photocycle with a brief flash of actinic light[3]. Clearly, the duration of the flash has to be very short to monitor early intermediates like K which are formed in picoseconds, whereas even microsecond flashes suffice to characterize later intermediates such as M which rise in 50–100 μs. Flashing membrane sheets containing bR (the famous purple membrane sheets) release protons into the medium with the same kinetics as the rise of M (50–100 μs), while the re-uptake of the proton follows the kinetics of regeneration of bR (5–10 ms).

Photoisomerization to 13-*cis* retinal generates strain in a binding pocket optimized for all-trans retinal. Formation of M involves loss of a proton on the extracellular side, while thermal relaxation back to bR requires re-uptake of a proton from the cytoplasmic side of the membrane[4]. The M intermediate was shown to have a deprotonated Schiff's base and a 13-*cis* chromophore by IR and resonance Raman spectroscopy in the eighties[5]. The crystal structures of many of the later intermediates have since been determined in the late nineties[6–8], leading to a delineation of the pumping pathway[9], which amounts to a bucket brigade relaying the proton from side chain to side chain across the membrane. However, the initial steps by which absorption of the photon sets-off the whole train of events – the cocking of the gun, as it were – are only now becoming amenable to experimental characterization.

Photoexcitation of bR occurs on a time scale faster than nuclear rearrangements can occur and the formation of a ground state, isomerized intermediate occurs later. The K state, which forms in a few picoseconds, has recently been crystallized and shown to have a 13-*cis* chromophore[10]. Theoretical studies predict the formation of a 13-*cis* ground-state intermediate in under 500 fs, corresponding to the J intermediate[11]. However, studies with sterically constrained retinal analogues appear inconsistent with this expectation[12]. The early intermediates had previously been characterized in kinetic experiments using a brief laser pulse to initiate the photocycle and then probing the system with brief interrogating pulses. These experiments require a very stable protein, and thus can be carried out with bR, but have not yet been extended to visual rhodopsin. The femtosecond experiments required to detect I and J had thus far been carried out at visible wavelengths, which report on the electronic state of the system but not directly on the configuration of the chromophore. Herbst and co-workers[13] have now carried out pump-probe experiments at infrared wavelengths with 200 fs resolution and have shown that all photoproduct vibrational modes rise with time constants of around 500 fs and are consistent with a 13-*cis* configuration.

The strain generated by isomerization is subsequently relieved by protein relaxation, leading to very different results in different proteins–proton pumping in bR; chloride translocation in halorhodopsin, and photoperception in visual rhodopsin. bR thus remains the beacon, guiding research into the mechanisms by which the signal transduction machinery is primed.

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COMMENTARY

Animal experimentation rules – Separating the reality from the rhetoric

Saionton Basu

An attempt has been made to analyse the Guidelines proposed by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and how they affect scientific research in India. An analysis of the conditions imposed by the CPCSEA has been made to see whether they fulfil the 'test of reasonableness' on whose touchstone every action of a statutory authority, in this case the CPCSEA, must be evaluated to be valid. The sole national regulatory and monitoring body has created several administrative bottlenecks, which are delaying the progress of scientific research, which will blunt the competitive edge of India in the 'pharma-biotech' sector.

There can be few more emotive issues in science than animal experimentation. To the researchers involved, such research is vital for continued scientific progress, while animal-rights activists term them as the worst kind of animal abusers, deserving public vilification[1]. This paper seeks to examine the guidelines (Breeding of and Experiments on Animals [Control and Supervision] Rules, 1998 framed under Section 17(1) of the Prevention of Cruelty to Animals Act, 1960) proposed

by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), and the subsequent amendments brought forth in April 2000, which have kicked up a storm in the scientific community. This paper will primarily outline the legal remedies available to the scientific community, which is under constant threat of having to shut down its laboratories under the new regime of animal experimentation rules.

A brief overview of the progression of rules

In February 1996, the Union Government constituted the CPCSEA to regulate animal experimentation in exercise of its powers under Section 15 of the Prevention of Cruelty to Animals Act, 1960 (hereinafter referred to as the Act). Section 17 of the Act empowers the CPCSEA to frame rules with regard to conduct of experiments on animals. The Ministry of Social Justice and Empowerment inviting objections and suggestions, brought out a draft notification. What transpired was a period of strong protests from the scientific community, which prompted certain changes to the draft notification. Thereafter, a notification issued by the Ministry of Social Justice and Empowerment brought into effect the Breeding of and Experiments on Animals (Control and Supervision) Rules, 1998 (hereinafter referred to as the Rules). These Rules decentralized the clearance procedure to the institutional committees, with representation from the CPCSEA. The Rules allow transfers only among laboratories already registered with the Indian government, in effect limiting the pool to domestic facilities[2].

In its April 2000 meeting, the CPCSEA decided that institutional ethics committees could grant clearances only to those project studies relating to experiments on *small laboratory animals*. While for *large animals*, the institution would have to send the proposals for clearance to CPCSEA, which will then send it to an expert consultant in Chennai, who in turn will route it to a sub-committee in New Delhi to assess the proposal. The comments of this sub-committee will then be communicated to the expert consultant, who will communicate the decision to the institution concerned through CPCSEA. The nominee of the CPCSEA in the Institutional Animal Ethics Committee (IAEC) can also reject any applications seeking permission for animal trials.

New regulations – Setting loose a bull in a china shop

The new regulations are in contravention to the guiding principles stated in the notification on 15 December 1998. The 1998 notification had stated that the permission from the IAEC recognized by CPCSEA, was necessary before commencing a project study using animals. The IAEC was required to represent experts from all aspects of relevant research and also a nominee from CPCSEA. Decisions should be taken by the IAEC after detailed discussion and in a democratic manner. These conditions, although quite tough, were acceptable to the scientific community. But, in April 2000 CPCSEA came out with a set of changes to the original notification[3].

According to these changes, (1) experiments on large animals should be avoided if the same result could be achieved by other means; and (2) IAEC can only grant clearances to project studies involving experiments on small laboratory animals but for large animals, the clearances should be obtained from CPCSEA.

Scientists complain that the new rules on animal experimentation are totally unreasonable, leading to inordinate delays in getting clearances, frustrating the research initiatives of the national institutes and pharma companies[4]. These procedures are actually hampering the plans of several research institutions in going ahead with international patenting procedures for new molecules. Maneka Gandhi describes the proposed rules 'as conforming to well-established norms adhered to in the West'. This again shows the ignorance about what the Western norms are with regard to grant of permits and clearances. Maneka Gandhi is reported to have said that Americans have won so many patent rights because they kept their animals in healthy conditions[5]. Through a combination of the Animal Welfare Act and the Health Research Extension Act in the United States, all animal researchers are now under the oversight of a local review committee known as an Institutional Animal Care and Use Committee. The committee is made up of a veterinