinded, severely mutilated, orwith open wounds.**
- **Some institutions had been without a veterinary official in attendance foryears.**
- **Rats and mice infected with disease, and infested with mites and tapeworms.**
- **Horses with theirhooves infested with maggots.**
- **Rats being blinded during orbital bleed procedures.**
- **Hot irons used to brand horses.**
- **Inadequate and often wholly unsuitable facilities, e.g. lacking in appropriate ventilation oreven a water supply.**

summary of findings

- **A lack of consistency of standards between the facilities, ranging from derelict buildings being used to house experimental cattle, to a variety of rusting cages forotheranimals.**
- **Animals severely restricted in theirmovements, and overcrowded in small, dirty cages.**
- **Animals self-mutilating and performing abnormal, repetitive & stereotypic behaviours.**
- **Inadequate provision of food and water.**
- **Brutal procedures such as drilling holes in the skulls of conscious sheep and then injecting rabies virus into the brain fora discredited vaccine.**
- **Placing live and conscious frogs in refrigerators, in orderto freeze them.**
- **Failure to identify orutilise non-animal methods when they are available.**

The CPCSEAguidelines state: *"The CPCSEA requires that genetically defined animals should be lawfully obtained from breeders; that experimental animals should be kept in standardised, hygienic experimental conditions during and post surgery to maximise reliable and reproducible data from experiments....."*

The UK government 'Code of Practice for the Housing and Care of Animals Used in Scientific Procedures' outlines the regulations for the use of animals. This states: *"In scientific work involving living animals, the most reliable results are likely to be obtained by using healthy animals that are well adapted to their housing conditions and, in quantitative assays or comparisons, precision is increased if those animals are uniform."*

This is reiterated in the UK government's 'Code of Practice for the Housing and Care of Animals in Designated Breeding and Supplying Establishments', which states that: *"Healthy animals are a prerequisite both for good animal welfare and for good science. Intercurrent infection in the animal population may call into question the validity of information obtained from scientific procedures and make interpretation of results difficult or even impossible."*

These policies are repeated frequently by the animal research community as a justification for self-regulation. Yet conditions in these Indian laboratories show the manifest failure of the vivisection industry to police itself – uncontrolled, the industry is incapable of providing an acceptable standard of animal welfare and good science. Even more damning is that papers from these institutions have been accepted and published in international scientific journals when the appaling conditions in the facilities should have ensured the data was rejected as wholly unreliable.

Above, left: AIIMS: CPCSEA report that this dog had been illegally taken from the street for this experiment because "...the size of the dog makes it more convenient...."

Above, right: College of Pharmacy, Delhi University: Rat blinded after orbital bleeding. As often as twice a week a glass tube is pushed behind the eye and twisted to puncture blood vessels.

If proper care is not taken, the tube may actually pierce the eye itself and create infection, swelling and damage, or it may pass through the skull behind the eye into the brain. Blood may build up in the area behind the eye after puncture, creating pressure on the eye itself. The accumulation of blood may also damage other parts of the eye,, and can cause blindness. Also, the handler may put pressure on the eye itself to limit bleeding, and this can cause inflammation.

In the UK, the procedure is said to be avoided unless the animal is unconscious and will never wake up. This procedures is unnecessary because there are clearly other ways of taking blood from animals.

BVA/FRAME/RSPCA/UFAW joint working group on refinement. Removal of blood from laboratory animals and birds. Laboratory Animals 1993; 27: 1-22

Animal welfare and science

Discussion about animal experimentation is generally focused on the purpose, and procedure involved in the actual experiments. When the procedure requires that an animal be either burnt, blinded, infected with disease, or given electric shocks, less attention is paid to conditions of animal husbandry or welfare.

There are strong arguments to be made against animal experimentation on scientific and ethical grounds, and we address these later in this report. However in the case of this study of Indian animal laboratories, there are strong arguments to be made on purely welfare grounds – just like animals on intensive (factory) farms, laboratory animals are kept in small impoverished environments.

Since laboratory animals are destined to spend their entire existence in impoverished environments (and for some this may be many years), the impact on the animal of animal management and husbandry must be considered. Moreover, overbreeding of animals in order to maintain supplies is common in many laboratories; studies have shown that this means that more than a third of the animals bred in laboratories are not used in experiments but killed because they are surplus to requirements. Others are reared and killed for their tissues.

AIIMS, New Delhi: Monkey no. 1411. This 27-year-old has spent 19 years in captivity.

At the time of the photograph it was being used in an experiment to see whether 27 year old monkeys can have sex and reproduce.

The need for this experiment should be questioned. It is inconceivable that the way this animal has been kept, will not have a dramatic impact on any research conclusions.

Evidence of the effect on animals of deprived environments in zoos and factory farms has instigated changes in the way zoo animals are kept, and even more dramatically, the banning of the battery cage for laying hens in Europe.

The UK government's Farm Animal Welfare Council has developed the 'Five Freedoms'strategy as a means of assessing animal welfare in captive situations:-

(1) Freedom from hungerand thirst – ready access to water and a diet to maintain health and vigour.
(2) Freedom from discomfort – by providing a suitable environment.
(3) Freedom from pain, injury and disease – by prevention ortreatment.
(4) Freedom from fearand distress – by providing conditions which avoid mental suffering.
(5) Freedom to express natural behaviour– by providing sufficient space and adequate facilities.

Using the Five Freedoms criteria enables identification of situations which compromise good animal welfare, that is, situations which cause fear, pain, discomfort, injury, disease, or behavioural distress. This policy has been adopted in many countries.

Although by the very nature of animal research there is often an intention to cause pain, fear and distress to animals, this does not mean that laboratories are not duty bound to do their utmost to minimise these negative experiences. There is never any justification for not providing laboratory animals with the best animal care and welfare standards.

Studies have shown animals in zoos performing abnormal, repetitive behaviours (stereotypic, or displacement behaviours) which have been brought about by their environment – restrictions on movement, lack of stimulation, environmentally impoverished enclosures, herd animals kept in isolation, or alternatively overcrowding, and conditions which prevent the animals from performing their natural behavioural repertoire. Many of these abnormal behaviours have been noted in animals in other captive situations such as laboratories and factory farms.

College of Pharmacy, Delhi University: Rabbit in a small, barren cage, suffering from dermatitis.

It is now widely accepted that the way animals are kept can cause suffering and damage to mental and physical health, and that it is is not enough to provide the bare minimum in order to merely keep them alive. Animals deserve a reasonable quality of life.

animal welfare & science

AIIMS: A line of monkeys in small, old, rusting cages, with no stimulation for the animals.

CPCSEA also report that the animals had no water. Such neglect of animals is both cruel and unprofessional; it is not without consequences to the science.

However what may be more compelling to the animal researcher, is that biochemical changes in animals caused by stress and environment (animal housing) have been shown to have a clear impact on experimental results.

In 1958 W. Lane-Petter noted in 'New Scientist', *"It has been said that animals are to the experimental biologist what chemical reagents are to the chemist. Chemicals can for the most part be stored on the shelf, but animals grow and alter in the course of their environment*[1]*."*

Trevor Poole, of the Universities Federation for Animal Welfare, wrote in 'Laboratory Animals'in 1996, *"To ensure good science, the animal should have a normal physiology and behaviour, apart from specific adverse effects under investigation."* And also, *"On scientific as well as ethical grounds, therefore, the psychological well being of laboratory animals should be an important concern for veterinarians, animal technicians and scientists"*[2].

Suffering and stress are therefore unwelcome and confusing additions to any experiment.

A basic principle of the proper construction of scientific experiments is that variables not under investigation should be strictly controlled. Ensuring standardisation within the experimental protocol is the only way of enabling other scientists to verify results. Reproducibility of an experiment, whatever the research discipline, is often a cornerstone of scientific credibility. These principles are reflected in the the UK government's 'Code of Practice for the Housing and Care of Animals Used in Scientific Procedures', and also, in the guidelines laid down by the CPCSEA.

The evidence contained in the report of the CPCSEAof their study of the use of animals in laboratories in India reveals that poor laboratory practice, poor science, and poor animal welfare are rife in the Indian animal research community – an unacceptable state of affairs in terms of both animal welfare and science.

The impact of poor welfare on experimental data

As mentioned above, it is well documented that any compromise in the well-being of animals can generate physiological and immunological abnormalities. For example, isolation in housing for some animals leads to changes in levels of neurotransmitters in the brain, social stress can lead to kidney and heart disease in laboratory mice, and stress generally has been found to contribute to extensive sclerosis (furring) of the arteries of monkeys even when they were fed a low cholesterol diet.

The immune system itself is very sensitive to effects from stressors. Adult macaques, for example, may show long-term changes in their immune system after only a brief separation from their mother at the age of six months[2]; the higher levels of stress and sex hormones characteristic of laboratory mice in subordinate positions is correlated with a reduction in immunological response to an antigen[3] (sheep red blood cell); overcrowding mice generally lowers their resistance to a particular parasite [4]. Housing conditions of experimental animals have also been reported to affect immune function when challenged with *Plasmodium berghei*[5]. In fact research has shown the interdependence of brain, behaviour, hormones and the immune system is such that disturbances in one of these systems commonly influences one or all of the others[6]. Joseph Garner, a behavioural scientist in the US, has found evidence that stereotypical behaviour, the name given to repetitive and apparently purposeless behaviour of humans and other animals, which was thought just to be superficial ticks of normal animals, is correlated with damage to the basal ganglia of the brain[7].

The problem of the affect of animal husbandry and welfare on standardisation of experimental data is compounded by the differences in response to stress, between different species. Even closely related species, e.g. rhesus, bonnet and cynomolgus monkeys, respond differently to stress[8]. Furthermore, the laboratory environment may contain stressors of which we are unaware. While humans can only hear up to about 20 kiloherz many animals used in laboratories can hear much higher frequencies[2], and this may have all kinds of significance for the animals in

question. For example, the visual display units of computers emit a highly pitched ultrasonic scream, almost indistinguishable from the fear cry of a rat[8].

It is obvious that the physiological and immunological variation introduced by such factors as animal housing, husbandry and laboratory conditions will have an effect on experiments. Enormous variation is introduced into toxicity study findings according to how familiar an environment is. For example, in nephrotoxicity studies (i.e. studies of toxicity to kidney cells) rats not allowed time to acclimatise to their surroundings recorded a level of 3-8mg/kg as a toxic dose while those allowed 21 days recorded a level of 220-650mg/kg as a toxic dose – a potential difference of over two hundred times[9]! Meanwhile drug metabolism in general may be affected even by simple husbandry routines. Cage cleaning was found to be responsible for a significant increase in heart rate in rhesus monkeys, an increase which persisted for 2 hours afterwards[10].

Jai Research Foundation, Ahmedabad: Dogs held in small cages with uncomfortable wire mesh floors.

CPCSEA also report that these dogs were strays, so no details of the animals' background, accurate age, or health status would have been available.

Most researchers working with animals make assumptions that the animals under investigation have normal blood pressure, heart rates, levels of stress hormones, immunological competence, digestion, appetite and behaviour. And as mentioned earlier, although there are strong arguments to be made against animal experimentation on both scientific and moral grounds, any deviation from an assumed backdrop of normal physiology and behaviour will constitute a departure from the accepted conventions of laboratory animal science and the resultant research will be confounded by variables which other researchers can only guess at.

The conditions prevailing in the animal houses at the National Institute of Virology, Pune, AIIMS, New Delhi, Maulana Azad Medical College, New Delhi, the Indian Veterinary Research Institute, Izatnagar, Bengal Chemicals, Kolkata, Vins Bioproducts Ltd, Hyderabad, Haffkine Biopharmaceutical Corporation Ltd, Pune, the King Institute of Preventive Medicine, the Patel Chest Institute, University of Delhi, the Indian Institute of Science, Bangalore, and Jawaharlal Nehru University, New Delhi, fall far below any standards consistent with humane practice and would generally be described as good laboratory animal science.

The point of reference which is available to us on the subject of basic welfare requirements for laboratory animals are the standards incorporated into the 1986 European Convention[11], and the standards laid down by the UK government's Home Office, and some of these provisions are discussed below.

Provision of food and water

The 1986 European Convention provides that "*Any animal used or intended for use in a procedure shall be provided with accommodation, and environment, at least a minimum of freedom of movement, food, water and care, appropriate to its health and well-being*[11]." This is elaborated on in sections 3.33 – 3.35 of the UK government Home Office guidelines which advise that clean drinking water must normally be available to all animals at all times, and since water is a vehicle for micro-organisms the water system should prevent contamination. Water should be checked daily. According to the UK Home Office Code of Practice diet must be formulated to satisfy the nutritional requirements of the animals and in all aspects relating to food, precautions must be taken to prevent its contamination. All food hoppers and utensils should

Maulana Azad medical College, New Delhi: A rabbit with newborn infants, in a dirty cage with a wire mesh floor and neither bedding material, nor water.

Note that the large gauge of the mesh is not suitable for the small feet of the baby rabbits; also, that one infant (in front of the mother) is already dead.

Vaccine Institute, Vadodara: Overcrowded sheep.

be cleaned and sterilised regularly. At Maulana Azad animals were without food or water because the attendant had not reported for duty.

CPCSEAinspectors found animals including rats, hamsters, guinea pigs, sheep and dogs being kept either without water, or the water was stagnant or contaminated with slime/faeces (National Institute of Virology, AIIMS, Maulana Azad Medical College, Indian Veterinary Research Institute.). At the National Institute of Virolgy in Pune, the inspectors reported finding mosquito larvae in the drinking water containers, indicating that the water had not been changed for some days.

The investigation highlighted deficiencies in feeding routines. Food for rats and mice was contaminated (National Institute of Virology) and rotting (Maulana Azad Medical College), while rabbits'food was found to be infested with mites, fungus, stale feed, rotten vegetables and faeces (Maulana Azad Medical College) or completely inadequate (Indian Veterinary Research Institute.) Food was generally inadequate at Bengal Chemicals, Kolkata, while at Jawaharlal Nehru University sacks of animal feed were not being kept free of contamination and as a result were infested with insects. There was also evidence of animals being fed inadequate diets; cattle and horses at Bengal Chemicals, Kolkata, and the King Institute of Preventative Medicines, Chennai, were emaciated and rabbits at Maulana Azad Medical College apparently were being fed straw.

Environmental control

Generally, the facilities were not purpose built and so lacked any environmental control – at the College of Veterinary and Animal Sciences, Marathwada Agriculture University, cattle were kept in a run down building without proper roofing. Consequently, control over ventilation, humidity, lighting and temperature is not possible, and so the environment varies widely on a daily basis. This is further compounded by the fact that so many of the facilities had animals in both overcrowded and unsanitary conditions.

At the National Institute of Virology in Pune it was found that light and ventilation were lacking in the rooms where monkeys, rats and mice were being kept. There was no ventilation in the room where sheep were kept. At Maulana Azad Medical College the air conditioning in the animal house was not effective and there was no arrangement for monitoring temperature and humidity. Moreover pesticides were being sprayed in the rooms, despite the presence of animals. At the Indian Veterinary Research Institute the room housing guinea pigs was very hot and there was no arrangement for measuring temperature and humidity. At the Patel Chest Institute the rooms in the animal house were dark, airless and without ventilation. The windows were shut and the air conditioner and exhaust fan were not functioning.

According to the UK Home Office Code of Practice animal house temperatures should be carefully controlled and continuously monitored by instruments which are checked at least once daily. It should be noted that if room temperatures are high, they may well be even higher within individual cages, and temperature requirements vary between species, furthermore, undue fluctuations create stress and are to be avoided[1].

Appropriate ventilation can be important in regulating the environment and may also be used to form part of the barriers to the movement of airborne

King Institute, Chennai: Rabbit with its nose and ears eaten away, and with a severe paw infection.

infection and contamination. The needs of the animals should dictate stocking densities, but the efficiency of ventilation may also be a factor. Any smell of ammonia probably reflects overstocking, too little ventilation, inadequate cleaning, or a combination of these factors; the causes should be investigated and rectified[1]. At Maulana Azad, for example, the inspectors found that it was difficult to breathe owing to overcrowding and lack of ventilation in the sheep pens.

Bengal Chemicals, Kolkata: A wounded and sick horse.

Cleanliness/hygiene

Standards of cleanliness and hygiene have caused concern throughout the investigation. The animal house at the National Institute of Virology was extremely dirty and mosquito larvae were found in drinking water pots. At Maulana Azad sheep had maggot wounds and rabbits had mange mites and dermatitis indicative of neglect and poor cage cleaning. Rat and mice cages had not been changed for so long that bedding material and faecal matter occupied more than 50% of the height of the cage. Rabbits were left to wander and reproduce on the floors. The straw and sawdust had caked on the floors and had been discoloured with urine. Cauliflower leaves thrown to the rabbits had rotted into the sawdust. Rotten and decayed bodies of new born babies were lying on the ground. At the Indian Veterinary Research Institute rooms were covered with cobwebs and accumulated dirt and dust. The post mortem room was full of dirt and poultry feathers and appeared not to have been cleaned for possibly years. In the room housing rabbits, collection trays for faeces were full of rotting faecal matter and fungal growth.

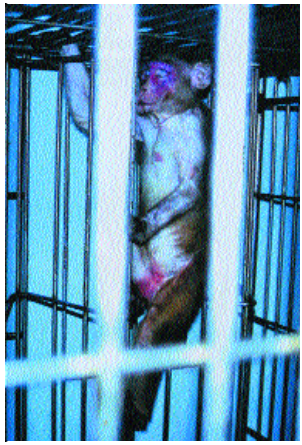
In short these facilities are filthy and unhygienic. Unless these establishments claim their studies are specifically related to animals living in their own excrement, any data collected is quite meaningless, since the impact of these conditions on health and welfare is obvious. The UK Home Office Code of Practice notes *"Good hygiene constitutes an important contribution to animal welfare and the attainment of realistic and reliable experimental results"*[13].

Animal health and background

As stated earlier, the UK Code of Practice emphasises the importance of the health of laboratory animals in scientific terms: 3.72: *"Healthy animals are an essential prerequisite for good science. Intercurrent infection in the animal population may call in question the validity of information obtained from scientific procedures and make interpretation of results impossible"*[1].

The CPCSEAreport indicates that poor animal health is commonplace in Indian laboratories. At the National Institute of Virology most of the primates had symptoms of skin disease, paralysis, diseases of the limbs and diarrhoea. Some primates were suffering from muscular dystrophy, anaemia, arthritis and had blood oozing from old unhealed fractures. Many primates did not have fingers or teeth. Sheep had overgrown hooves which might cause injury, and had discharge from the nostrils. Fowl had white flaky scaly lesions. At AIIMS monkeys were suffering from tuberculosis. Young animals had died from a range of problems including dehydrated kidneys, congestion of the lungs, haemorrhage and pneumonia. At Maulana Azad Medical College there was a large number of chronically sick animals, including sheep with maggot wounds, rabbits with ear mites and a twisted neck, guinea pigs with gaping wounds on their backs.

King Institute, Chennai: This horse has a severe hoof injury that has been neglected and become infested with maggots (animal subsequently rehabilitated by the CPCSEA).



National Institute of Virology, Pune: A blind monkey.

Most of the monkeys had symptoms of skin disease and diarrhoea.

It was reported that some were so old and in such poor condition that they could not extend their limbs and many had fingers and teeth missing.

Rabbits and guinea pigs had dermatitis. At the Indian Institute of Science monkeys were found to be suffering from skin diseases.

Good laboratory practice recommends a number of screening procedures since infections in laboratory animals may affect research conclusions and may have consequences for human health. Some viruses in mice are potentially fatal to humans while others cause subclinical infections. Viruses affecting mice which commonly affect research data are MVM (minute virus of mice) and LDHV(lactate dehydrogenase elevating virus). MVM and many others can infect transplantable tumours and tissues, and LDHV causes increases in the levels of several enzymes, interfering with results[12]. It is recommended that a host of other infections in mice be monitored where there is evidence of interference with physiological parameters.

Rats are susceptible to a number of diseases which may be zoonotic (Hantaan virus and leptospirosis), have effects on the animals when under stress, or affect research data. Sendai virus, pneumonia virus of mice, SDA/RCVor *Mycoplasma pulmonis* may all have effects on the respiratory system, particularly in the stressed animal, and Kilham rat virus may infect transplantable tissues and may cause birth defects[12].

Rabbits suffer from bacterial infections the most important of which is *Pasteurella multocida*. Adequate environmental conditions are essential to prevent major outbreaks of this, in particular certain conditions of humidity, meticulous hygiene, low stocking density and the avoidance of stress. The stress of scientific procedures often precipitates the outbreak of clinical disease. In general many of the commonest diseases of rabbits are husbandry-related, so it is very important that the diet, housing, environment and general management of rabbits are kept up to a high standard[12]. A glance through photographs of Maulana Azad Medical College and AIIMS indicates that this clearly was not the case at these establishments.

For dogs, depending on the type of research, many diseases can confound results. Respiratory or cardiovascular research may be affected by diseases such as kennel cough caused by organisms including *Bordetella bronchiseptica* and parainfluenza virus. *Toxocara* infections interfere with toxicology studies because visceral larva migrans causes histological lesions which may be interpreted as being due to the compound under test[12].

Good hygiene is absolutely essential with primates, which may carry a large number of zoonotic diseases, and which may contract diseases that are mild in humans but severe in monkeys. Tuberculosis causes a chronic fatal disease in monkeys which can remain subclinical for six months or more. Regular screening is also essential for a number of zoonoses which can cause explosive outbreaks of disease and death if not controlled immediately[12].

In sheep many diseases may have effects on research. Sheep are often used in anaesthetic and cardiovascular research. They are, however, particularly prone to respiratory diseases including *Pasteurella pneumonia*[12].

The UK's Animals (Scientific Procedures) Act 1986 requires that each establishment which is licensed to perform animal experiments must nominate a Named

AIIMS: A blinded post-operative rabbit with a deformed ear, living in a dirty cage.

The picture was taken in September 2001. During the period 1999 to 2001, there was no veterinarian for the small animal house.

Veterinary Surgeon and a Named Animal Care and Welfare Officer (NACWO). In addition to monitoring the health of the animals they are also responsible for maintaining animal health records, laboratory and animal house environmental conditions, advice concerning treatment given, and source of animals; a named Designated Establishment Certificate holder is ultimately responsible for legal compliance[14].

During CPCSEA's study of the Indian laboratories, the absence of a veterinary officer or proper record-keeping is notable in a number of establishments.

Bombay Veterinary College, Parel, Mumbai: An overcrowded rabbit cage.

Overcrowding and severe confinement was apparently common throughout the investigation.

Overcrowding alone can lead to poor health and increased stress which undermines experimental data.

It can also lead to fighting with severe injuries and even fatalities.

At the National Institute of Virology there were no records regarding the health of the animals, history of medical treatment nor even history of experiments on animals. At AIIMS there was no veterinary doctor for the small animal house during the period 1999-2001 and no health records of individual primates or their history. At Maulana Azad, there has been no veterinary doctor in the college for the last eight years. There was no record being maintained of temperature and relative humidity in the rooms of the animal house, breeding charts were not available for sheep and rabbits, and there was no record of the health of the animals. Despite some improvements at Bengal Chemicals, record-keeping of blood smear examinations and veterinary care in general remained poor. At the Indian Institute of Science, random checking of records showed deficiencies in data maintenance on primates. At the time of the inspection at Jawaharlal Nehru University, New Delhi, it was observed that there had been no veterinary doctor at the institute for a number of years, although it is hoped that this situation will improve.

The following have been suggested by researchers as sources of variability in experimental procedures involving animals, hence they are factors over which there must be strict regulation and record-keeping[15]:

Environment – temperature, humidity, season, barometric pressure, lunar cycle, noise, air movement, light, smells, room characteristics, cage size and design, bedding material, nest box design, nest materials, number of animals in group, water quality, diet type, diet availability, diet quality, frequency and duration of handling.

Bombay Veterinary College, Parel, Mumbai: An overcrowded rat cage.

Animals – species, sex, age, strain, genotype, health status, batch, supplier, body weight, litter size, oestrus stage of females, level of inter-animal aggression.

Where such records have not been kept, and research has proceeded with no apparent knowledge of background or health status of animals, the data produced must be considered compromised.

Such problems are further compounded by the use of wild animals and at AIIMS, New Delhi, experiments on stray dogs, while at the Indian Veterinary Research Institute animals were either procured from illegal suppliers or caught from the campus.

Animal housing

The investigation found overcrowding and substandard animal housing (small, rusty caging) to be commonplace.

At AIIMS primate groupings were not appropriate to the species' social behaviour patterns which in itself, causes problems. Cages were very old and rusty. At Maulana Azad one of the guinea pigs had a gaping wound on its back, indicating that animals were not being kept in appropriate social groups. Cages for rats/mice were

AIIMS: Monkeys are housed in these small, barren cages with metal grid floors, for months, even years.

They live alone, with minimal social contact with the animal in the adjoining cage.

Stress, disturbed stereotypic behaviour, and self mutilation are common in monkeys kept in this way.

extremely filthy and overcrowded. At the Indian Veterinary Research Institute there were up to six rabbits in a medium-sized cage. At Bengal Chemicals the cages for small animals were found to be old and rusted. At the Patel Chest Institute rats were overcrowded in individual units. At the Indian Institute of Science, Bangalore, more than 40% of the monkeys have been in cages for more than 10 years; some of the cages were small and kept on top of one another. The mesh structure of the cages was causing deformity or permanent disability in the animals.

For the majority of species, standards of laboratory housing are woefully poor, worldwide. Design of laboratory animal housing has evolved for the convenience of those looking after the animals, with often little consideration given to their needs. Small cages take up less space, so more animals can be kept in less space, less people are required to care for them, and manipulating or handling the animals is easier if they are closely confined. However in recent years, greater knowledge of the needs of other species, combined with knowledge about the detrimental effect that poor animal husbandry and housing has on the results of experimental procedures, has prompted new legislation.

Article 5 of the 1986 European Convention on Animal Experiments requires that an animal has some freedom of movement and the freedom to satisfy its physiological and behavioural needs *"as far as is practicable"*[1].

The minimum space allowed for a single rat, under European guidelines, is less than two thirds of the cover of a typical magazine; however because they are housed in groups, each animal has, in fact, less space than this[1]. It seems extraordinary that laboratory rat cages have been designed too small to allow the animal to stand upright, when even the most rudimentary observations will witness this common rat behaviour. For the workers, keeping the animals so confined means that they can be quickly and easily caught.

Animal welfarists are often accused of being anthropomorphic, of attributing to animals human needs and emotions. However, it is animal welfarists who argue that it is the different needs of animals that are ignored by intensive husbandry systems, such as those commonly used in laboratories.

However, the Indian laboratories visited by CPCSEAfall below the minimal standards set by UK and European legislation. For example, it is generally acknowledged that primates have special needs.

The UK Home Office Code of Practice pays special attention to the conditions for primates in laboratories, *"it is best to work from a thorough understanding of the biological, psychological and behavioural needs of the individual species. Primates have high intelligence, most have arboreal habits and all need complex, stimulating environments"*[1]. In fact the Code is more detailed on primate species than any other. (It should be noted, however, that we have criticised the UK's Home Office for its failure to enforce this Code).

The Code recognises the importance of social contact. *"Most species are highly sociable and benefit from being housed with companions and should be so housed that they have the opportunity for social interaction."* Also, *"Single housing should be avoided wherever possible but care should be taken to ensure that animals which are housed together are compatible"*[1].

National Institute of Virology, Pune: Sheep with deformed hooves.

Left: College of Veterinary Sciences, Marathawada University: An experimental calf with open wounds.

Right: Vins Bioproducts Ltd., Hyderabad: A weeping abscess at an inoculation site. Overcrowding, poor quality water, bleeding of pregnant mares leading to the birth of blind foals, and high mortality.

After implementing CPCSEA guidelines, the organisation reported a reduction in mortality from 20% to 8%, an 80% reduction in sickness, and an increase in the weights of animals.

Yet at India's National Institute of Virology all primates were individually housed; at AIIMS caging took no account of social grouping needs, and at the Indian Institute of Science in Bangalore 40% of the monkeys were in cages for more than 10 years. For animals which, in the wild, would live in groups with well-developed social structures[12] enforced isolation and inappropriate accommodation will clearly cause distress.

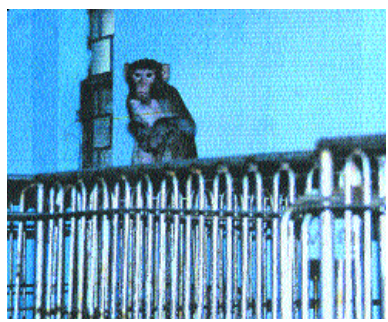
A lack of environmental enrichment rapidly results in boredom for most primates, and this soon leads to stereotypic or other disturbed behaviour[12]. At the Indian Institute of Science monkeys were found turning around in circles in their cage and constantly grabbing, biting and gnashing their teeth in a nervous manner. As already mentioned it has been suggested that stereotypic behaviour is linked to and perhaps caused by brain damage[7]. In general substantial evidence links psychological stress with increased illness and possibly increased susceptibility to infection through stress-related impairment of functional immune responses. For example, stress has been shown to trigger relapses of colitis in animals, and long-term stress seems to increase the risk of exacerbations of disease. This finding has parallels with cotton-top tamarins, primates that develop spontaneous colitis only in long-term captivity[18].

The investigation also highlighted deficiencies in the provision of exercise for laboratory animals. At the National Institute of Virology and at the Patel Chest Institute sheep were found to have overgrown hooves, which is usually the result of a lack of exercise. Overgrown hooves lead to lameness, bad posture, cracking of the hoof wall and infection running into damaged white line areas[13].

The failure to provide adequate space to fulfil the animals'physiological needs or to provide adequate stimulation to keep them healthy was apparently universal in the laboratories examined.

Biohazard

The presence of a variety of species from different continents, in close proximity to each other and confined conditions presents a biological hazard to the local community. Prevention of cross-species infection and escape of organisms is a major consideration for laboratories, worldwide. The CPCSEAinvestigation revealed considerable potential for the spread of disease between species and to animal house personnel.



National Institute of Virology, Pune: This monkey had escaped from its cage.

Primates can carry a number of virus that are lethal to people and can inflict a serious injury with a bite alone.

It is disturbing to note such a failure in containment at a laboratory working with the AIDS virus.

In particular the failure after 23 years to complete a Microbial Containment Complex for handling hazardous viruses and protecting workers from laboratory infection at the National Institute of Virology (NIV) is a serious cause for concern as is the failure by the Indian Council of Medical Research to monitor the construction of the facility. At NIV, an establishment where HIV/AIDS research is carried out, one monkey was photographed having escaped from his cage. Dr Qadri, the consultant, remarked on the absence of a basic infrastructure for carrying out research, including the fact that there was no quarantine facility at the Institute.

At AIIMS inspectors photographed an experiment on a rat, which was being conducted on the floor, with the animal in a bread box. At the Indian Veterinary Research Institute at Izatnagar the cages for mice/rats were broken and the animals could easily escape. Some rats were seen in the corridors. At Maulana Azad, undernourished mice were able to squeeze through the grills at the top of their cages. Incursion by other animals into experimental facilities was also noted, e.g. at Bengal Chemicals and Jawaharlal Nehru University, and ventilation and hygiene systems were deficient in a number of institutions. Disposal of bodies was unsatisfactory at the King's Institute, Chennai, where the decomposing bodies of horses could be seen above ground level, and bodies were left to decay at Maulana Azad.

All animals can harbour infectious agents that may be transmitted to man as zoonoses (animal diseases which may be transferred to humans)[2]. However, because of their evolutionary closeness nonhuman primates and humans share susceptibility to many species-specific pathogens that do not infect other animals. Over 150 zoonoses have been recognised and described and include viral, bacterial, parasitic and allergic diseases[25].

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discredited rabies vaccine production



Haffkine Biopharmaceutical Corp. Ltd., Mumbai: The most appaling suffering is inflicted on sheep, for the production of a discredited and dangerous product.

The sheep are tied by their legs and restrained by being wrapped in a cloth, then whilst they remain fully conscious, a hole is drilled into their skull.

Above, right: Trussed up, conscious, sheep lie below the table where a hole is being drilled into the head of another animal. These brutal operations take between 5 and 10 minutes to perform.

Discredited rabies vaccine production

Sheep are suffering in the most appalling and inexcusable manner, to produce a rabies vaccine that has been discredited by the World Health Organisation (which has recommended a global ban), and which is already banned by several State goverments in India including Karnataka, Tamil Nadu and Kerala[1].

The Semple or Neural Tissue Anti-Rabies Vaccine (NTVor ARV) is outmoded. There is a safer vaccine available, which is produced from human cells, without animal suffering.

NTVis made by injecting rabies virus into the brains of living sheep through a hole drilled into their skulls. After one to two weeks the sheep become paralysed and are then killed by decapitation so that their brains can be removed[1] and homogenised in a blender. The virus is inactivated by physical or chemical means[2]. Annually, 35,000 litres of anti-rabies vaccine are produced by this shocking method, using 30,000 sheep[1].

NTVcauses suffering not only to the sheep involved but also to many of the human patients injected following a bite from a potentially infected animal. A series of 14-21 painful injections of inactivated virus vaccine is given into


Haffkine Biopharmaceutical Corp. Ltd., Mumbai: Tied by the legs, these sheep await drilling.

Haffkine Biopharmaceutical Corp. Ltd., Mumbai: On a table just above the heads of the tied up sheep the drilling production line continues.

the skin of the abdomen to produce antibodies (blood proteins which attack foreign invaders) to the rabies virus[2]. Side-effects range from painful abdominal swellings, asthma and nosebleeds to serious nerve complications resulting in paralysis and death, and can affect up to 70% of vaccine recipients[1].

The Tissue Culture Vaccine (TCV) is produced, as its name indicates, in a culture dish. Tissue cultures, commonly grown from human cells[3], are infected with a strain of rabies. The virus is then inactivated, purified and administered by 4-6 injections into the arm. In addition to being a humane alternative option and being more potent it is safer for people too, having no known side-effects[2].

The Indian Ministry of Health appears unwilling to abandon the outdated sheep brain vaccine and comply with the WHO's recommended ban and switch to the TCV. All other countries, with the exception of Tunisia, have already done so[1]. Cell culture vaccines cost around a hundred times more than the nerve tissue vaccine[3] but the financial cost should be weighed against the cost in animal and human suffering.

Three centres in India are already producing TCV. The National Dairy Development Board (NDDB) is currently producing around 4 million vials of the TCVbut is reported to have the capacity to meet the entire 14 million vial requirement for the entire country and has said it is prepared to drop the price[1].

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Unaccountable, pointless and brutal research

The production of NTVprovides a shocking and pertinent example of a vaccine production institute falling behind the times at the cost of both animal and human welfare. It confirms that research institutions and drug producers, left to themselves, will not necessarily drive the boundaries of science forward, but rather will continue what they have always done – do what is cheap and convenient. The CPCSEAinvestigation reveals that work involving animals is carried out year after year with apparently no purpose.

At the Indian Veterinary Research Institute at Izatnagar it was found that out of 120 projects 96 were declared closed without attaining their objectives – a staggering 80% project failure rate. At AIIMS, of the 339 projects completed between 1991 and 2000 final reports had not been received in respect of nearly half. A database search for the same period revealed only 176 papers, that is, only just over half of the research projects resulting in publication in respected journals (although this figure could of course be much lower as one research project may result in more than one published article). Likewise at the Indian Veterinary Research Institute at Izatnagar a database search for the period 1995- 2000 revealed that fewer than half of the 232 projects had reached publication. This failure to achieve publication of results in respected science journals may indicate a concern by some publications that the research is fundamentally flawed, for the reasons outlined earlier.

AIIMS: Street dogs used in experiments, apparently for no other reason than the size of the dogs was more "convenient" for the researchers.

It is extremely disturbing, however, that these researchers have continued to receive funding to carry on with such brutal, unscientific and unreliable experiments in institutions with inadequate controls and poor facilities.

Based upon the report by CPCSEAand our review of the international scientific literature, Animal Defenders International and the National Anti-Vivisection Society UK can see no evidence of proper critical scientific peer review of proposals to use animals in laboratories in India. For example, at AIIMS, 32 out of 42 projects were approved in a single day. It is inconceivable that these projects were reviewed with the necessary thoroughness and vigor which should be demanded by proposals to use animals.

In the next section, we discuss the research from animal laboratories in India which did achieve publication.

Rabbits in an Indian laboratory: CPCSEA report that we are unlikely to know why many of these animals have been used in experiments.

Published Indian research

Our review of the state of scientific and medical research in India draws the conclusion that Indian researchers are many years behind researchers elsewhere, who are utilising cutting-edge techniques.

The future of scientific and medical research is in the use and development of sophisticated, human-centred non-animal techniques which increasingly study function at the cellular level.

Given the deplorable standards of animal welfare and failure to embrace these new techniques, it is probably not surprising that most of the research undertaken in Indian laboratories simply disappears without trace.

What is more surprising is that some science journals see fit to publish this work, and these papers cite collaboration with research facilities such as the California Regional Primate Research Center and funding bodies from as far away as Canada and Denmark.

The scientific community vigorously claims to be best positioned to police itself. Yet such claims are at odds with the findings of the CPCSEAreport, and many years of studies of laboratory research by ADI and NAVS. In light of similar conclusions drawn from investigations of the use of animals in research in other countries, such protestations ring hollow.

ADI and NAVS UK believe the scientific community as a whole must take responsibility forthe appalling conditions which CPCSEAhave found in these Indian laboratories.

The international scientific community must not simply duck these issues, keep silent, or respond to these criticisms with slogans such as the claim that all critics are anti-science.

Animal Defenders International and the National Anti-Vivisection Society are pro-science, but against animal research. We are in favour of modern, sophisticated, non-animal research techniques which are more relevant to our own species. We fund such research, and through our Lord Dowding Fund for Humane Research, for example, the NAVS'annual budget for non-animal scientific and medical research projects is similar to that of the UK government's Home Office.

The following leading international science journals have published research from establishments criticised by the CPCSEAand ADI/NAVS:

Journal of Andrology:

published the **fertility research on bonnet monkeys** which took place at the Indian Institute of Science, Bangalore. This research is fundamentally flawed, for the following reasons:-

- Conditions and husbandry at the laboratory were not conducive to controllable, reliable, or repeatable data;
- it was repetition – similar experiments have been repeated many times;
- the results were either already known or were predictable;
- the results were available elsewhere;
- species differences between macaques and humans are known;
- humans can be studied, indeed human volunteers were already being studied;
- data is already available from previous human studies;
- insufficient purpose – no proper objective or reason was given for the study;
- *in vitro* alternatives are available, and in use elsewhere.

Haffkine Biopharmaceutical Corp. Ltd., Pune: CPCSEA noted animals in very poor health, some with open, bleeding wounds. Hygiene was poor and the smell of ammonia was present. Mortality was high.

Since the CPCSEA inspection (but not before the published research was undertaken) some improvements are said to have been made.

Mutation Research:

published the experiments on rats with cancer-causing chemicals at the V. Patel Chest Institute, University of Delhi. Our critique of this project reveals the following flaws:-

- Conditions and husbandry at the laboratory were not conducive to controllable, reliable, or repeatable data;
- this was repetition of other work;
- species differences – the differences in metabolism between rats and humans are already known;
- specifically with the substances being tested, species differences are known;
- a superior, *in vitro* method is already available and has been in use for many years.

Haffkine Biopharmaceutical Corp. Ltd.: Horse with a large abscess on the neck.

published research

Journal of Hepatology:

Published the work on rhesus macaques and hepatitis E, undertaken at the National Institute of Virology in Pune. Our critique summarises the main flaws of this research:-

- Conditions and husbandry at the laboratory were not conducive to controllable, reliable, or repeatable data;
- the experimental design was faulty;
- repetition of previous studies (key facts already established);
- human data was available/other sources of the information required were available;
- biochemical differences between the monkey model of the disease and the disease in humans are known – the animal model has different symptoms.

Journal of Molecular Endocrinology:

published the paper which used castrated rats in hormone studies at the Indian Institute of Science at Bangalore. The main flaws of this research which we have highlighted are:-

- Conditions and husbandry at the laboratory were not conducive to controllable, reliable, or repeatable data;
- inadequate purpose was outlined for this research;
- a distressing and unsafe procedure was used to anaesthetise the animals;
- species differences between rats and humans were already known.

Contraception:

published a paper in which the abdomen and womb of female monkeys was cut open without proper anaesthesia, in contraception experiments. Our critique of this work reveals that:-

- Conditions and husbandry at the laboratory were not conducive to controllable, reliable, or repeatable data;
- unnecessary suffering was caused in painful surgical procedures, without adequate anaesthesia;
- the workers gave no indication of their reason for the experiments, neither did they relate the work to the clinical situation;
- the work was repetition of earlier work;
- it is of some concern that the funding organisations issued a caveat, distancing themselves from the research.

Taking Responsibility

Each of the journals named above has a responsibility to ensure that the papers it publishes not only represent good science, but good laboratory practice.

The scientific community, as represented by these journals, should uphold standards of good animal welfare, good laboratory practice and good science, by ensuring that non-animal methods have been explored before animals have been used; that where animals have been used pain and suffering has been minimised and proper controls are in place.

In the following section, we discuss the examples of published Indian research as mentioned above, with a full critique of the papers.

In addition to our questions about the reliability of this data, given the conditions in which the research was undertaken, we have questioned the scientific value of the work, and suggested where superior techniques were available which do not involve the use of animals.

All India Institute of Medical Sciences, New Delhi

Source: Ghosh, D., Dhawan, L., Lalitkumar, PGL., Wong, Viviana, Rosario, JF., Hendrickx, AG., Lasley, BL., Overstreet, JW., Sengupta, J. Effect of vaginally administered (Ala8,13,18)-magainin II amide on the morphology of implantation stage endometrium in the rhesus monkey. Contraception 63 (2001) 335-342.

All India Institute of Medical Sciences (AIIMS): Small, barren, impoverished environments such as these for primates are perhaps so common in the world of animal experimentation that they raised no concerns with with international collaborators, funding bodies, or science journals in which publish the results.

Female rhesus monkeys were mated and a tampon containing an antibiotic drug, known to act as a contraceptive in monkeys, was inserted into the vagina. Tissue samples were collected from the lining of the womb after administration of an immobilising drug. This project was undertaken in collaboration with the California Regional Primate Research Center, University of California, Davis, and was funded by the CCIR program of Contraceptive Research and Development Program, Eastern Virginia Medical School.

In earlier experiments in monkeys the researchers discovered that drugs that prevent cell division, such as magainin II and fumagillin, can also prevent a developing embryo from implanting in the lining of the womb, hence acting as contraceptives. In another experiment the same research team examined changes in the lining of the womb (endometrium) induced by fumagillin. For the present study they decided to repeat the experiment by examining endometrial tissue changes caused by magainin II.

Macaques were placed in individual cages for around two months, until females were in their third menstrual cycle when they were housed with males for mating. However, the CPCSEAstudy indicates that it is normal for monkeys at AIIMS to be kept isolated for months or even years at a time, sometimes in small rusted cages with several layers of mesh, making it difficult to see out. The stress of these long periods of isolation results in the self-mutilation witnessed by inspectors. It was also noted that there were no health records for individual primates, nor are details of age, sex, or research project being maintained.

Following insemination, tampons containing magainin II were inserted into six of the females. Tampons inserted into the other five females contained a carrier solution only to serve as controls for comparison. Blood samples were collected daily for measurement of hormone levels in order to assess pregnancy. Tissue for examination was taken from the lining of the womb and an incision was made in the womb itself. The animals were immobilised for the procedure by administration of 12 mg ketamine per kilogram of their body weight.

Critique

Unnecessary suffering:

The dose of ketamine administered was only enough to immobilise, produce moderate sedation and some pain relief in a non-human primate[1]. Doses between 10-25 mg/kg are considered sufficient for minor surgical procedures[2] but an abdominal laparotomy, as performed here, involves cutting through layers of tissue including muscle, as does removing tissue from the womb; this procedure can hardly be considered 'minor'. Furthermore, ketamine given alone is unsuitable for invasive surgery as it increases muscle tone[2].

No properobjective:

The researchers gave no indication of their reason for wanting to assess how the drug prevents pregnancy in macaques at the cellular level. No relationship with regard to contraception or otherwise to humans was mentioned and no comparison was even attempted. Neither was there any indication that the research was with a view to monkey population control. In addition, the researchers had already conducted a similar experiment using a similar drug.

Repetition:

The workers had already conducted a similar experiment using a similar drug.

It is of concern that the organisations which funded this research issued a caveat stating that *"the views expressed by the authors do not necessarily express the views of CONRAD or CICCR"*.

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published research

Haffkine Biopharmaceutical Corp. Ltd., Mumbai: Blind and injured, this horse continued to be bled up to 18 litres every month.

Haffkine Biopharmaceutical Corporation Limited, Mumbai

Source: Kankonkar, RC., Kulkurni, DG., Hulikavi, CB. Preparation of a potent anti-scorpion-venom-serum against the venom of red scorpion (*Buthus tamalus*). Journal of Postgraduate Medicine, Oct-Dec 1998; 44 (iv): 85-92.

In a project funded by the Government of Maharashtra, to determine the lethal dose of red scorpion venom, various dilutions of the venom were injected into mice and guinea pigs, dogs and langurs – some animals took hours to die. Ponies were used to raise antibodies (blood proteins which fight a foreign invader) to the red scorpion venom; they were injected into the muscle with increasing strengths of venom over a course of several weeks, being bled at random throughout to check for antibodies. If antibodies were present, the ponies were bled further for removal of the cells from the blood, and the remaining plasma purified to extract the antiserum, or antivenin – the proposed antidote to the red scorpion venom.

To test the efficacy of the antiserum, mice, dogs, guinea pigs and langurs were injected with red scorpion venom, followed by antiserum at various intervals. The antidote was effective in preventing death. Control animals received no antiserum and were left to die. This took up to 80 minutes for guinea pigs, 3 hours for dogs and up to 6 hours for langurs. Langurs in the treatment group suffered collapsed veins after 2 hours unless they received 20 mls of antiserum. There was no mention of any anaesthesia or analgesia, nor were any of the animals humanely killed to relieve their suffering.

The researchers cited studies which concluded that Indian red scorpion stings produce inflammation of the heart and pancreas, high blood pressure, shock, blood clotting, bursting of red blood cells, low blood sugar, and excess fats in the blood. These altered states in the body are believed to be caused by severe malfunctioning of the unconscious nervous system, resulting in a massive release of hormones.

The researchers did not clarify which of these devastating reactions are attributed to which animal species in all cases, but either alone or in combination, these reactions are bound to result in extremes of pain and suffering in conscious animals.

Also given the health condition of other animals used by Haffkine, one has to question whether any effects could be accurately monitored and clearly attributed to the test substance.

The experiments on mice, guinea pigs, dogs and langurs were repeated using black scorpion venom to see whether the red scorpion antiserum could also neutralise black scorpion venom. It could not.

The researchers noted differences in lethal dose values of guinea pigs, dogs and langurs – these *"show variation in species susceptibility"*. Human susceptibility to the venom would be expected to be different again – since there is data available in this field one has to question why these animals were used. According to HS & PH Bawaskar of Bawaskar Hospital and Research Centre, in Maharashtra, India, who have been treating victims of red scorpion venom since 1976[1], *"Human scorpionism is entirely different from experimental"*[2].

There is also a difference between species in the action and effect of the venom. For example, in another experiment published in 1998, red scorpion venom injected into dogs caused a decrease in the levels of thyroxine, a hormone released from the thyroid gland. In rabbits injected with the venom there was no change in thyroxine[3]. The antivenin may have been lifesaving in the animals but this does not guarantee the same result for human beings.

Haffkine Biopharmaceutical Corp. Ltd., Mumbai: A horse has been blinded by repeated doses of venom, but still used for ASVS production.

Indeed, human clinical studies, published in 1994, found that the antivenin to the red scorpion did not have any beneficial effects on children who had been stung. It has not been found to have a protective effect on the heart.[1] In fact, as early as 1987, Gueron and Ovsyshcher maintained that the treatment was ineffective. Others have claimed that the antivenin effectively treats heart and circulation events caused by red scorpion sting in rats but, to reiterate, this is not an indication of its effectiveness in people – as demonstrated by the findings in children.

A drug called prazosin, in use for patient care since 1984, is recognised to be the first line of treatment for red scorpion stings as it is successful in alleviating cardiovascular (heart and circulation) manifestations such as high blood pressure, fluid-filled lungs and circulation failure[1,4]. Cardiovascular effects are the most predominant effects of the red scorpion sting[5].

Previous research indicates that *in-vitro* testing should be possible, and at the very least should be developed instead of using animals the way they were used at Haffkine. Research in Singapore, published in 1994, demonstrated the effects of drugs on the contractile properties of rat muscle, pre-treated with red scorpion venom, in a test tube situation[6]. Results of similar experiments, but using muscle tissue from mice and chicks were published in 1993[7].

The experiment was further undermined by the use of stray dogs. As outlined earlier it is important for animals to be uniform and healthy to minimise the introduction of variables in experiments[8]. This is particularly true in studies where precision is required, such as in those which involve quantitative assays or comparisons – as in this research. There is also evidence from CPCSEAof the ponies being used at Haffkine to raise antibodies in other research, being in extremely poor health – something not indicated in the research paper.

Critique:

In summary, our critique highlights the following flaws with this project:-

- the workers admitted that they were aware of the differing susceptibility between species;
- the effects of the antivenin were already known;
- effective treatment was already available;
- animals were allowed to experience extreme suffering; no analgesia or anaesthesia was administered, nor were they humanely killed to relieve their suffering.

We submit that the funding of such a poorly-devised, cruel, and unscientific project was a waste of public money.

1 Bawaskar, JS & Bawaskar, PH. Peripheral doctors form backbone for management of acute life-threatening medical emergency evoked due to envenoming by Indian red scorpion, Mesobuthus tamulus. Bombay Hospital Journal, October 1997
2 Radha Krishna Murthy, K (2002) On scorpion envenoming syndrome. Problems of medical ethics and accountability in medical research in India. The Journal of Venomous Animals and Toxins 8 (1): 3-17 Letter to the Editor
3 Medline abstract: Murthy, KRK & Zare, MA (1998) Effect of Indian red scorpion (Mesobuthus tamulus concanesis, Pocock) venom on thyroxine and triiodothyronine Experimental Biology; 36 (1): 16-21
4 Bawaskar, HS & Bawaskar, PH. The Lancet March 1986 Letters, 510
5 Mahadevan, S (2000) Scorpion Sting. Editorial, Indian Pediatrics; 37: 504-514
6 Gwee, MCE et al. (1994) Prejunctional action of the venom from the Indian red scorpion Mesobuthus tamulus on adrenergic transmission in vitro. Toxicon; 32 (2): 201-209
7 Vatanpour, H et al. (1993) Effects of scorpion (Buthus tamulus) venom on neuromuscular transmission in vitro. Toxicon 31 (11) 1373-1384
8 Home Office Animals (Scientific Procedures) Act 1986 Code of Practice for the Housing and Care of Animals in Designated Breeding and Supplying Establishments.

Indian Institute of Science, Bangalore

Source: Krishnamurthy, H., Kumar, K.M.P., Joshi, C.V., Krishnamurthy, HN., Mougdal, RN., Sairam, MR. Alterations in sperm characteristics of follicle-stimulating hormone (FSH)-immunised men are similarto those of FSH-deprived infertile male bonnet monkeys. Journal of Andrology, March/April 2000; 21 (2): 316-327.

Monkeys were immunised with a sheep hormone, ovine follicle-stimulating hormone (oFSH), to prevent production of FSH which stimulates sperm production. The aim was to see the effect of this on the quality of their sperm and to compare the results with sperm samples from men who had voluntarily undergone similar treatment.

The research was in collaboration with Ramaiah Medical Teaching Hospital, Bangalore and Clinical Research Institute of Montreal, Canada, and funded by

Indian Institute of Science, Bangalore: The mesh structure of the small cages caused disabilities.

Over 40% of the monkeys at the Institute were in such cages for more than 40 years. Most had not seen natural daylight for years.

A large number of animals displayed fear and aggression; some displayed disturbed and stereotypic behaviour.

As of 29th may 2002, there were 172 monkeys in the animal house. between January and May 2002, 25 monkeys had died or been euthanased – 17 of these since April 10 2002.

Department of Biotechnology, Government of India, the Indian National Science Academy, the Jawaharlal Nehru Center for Advanced Scientific Research, the Rockefeller Foundation, New York, and the MRC Canada.

Adult male bonnet monkeys (3-4) were injected with oFSH four times over 24 days, followed by boosters around four times a year, for over 5 years. Blood samples were taken periodically for the assessment of male hormone and antibody levels. Sperm samples were collected by electrical stimulation. For comparison (controls), sperm from three monkeys which had artificially been rendered infertile were also used for analysis as well as from normal, fertile monkeys (3-4). Needle biopsies for analysis of immature sperm cells were taken from the testes of all monkeys.

Additionally, in a study at Ramaiah Medical Teaching Hospital in Bangalore, sperm samples were donated by five human volunteers who had also been injected with oFSH periodically for up to 70 days. The men acted as their own controls for comparison by donating sperm samples prior to treatment and at 110 days and 140 days, when oFSH treatment had stopped. As a result of immunisation with oFSH, sperm counts had decreased considerably in both monkeys and men.

Critique:

The researchers stated that some of their results regarding sperm quality concur with earlier observations from oFSH immunised monkeys, published two years previously. Similar results were observed in the human volunteers in the current study. It was not necessary to repeat the experiments on monkeys, particularly as similar experiments have been repeated many times. Relevant data was available before this experiment and it should also be noted that there had been a number of earlier studies to assess the quality of sperm, conducted using samples from patients attending infertility clinics. Research has already shown that there is a difference between macaques and humans in terms of when Sertoli cell (responsible for generation of new sperm cells) division occurs[4].

It is well known by those who specialise in reproductive biology that FSH is partly responsible (with another hormone, LH) for the maintenance and functioning of the reproductive system in both male and female mammals, in which they are responsible for stimulating the maturation and production of sperm[1]. Conversely, a lack of FSH would have an adverse effect on sperm production.

The researchers stated that: As the quality of the sperm was shown to be low, evidenced by *"poor chromatin packaging"* their results lend credence to their thinking that *"any method that results in blockade of FSH support in primates significantly affects sperm production."* It has been known since at least 1983 that sperm production in primates is inhibited following immunisation with FSH1, and since 1979 that blocking of FSH production leads to infertility.

Scientists are progressing in the field of infertility research using methods which can be directly related to the human condition. For example, the NAVS'department the Lord Dowding Fund is supporting a research group in Birmingham, UK, which uses a bank of human testicular tissue for test-tube studies of male infertility[2].

In summary, the flaws in this project are:-

- species differences are already known;
- the research was repetitive;
- the results were already known, and were predictable anyway;
- the results were available from other sources;
- the objectives were not clearly defined, and there was insufficient purpose for the experiment;
- humans can be studied, and elsewhere, human studies have been conducted;
- *in vitro* alternatives are available

1 In: Woodman, D. Laboratory Animal Endocrinology (1997). John Wiley & Sons: 123-126, 456
2 The Campaigner May-August 2002; 52: The National Anti-Vivisection Society
3 Collins English Dictionary, 2nd Edition
4 Sharpe, RM et al. (2000) Biology of Reproduction; 62: 1685-1693

Indian Institute of Science, Bangalore

Source: Desai, KV., Kondaiah. Androgen ablation results in differential regulation of transforming growth factor-ß isoforms in rat male accessory sex organs and epididymis. Journal of MolecularEndocrinology (2000) 24: 253-260.

In a project funded by the 'Contraception 21'programme of the Rockefeller Foundation, USA, rats were castrated and killed after a few days for an investigation of the effects of castration on male hormone-dependent tissues. Sham-operated rats were used for comparison.

Male sex hormones (androgens) control the growth, development and specialisation of the tissues in male sex organs, and glands such as the prostate. Depletion of androgens causes these androgen-dependent organs to regress, by the process of natural cell death (apoptosis). In this experiment, the researchers were investigating the role of a certain type of growth factor (TGF-ß) in apoptosis, following depletion of androgens due to castration.

Rats aged 60-70 days were castrated surgically, by an incision in the scrotum, under ether anaesthesia. Sham-operated rats were used as controls for comparison. The animals were killed on day 1, day 3 and day 5 after the operation, by breaking the neck. The accessory sex organs (such as the epididymis – the tube which stores and conveys sperm) were dissected out for analysis of the tissues. The results indicated that following androgen depletion, different types of growth factors, or isoforms, regulated the growth of these organs differentially, depending upon the tissue in question.

Critique:

Distressing and unsafe procedure:

Ether was used to anaesthetise the rats prior to surgery. Induction of anaesthesia by ether is painful and distressing to an animal. It is extremely irritating to the lining of the mouth, throat and lungs, causing coughing, profuse fluid secretion from the lungs, salivation and occasionally the throat can go into spasm. Severe infection can develop in the respiratory system during recovery from the anaesthesia, if there is already respiratory disease present[1,2].

Insufficient purpose/not related to clinical use:

The researchers did not indicate why it is "*important to study the pattern of TGF-ß isoform expression following castration.*" except that they are indicated in apoptosis, and hence are implicated in regression of sex organ tissue following androgen depletion.

Species differences:

Control of the reproductive systems of rats and humans are known to differ, so caution should be exercised when transferring the results of experiments involving the sex organs of rats to men. For example, immunisation of rats against a hormone (FSH) which regulates sperm production does not decrease sperm production, whereas the opposite is true in primates, including humans[3].

In summary, these experiments demonstrate:

- poor welfare considerations in terms of technique, and consequent effect on results;
- species differences are already known;
- a pointless experiment, badly conceived, not properly related to human situation.

1 Green CJ. Animal Anaesthesia ñ Laboratory Animal Handbooks 8 (1979). Laboratory Animals Ltd.
2 Flecknell, PA. Laboratory Animal Anaesthesia, 2nd Edition (1996) Academic Press

3 In: Woodman, D. Laboratory Animal Endocrinology (1997). John Wiley & Sons: 123-126

Indian Veterinary Research Institute, Izatnagar

Source: Amarpal, Kinjavdekar, P., Aithal, HP., Pawde, AM., Pratap, K. Analgesic, Sedative and Haemodynamic Effects of Spinally Administered Romifidine in Goats. Journal of Veterinary Medicine 2002; 49: 3-8.

A pain-reliever was injected into the spines of female goats and blood taken from a vein in the neck. 15 days later, most of the animals were restrained by tying up their legs and parts of the main vein and artery in the neck brought outside the body and connected to various measuring devices. The funding body for these experiments was not stated.

Ten goats divided into groups of five were starved for 24 hours and deprived of water for 12 hours. Romifidine was then injected into the spine at two different dose levels. Blood was taken from a vein in the neck before the injection and then every thirty

Indian Veterinary Research Institute, Izatnagar:

CPCSEA report that out of 232 projects undertaken at the establishment between 1995-2000, only 120 were completed, and of these, 96 were declared closed without attaining their objectives.

minutes for two hours. Pin prick tests were used to establish pain relieving properties of differing dosages of the drug, and sedative effects and co-ordination were observed. 15 days were allowed to elapse and then 4 goats from each group were restrained on a table, their legs tied, and parts of the main vein and artery in the neck were brought outside the body. Tubes were inserted into the blood vessels, the one into the vein being inserted up to the entry point into the heart, for the recording of heart rate and blood pressure. Romifidine was then injected into the spine at two dose levels and various measurements taken, for a period of two hours.

Critique:

Repetition/effects already known:
It is difficult to understand why the experiment was conducted. The authors state that they are aware of other research which has reported that the effects of romifidine are, with only minor differences, similar to those of other drugs which operate using the same kind of biochemical process. Given that the parameters of the drug had already been tested intravenously and that its similarity with others had been established, the results of the present experiment would have been predictable. The drug has been used on horses, dogs and sheep. A comparative study of romifidine and xylazine had been undertaken five years before the publication of this paper.

Purpose of experiment:
Xylazine may be used as a sedative and a pre-anaesthetic medication. The only side-effect listed in The Veterinary Formulary is vomiting in cats and dogs[1]. It is a drug which operates via similar biochemical activity as romifidine. No reason is given for testing romifidine when the same sort of drug is already in use and without listed side-effects for goats. One of the authors of the present paper has already published research on xylazine in goats. Nine painkillers already in use are listed in the 1998 edition of the Merck Veterinary Manual[2].

The purpose of further proposed research is also not explained. The results for rectal temperature of the goats showed levels above that indicated prior to the procedures. These changes in rectal temperature are *"only mild and non-significant."* Later in the paper the authors comment that the available literature does not appear to explain the increase in rectal temperature and state: *"Further studies are therefore, required to investigate the mechanism responsible for changes in rectal temperature following epidural analgesia in animals."* It seems incredible that the researchers are proposing research into what they themselves regard as a mild and non-significant feature, neither do they appear to acknowledge the effect that poor laboratory practice and animal welfare would have on the results of their experiments.

Poorplanning/poorprotocols:
One of the aims of the experiment was to investigate the analgesic properties of the drug at two dose levels. However this was assessed by sticking a pin into the skin of the animal in various places and then subjectively grading the responses. Differences in analgesic effect were recorded for the two dose levels. The conclusion of the paper is that analgesia is the same but side-effects are different for the two dose levels. Yet in calculation of dose responses, and in respect of measurements which are key to the paper's findings, something more accurate and objective than the gradings, 'no response, mild response, moderate response, strong response'should be used, especially in the absence of details of how the response was recorded.

In summary, this research is fundamentally flawed due to the following:-

- the drug under investigation is known to be similar to others;
- other satisfactory drugs are available;
- poor planning/poor protocols, subjectivity in respect of key findings.

1 Dabuf, Y (ed). Veterinary Formulary. 1st edition. London: The Pharmaceutical Press; 1991: 181.
2 The Merck Veterinary Manual. 8th edition. New Jersey: Merck & Co. 1998.

Indian Veterinary Research Institute, Izatnagar

Source: Kumar, H., Yadav, MC., Meur, SK., Parihar, NS. Effect of buffalo follicularfluid treatment on follicle population and ovulation rate in guinea pigs. Indian Journal of Experimental Biology, December 1999; 37: 1182-1186.

In a repetitive experiment, guinea pigs were injected with buffalo follicular fluid (buFF). Follicular fluid surrounds the eggs in the ovaries of female mammals and is known to influence, via the substances it contains, female reproduction. The aim of the experiment was to determine the effect of buFF on the reproductive cycle of female guinea pigs, which were killed at the end of the experiment for analysis of their ovaries. The funders of this project were not stated.

Eighteen mature, female guinea pigs were divided into three groups of six, dependent upon the phase of their reproductive cycle. They were injected with buFF to see what affect it would have on the onset of oestrus. Another six guinea pigs were injected with weak salt water as a control group, for comparison. The onset and duration of oestrus was determined by examination of cells in vaginal smears taken at intervals. All animals were killed (method not stated) 24 hours following the onset of oestrus, and their ovaries examined. The result of injecting the guinea pigs with buFF was that it delayed oestrus in all animals except for those at a particular phase of their cycle.

Critique:

Repetition/results already available:
The effects on oestrus of injecting FF from other ungulates ie cattle, pigs and sheep, into several species were already known. Furthermore, cattle and Indian buffalo are of the order Bovidae. Also, similar experiments had been carried out on sheep, goats and cattle using buffalo follicular fluid.

Unclearobjectives/application for results:
It is unclear why the researchers repeated what had been already been done in similar experiments using follicular fluid from similar animals. The researchers stated that although there was information in the literature about the effects of FF from cattle, sheep and pigs, there has been little documentation about the use of buffalo follicular fluid (buFF). They did not give a reason for investigation of buFF's action in guinea pigs, except that they believe the guinea pig reproductive cycle is similar to cows. This is not a valid reason as the action of buFF in cows had already been investigated.

Results predictable:
The function of buffalo follicular fluid was already known by the researchers. They knew it contains a protein called inhibin, which helps to regulate reproduction. A thorough literature search would have brought to light the fact that another protein, follistatin, was discovered in follicular fluid in 1987 and is known to have an influence on the control of the reproductive cycle[1].

Species differences:
Similar experiments had already been carried out on sheep, goats and cattle treated with either bovine FF or buffalo FF. The guinea pigs in this experiment appear to have been used as a model for cows. The differences between the species are obvious. Guinea pigs are rodents whilst cattle are bovine animals; there is a huge difference in size and weight; the lifespan of a guinea pig is 4-8 years, whereas cattle can live up to 20 years; female guinea pigs reach puberty at 30 days while for female cattle, it is 12-15 months; the guinea pig gestation period is 59-72 days, compared to an average of 282 days in cattle; the oestrus cycle of a guinea pig is around 16 days while for cattle, the average is 21 days[2].

In summary, we find that this work is flawed due to:-

- repetition;
- results available elsewhere;
- no proper reason for conducting this research;
- predictable – results to be expected;
- species differences already known.

1 In: Woodman, D. Laboratory Animal Endocrinology (1997). John Wiley & Sons: 473
2 Wolfensohn, S & Lloyd, M (2001) Handbook of Laboratory Animal Management and Welfare, 2nd edition. Pubs. Blackwell Science: 204 & 276

Maulana Azad Medical College, New Delhi

Chaturvedi, HK., Bapna, JS., Chandra, D. Effect of fluvoxamine and N-methyl-D-aspartate receptor antagonists on shock-induced depression in mice. Indian Journal of Physiology and Pharmacology (2001); 45 (2): 199-207.

Mice were given frequent electric shocks to their feet over a period of an hour and then forced to swim in a beaker of water in an attempt to create an animal model of depression, in order to test the effects of anti-depressant drugs. The experiment was funded by the Council of Scientific and Industrial Research, New Delhi.

Maulana Azad Medical College: A mouse that has escaped from the cage.

CPCSEA described poor levels of care, including a lack of adequate food and failure to clean out the animals regularly, at this facility.

published research

Mice bred in the animal facility of Maulana Azad Medical College, were given various anti-depressant drugs, including fluvoxamine, by injection into the abdominal cavity. The aim was to asses how fluvoxamine would act when combined with antidepressants from a different chemical group.

Between 30 minutes and an hour following drug treatment, the mice were placed on a stainless steel grid floor. A glass beaker was placed over each mouse to stop them escaping or coming into contact with each other. Over a period of one hour, a two second electric shock was delivered every 9 seconds to the animals'feet.

Twenty four hours later, in an attempt to find out if the mice were "depressed", the researchers counted the number of lines drawn in circles the mice crossed in 5 minutes, or noted whether the mice were demonstrating exploratory behaviour by standing on their hind legs. Immediately afterwards, each mouse was put into a beaker of water for 6 minutes. Each mouse tried to climb out and was forced to swim until they became immobile. The period of immobility was recorded. All mice given electric shocks displayed reduced activity in both tests when compared to mice which had not been shocked. It was concluded that fluvoxamine partly reversed the behavioural effects of shock.

Critique:

Repetition/insufficient purpose:
The research was nothing new, the researchers reported that their findings are in agreement with others, citing similar experiments carried out in rats in 1988 and in 1994. The effects on behaviour of the other drugs used in the experiment, following induction of shock in rodents, had also already been established. The reason for attempting to determine the effects of the drugs in combination with others was not even reported.

Effects of the test drug already known:
The workers concluded that the drug is an anti-depressant, yet fluvoxamine has been in clinical use for the treatment of human depression since at least 1988, so its effects in people are already known. It was therefore unnecessary to test the effects of the drug in mice[1].

Poorconclusions:
The researchers suggested which mechanisms of nerve transmission in the brain are activated as a result of the shock treatment. This is mere supposition with no evidence provided. No chemical, brain imaging or other biomedical tests were carried out to prove this theory.

Species differences:
There are particular problems with extrapolating the results of such crude experiments to the human condition. Reduced levels of behavioural activity in animals are not the same as the depression experienced by people. There is no laboratory experimental animal model for the psychiatric disorder of human beings[2]. Animals cannot tell us if they feel sad with a depressed mood, or be tearful[3]. There are gross anatomical differences between the human brain and the rodent brain. For example, a human brain is gyrencephalic which means it has a folded cerebral cortex, whereas this part of a rodent brain is smooth or lissencephalic. There is evidence to suggest that there are functional differences between a gyrencephalic and lissencephalic brain[4]. A mouse brain is therefore an especially poor model for a human brain.

Maulana Azad Medical College: The feed tray of these guinea pigs is full of excrement.

Severe suffering unacceptable:
The cruelty inflicted on these animals in the name of science is completed unjustifiable. Experiments such as this can never bring benefits to humans or to other animals.

Unnecessary:
These experiments were entirely unnecessary, and a waste of money. Should there be a need to examine the drug further there are many non-invasive neuro-imaging techniques, such as PET, fMRI, MEG and SAM, which are available to study such drugs in human subjects.

How was it authorised:
We are astonished that such a poorly-designed and cruel project was authorised, and the fact that it was undertaken, indicates a lack of any real critical review process.

In summary, this project is:

- painful, distressing, and unnecessary
- repetition of previous experiments
- the effect of the drug in human patients is already known
- pointless experiment, bad science
- species differences are known
- humane alternatives already available

1 British National Formulary, No.15; 1988
2 Nodine, JH and Siegler, PE, eds.; Animal and Clinical Pharmacological Techniques in Drug Evaluation. Year Book Medical publishers Inc., Chicago 1964: 330
3 Deakin, JFW (1997). Psychopharmacology 134: 347-48
4 Smith, JM et al. (2001). Journal of Anatomy 198: 537-554

National Institute of Virology: This macaque monkey was displaying disturbed behaviour, repeatedly circling the cage. The animal apparently has a skin disease, whilst others were suffering from severe hair loss.

National Institute of Virology, Pune

Source: Arankalle, VA., Chadha, MS., Chobe, LP. Long-term follow up and cross-challenge studies in rhesus monkeys experimentally infected with hepatitis E virus. Journal of Hepatology 1999; 30: 199-204.

Pregnant and non-pregnant rhesus monkeys were repeatedly infected with hepatitis E virus, and their antibody levels monitored over a seven year period. The funding body for this research was not disclosed.

One to two-year old rhesus monkeys were caught in the wild and three pregnant and six non-pregnant animals were infected with a strain of hepatitis E taken from a human patient. One and a half years after the initial infection a second strain of hepatitis E was administered to two of the pregnant macaques, two years after the initial infection a third strain was administered to three of the non-pregnant macaques, and a fourth strain was administered to the remaining pregnant macaque two years and nine months after the initial infection. Five years after the initial infection the second strain was administered to the three non-pregnant macaques (who had received the third strain after 2 years) and to two additional macaques who had not hitherto taken part in the experiment.

Blood samples were taken weekly two months before initial infection, twice weekly for three months after, once a week for the following three months, once a month for the next three years, and then once every two to three months for the remainder of the seven years. Bile samples were taken by cutting open the abdomen and inserting a needle directly into the gall bladder.

None of the monkeys who were initially infected with hepatitis E and developed hepatitis showed evidence of the disease when the variant strains were administered at intervals afterwards. The researchers concluded that the immune response as a result of the initial infection offered protection against infection with other strains of hepatitis E for a long time and that reinfection was precluded by low levels of antibodies which would have been produced at the time of the original infection.

Critique:

Repetition/othersources of information available/human data available:
A considerable amount of data already existed before this research – Hepatitis E (HEV) is responsible for large epidemics in India and parts of the former Soviet Union[2]. Indeed the sources of experimental infection in this study were from patients suffering from the disease during epidemics in Western India. A wealth of epidemiological data is therefore available. The anti-HEVantibodies of humans can be investigated and the possibilities of reinfection from different strains of the virus monitored. In fact the authors note their observations from human epidemic situations in which they did not encounter reinfection, and this is used to support their conclusion of long-lasting immunity to HEV. In addition, research (published in 1994) established the protective effects in macaques of different concentrations of antibodies to hepatitis E[1].

Species differences:
The HEVinfection is less severe in the purported animal models of the disease than it is in humans[3]. Certain biochemical features of the disease are different in monkeys to those observed in humans. For example, in a human study a distinctive feature of the disease was the unusually long phase (about 3 months) during which a particular protein was found at an abnormal level in the blood, whereas the same protein in monkeys was only found at

abnormal levels for 2-3 weeks[3]. The paper's authors themselves admit that the infection of the pregnant monkeys does not lead to severe disease or mortality. Yet one of the key features of hepatitis E is that it is dangerous to pregnant women. Mortality rates are greatest in pregnant women and may be as high as 20%[4].

In general it cannot be overemphasised that the introduction of a species difference into the study of human disease will produce a factor which will undermine the very findings which are sought.

For example, in an experiment in which HEVantibodies from a human volunteer were used to attempt to immunise monkeys it was found that passive immunisation was not successful. The researchers conclude that long-persisting HEVantibodies alone in humans may not be protective in passive immunisation. However the fact that they may or may not – remains uncertain[5].

Poorplanning:

One of the aims of the experiment was to assess how long antibodies remain in the system after an HEVinfection and what sort of protection the resulting levels of immunity offer. One of the conclusions is that low levels of antibodies confer protection in monkeys and that probably in humans there will be long-lasting immunity on re-exposure to the disease. Yet if the argument is that certain levels of antibodies confer immunity there is no supporting research which is conclusive to show what levels of antibodies may be expected in humans who have undergone the disease. The results the authors cite range from 6 months to 14 years before disappearance from the blood. In this sense it is difficult to see how it was intended that the research be applied.

There are no clear criteria given for what constitutes reinfection and a new outbreak of the disease. For this reason it is not clear why faecal samples (which contain certain proteins) collected from one of the monkeys to whom HEVwas administered after 5 years are not indicative of reinfection. This is especially pertinent given that the disease is milder in monkeys than in humans anyway[3].

It is tentatively claimed that a level of antibody against HEVas low as 1:50 is protective against disease from a subsequent administration of the virus. However only one of the monkeys concerned reached this level within the time-scale of the experiment. This is clearly an insufficient sample-size for such a claim. Moreover the monkey in the above paragraph who had viral proteins in faecal samples had a level of antibodies eight times higher than this. This is also another reason for better use of epidemiological data, where the sample size could be large enough to facilitate more reliable inferences. Clearly no manageable number of laboratory animals can replicate the available sample size of actual epidemiological data under the circumstances.

Disease context:

Infection with hepatitis E is via sewage contamination of the water supply[6]. The money spent on poor animal research such as this, would be better spent on clean water supplies.

In summary, this project is flawed for the following reasons:

- Repetition
- Other sources of the information available (human data available)
- Species differences
- Experimental design faulty

1 Tsarev, SA et al. Successful passive and active immunisation of cynomolgus monkeys against hepatitis E. Proceedings of the National Academy of Sciences of the USA 1994 October 11; 91(21): 10198-202.
2 Zuckerman, AJ. Hepatitis E Virus. British Medical Journal 1990 June 9; 300: 1475-1476
3 Chauhan, A. Hepatitis E virus transmission to a volunteer. Lancet 1993 Jan 16; 341: 149-150.
4 Clarke, SC. An Introduction to Viral Hepatitis. Biomedical Scientist 1999 April; 278-9.
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Source: Raj, HG., Kohli, E., Rohil, V., Dwarakanath, BS., Parmar, VS., Malik, S., Adhikari, JS., Tyagi, YK., Goel, S., Gupta, K., Bose, M., Olsen, CE. Acetoxy-4-methylcoumarins conferdifferential protection from aflatoxin B1 – induced micronuclei and apoptosis in lung and bone marrow cells. Mutation Research 2001; 494: 31-40.

Joint project with: Institute of NuclearMedicine and Allied Sciences, Delhi, the University's Dept of Chemistry, and the Royal Veterinary and Agricultural University, Copenhagen, Denmark.

Rats were injected with a cancer-causing poison and a test substance, to determine whether the latter could inhibit the poison. They were killed after 26 hours and tissues analysed.

The research was funded by the Danish International Development Agency.

Approximately 140-160 male wistar rats were divided into a number of groups, most of which received either a cancer-causing agent at different dose levels, or that agent plus one of four test substances also at various dose levels. The test substance was injected twice into the abdomen and the cancer-causing substance was either injected into the abdomen or the windpipe, depending on whether bone marrow or lung cells were to be studied. The animals were killed twenty-six hours after the toxic injection. Cells taken from the animals were analysed for the effects test substances had on inhibition of damage to genetic material by the cancer-causing agent and other effects. It was concluded that one of the test substances was an effective inhibitor of certain biological effects in bone marrow cells.

V. Patel Chest Institute, University of Delhi: An overcrowded container of rats.

CPCSEA also noted that the animal house was dark and lacked adequate ventilation – the air conditioning and extractor fan were not working – compounding the environmental problem caused by overcrowding the animals.

Critique:

Repetition/species differences:

It was unnecessary to use animals for this test, since *in vitro* tests of a significant number of substances from the same family of test compounds had already been performed using rat tissue to study the effects of the poisonous substance on the genetic material in certain cells[1].

The test substances reviewed in the present paper are based on a compound called coumarin. However it has been shown that most rodents break this substance down in the body by a different method to that used in the human body. In particular coumarin, in the presence of a poison of the kind used in the present study, stimulates the human liver in ways different from those found in other species. It is for this reason that the suitability of rodents as a model of coumarin effects has been questioned[2] and it has been asserted that there are marked species differences in the protection against damage to genetic material provided by coumarin[3].

Differences between rats and humans render extrapolation of findings from laboratory rodent studies to the human situation very dangerous. The fact that an agent inhibits cancer in an animal model does not mean that it will have the same protective effect in humans. Despite retinol being proven to have anti-cancer properties in animal studies it was not effective for human cancer patients[4]. In the present study rat lung cells were investigated for a series of biological effects relevant to cancer yet it is known that the anatomical location and distribution of tumour types observed in rat lungs are not typical of the lung cancers seen in humans[5]. In general, the behaviour of cells in animal tumours is quite different from that of the cells of most human cancers[6] and cancers in rodents involve changes in genetic material which are seen much less frequently in human tumours[7].

Non-animal alternatives available:

The study was designed to investigate the capacity of test substances to inhibit certain biological processes associated with the inception of cancer. However it is possible to study the inhibitory effects of compounds on the inception of processes associated with cancer inception *in vitro*. For example, the Ames test can be used to determine the efficacy of a compound in inhibiting damage to genetic material. In such a case effects of compounds on a bacterium, *Salmonella typhimurium*, are studied. Also a mutagenicity/antimutagenicity test (i.e. one which tests the capacity of a substance to give rise to mutations following damage to genetic material) is possible using yeast and an anticlastogenicity test (a test for damage to chromosomes, the structures containing genetic material) is possible using plant material[8, 9].

In summary, this work is flawed for the following reasons:-

- Repetition
- Species differences
- Non-animal alternatives available

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7 Vogelstein, B et al. Carcinogens leave fingerprints. Nature 1992†; 355†: 209-210
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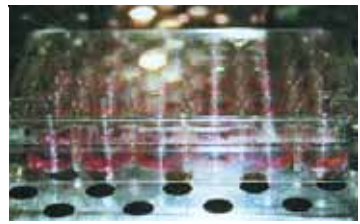
9 Dashwood, RH et al. Cancer chemopreventive mechanisms of tea against heterocyclic amine mutagens from cooked meat. Proc Soc Exp Biol Med 1999 April; 220(4): 239-43

research without animals

Research without animals



CPCSEAinspectors found awareness of non-animal techniques to be low, or non-existent. Yet non-animal testing methods are more effective, with faster results. In the longer term, they are also cheaper. Alternative, non-animal techniques are also more relevant to humans, as they avoid the problems of species differences which make animal tests unreliable as a predictor of likely effects in humans.

Sophisticated non-animal techniques are good science, and the methodology of choice for the future. Many new discoveries about disease, for example, are now being made at the single cell level – at the level where the disease operates – and new technology is being developed which is set to take over from animal-based methods.

UK and European legislation regulating animal experimentation demands that, wherever possible, non-animal methods be sought before recourse to the use of animals.

Public opinion in the UK and across Europe strongly favours the use of non-animal approaches to medical research wherever feasible. A poll undertaken for the Medical Research Council in 1999 indicated that of those polled 91% agreed that "there needs to be more research into alternatives to animal experiments".

The NAVS department responsible for funding non-animal scientific and medical research, the Lord Dowding Fund for Humane Research, has awarded over £2 million on such projects.

Examples of animal tests and non-animal replacements:

Animal test:	Skin cancer test (chemical & physical agents).
Humane alternatives:	Episkin: tissue cultured skin grown in layers. Epiderm: 3-D reconstituted human skin derived from neonatal foreskin.
Animal tests:	Skin corrosion/irritancy testing. Substances applied to shaved skin,usually of rabbits.
Humane alternatives:	Corrositex: test chemicals applied to non-living biomembrane constructed to have similar properties to skin. Colour change. Episkin - see above. Cultured skin fibroblast cells.
Animal test:	DNAmutagenesis (alterations) in transgenic mouse models e.g.Mutamouse. Known to be oversensitive & overestimate human risk.
Humane alternatives:	Millimeter wave spectroscopy: measures sound waves in DNA. Resonances change when DNAis damaged.
Animal test:	Draize eye irritation (products placed in rabbit eye for several days.
Humane alternatives:	Irritection (formerly Eytex). Fluorescein leakage assay: Fluorescein will leak through cultured cells to varying degrees in presence of chemicals. Artificial human cornea: chemicals applied to corneal cells grown into layers on a scaffold.
Animal test:	Insulin action in muscle.
Humane alternatives:	Human muscle cells in culture with glucose and insulin.
Animal test:	Toxicity testing, systemic.
Humane alternatives:	DEREK (Deductive Estimation of Risk from Existing Knowledge) is a computer-based system whereby toxicity predictions are made on the basis of a series of rules relating to chemical structure and possible toxicity. DNA'chips'or microarrays: identification of damaged genes when human cells have been exposed to test chemicals *in vitro*.
Animal test:	Use of living animals as vertebrate biology teaching aids.
Humane alternatives:	University of Portsmouth has developed a fully comprehensive CD-Rom in response to growing demands for an effective alternative to live animals for the teaching of vertebrate biology. Teaches anatomy and dissection, physiology, histology (ultrastructure of tissues) evolution.

Animal use:	Dissection of rat.
Humane alternative:	PracticeRat synthetic model.
Animal test:	Medicine efficacy and mode of action.
Humane alternatives:	Testing efficacy and action of a drug on human organs and tissues eg a new anti-asthmatic was tested on human lung tissue *in vitro*.
Animal test:	Rabies vaccine: potency testing, vaccination challenge test using mice.
Humane alternatives :	ELISA(Enzyme-linked immunosorbent assay) using monoclonal antibodies.
Animal test:	Rabbit pyrogen (fever-inducing substance) test.
Humane alternatives:	Human cell culture test; cells produce a chemical (TNF or tumour necrosis factor) in response to a pyrogen.
Animal test:	Toxicity testing of dental filling materials.
Humane alternative:	Use of a dentine slice from a human molar tooth, removed during normal dental procedures. Included as a British Standard Test in 1987.

New technologies are opening up new avenues of research, for example, **brain research on animals** for diseases such as Parkinson's, Alzheimers, and psychological problems, can be replaced with better methods, which avoid the problem of the differences between human and animal brains:-

Human brain imaging:
Functional magnetic resonance imaging (fMRI) tracks brain activity by monitoring blood flow. This has allowed neuroscientists to understand which areas of the brain are active during specific tasks;
Positron Emission Tomography (PET) allows areas of the brain which are active during a specific task, such as thinking or experiencing pain, to be identified;
Cortical Evoked Potentials (CEP) measures the electrical component of electromagnetic brain pulses and Magnetoencephalography (MEG) measures the magnetic component. In combination, CEPand MEG accurately identify areas of the brain involved in processing information for a specific activity;
Transcranial magnetic stimulation (TMS) applies magnetic pulses to the brain which then stimulate or suppress activity. This has been used to study visual attention, memory and recognition;
Repetitive TMS (rTMS) creates a virtual lesion for neuroscientists to experiment on just as they would by cutting the nerves in an animal's brain to see the functional response. Thought processes have been investigated using rTMS. A combination of TMS and fMRI is being used to probe changes occurring in the brain associated with diseases such as schizophrenia;
Synthetic Aperture Magnetometry (SAM); by using measuring electrical and magnetic pulses SAM can identify the region of the brain responsible for signals and their depth when triggered by particular stimuli. SAM is currently being used to study the experience of pain associated with irritable bowel syndrome and non-cardiac chest pain.

Molecularmodels:
Certain strains of *Escherichia coli* produce amyloid fibres similar to those that accumulate in the brains of Alzheimer's and other degenerative brain disorder patients. *E coli* is therefore used as a molecular model to study amyloid formation during the design of drugs to treat or prevent human amyloid diseases;
brain cells which need dopamine to function and those that do not can be isolated from human foetal brain tissue. Using this molecular model a study was performed to understand why the degeneration of dopamine dependent brain cells occurs in neurodegenerative disorders such as Parkinson's disease. A particular protein was identified as a causal factor in dopamine dependent brain cell death.

Patient studies:
Using Parkinson and schizophrenia patient volunteers to investigate visual abnormalities caused by the failure of dopamine systems in the brain. The effectiveness of potential therapies are assessed by observing the effect on the patient's vision.

Epidemiological studies:
In the United States, nuns have donated their brains after death for research. This allows a unique insight into potential causes of Alzheimer's by studying the brains of people who have led similar lives so that many epidemiological variables are absent. It has already been discovered that the likelihood of someone contracting Alzheimer's can be predicted from linguistic abilities in their early twenties.

Research without animals has the great advantage that it is an expanding technology, moving into all fields of scientific and medical research; it is the area where companies are investing in new technology forthe future. India has a remarkable opportunity, ratherthan invest in rebuilding its crumbling, redundant animal laboratories, it can instead invest in this future.

conclusion and recommendations

Conclusion and Recommendations

Poor accountability, poor controls and poor science are rife in Indian laboratories. The level of suffering being inflicted on animals is shocking and quite rightly brings shame upon the scientific community in India.

Our critique of the scientific papers published by Indian laboratories, and examination of the evidence supplied by the CPCSEAdraws the conclusion that years of scientific research in India has been invalidated by poor scientific procedure, poor laboratory practice and lack of appropriate animal care.

There appears to be no rigorous critical scientific review of proposals to use animals, and no functioning legal mechanism to ensure compliance with legislation, or with the welfare standards laid down by the government's CPCSEA.

Permission to deliberately inflict pain and suffering on animals should never be taken lightly, it should require the utmost questioning, review, and deliberation. Those requiring permission must fully explore other sources of the information they require. It is imperative that an independent body is in place to verify that non-animal methods have been explored. The law should provide for real control, real accountability.

Laboratory managers should be made legally accountable for what happens to animals in their laboratories. Lack of funds should not be an acceptable excuse – poorly funded and conducted research is worse than no research at all.

The findings of these studies have shown that unfettered science is not good science. Like other professions where the vulnerable are involved, animal research needs to be effectively regulated, policed, and those responsible must be held accountable.

Furthermore, these investigations have highlighted apparent complicity and even apathy amongst international funding bodies, science journals, and collaborating scientists.

Animal Defenders International and the National Anti-Vivisection Society recommend that:-

1. Licensing & enforcement:
In place of the current system, laboratories in India should be licensed. Such licences should only be awarded if an establishment meets modern standards as laid down by CPCSEA, and a named individual on the licence must take responsibility for ensuring that experiments and procedures conducted on animals are within the law, that animals are only sourced from approved suppliers, and that animal house and experimental laboratory management practices meet with required standards.

2. Welfare and standards of good laboratory practice:
The welfare and good laboratory and animal house management guidelines laid down by the CPCSEAshould be made compulsory, and provision made for regular review and updating; deliberate or negligent flouting of any code of practice should be liable to prosecution.

A review of codes of practices for use of animals in laboratories and for laboratory animal breeding and supply establishments in other countries should take place, and the Indian authorities should not only adopt best practice from those countries, but make these measures enforceable.

3. One yearforcompliance:
It is reported that India has in the region of 5,000 animal laboratories, and only a handful have been accredited as compliant with standards of good laboratory practice. CPCSEAinspected 467 laboratories, of which 400 were found to have inadequate facilities or management practices in relation to the use of living animals. India's animal laboratories should be given one year to meet the standards; if a laboratory fails, then it cannot use animals.

4. Public access to information:
Full public disclosure of all animal research undertaken in India each year. To include the numbers of animals used, by species, source, the purpose of the research, funding bodies, papers published and projects started/completed by each laboratory.

5. The immediate prohibition of:
Production of rabies by the live and conscious sheep method, described at the Haffkine Corporation; blood sampling by orbital bleeding; use of non-purpose bred animals, with immediate action on use of feral dogs and wild primates.

The Indian government and the CPCSEAshould take the opportunity to **bring Indian legislation into line with the most advanced legislation elsewhere**, by proscribing experiments which are already banned elsewhere, such as the ascites method of antibody production, and other similar measures.

6. Budget foralternatives education:
CPCSEAto be provided with an annual budget for the dissemination of information on non-animal research techniques and for re-training of laboratory personnel in the new techniques.

7. Obligation to use non-animal methods/formal applications:
All applications for permission to use animals to contain a requirement for animal experimenters to justify their wish to use animals, and explain why the proposed animal work cannot be achieved with non-animal methods.

8. Incentives to move to non-animal research:
Government funding to laboratories which do not meet CPCSEAstandards, or generate useful work (i.e. completed and published projects) should be stopped. This funding should be re-directed to those facilities moving to modern non-animal research.

The Indian government could provide incentives in terms of financial support for research without animals. This would have the added advantage of actually moving India towards the forefront of new technology and leading-edge medical research.

9. Critical review of proposals to use animals, *before* licence is granted:
A wider scientific and public critical review of the need to use animals *must* take place before work on animals is permitted. Via the internet, it would be possible for all institutions to make a central application to the CPCSEAfor permission to use animals, once this has cleared the Institutional Animal Ethics Committee.

10. CPCSEAand Institutional Animal Ethics Committees:
IAECs should only review applications and make recommendations to CPCSEA; the final decision as to whether a licence should be granted should not be made locally as this is open to corruption, as has already been suggested elsewhere.

11. Audit of animal research:
The evidence we have presented in this report draws the conclusion that there appear to be funds available in India to run laboratories which never generate significant research results, and also to support hundreds of research projects that are either never completed, or are not good enough for publication. Yet some have claimed that they do not have the funds to improve their facilities.

It is clear that money is being wasted in India's laboratories on a massive scale. An audit of current costs against scientific results at each laboratory should be undertaken as a matter of urgency.

12. Public accountability and the decision-making process:
It is vital that the scientific community in India is not left to make decisions about animal use without full public information, involvement and consent. This is an important public debate for the whole of society, not for the scientific community only. The role of the scientific community in this debate is to simply translate the scientific jargon into everyday language to enable the public to make an informed choice.

Everyone has the right to participate in a debate about allowing deliberate infliction of pain and suffering on other creatures – a debate that also extends from work on the AIDSvirus, to creation of genetically modified animals, plants, and viruses – all of which may affect the future of this planet.

International

We emphasise here our view that it is time for the science journals, the funding organisations (including government departments) and the research community as a whole to take responsibility for situations such as we have described in India.

All are implicated and all should therefore bring pressure on those facilities we have highlighted, where animal welfare and standards of good laboratory practice are disregarded.

All those mentioned in this report who collaborated, funded, or encouraged by publication, or just turned a blind eye, are shamed by what has happened in India.

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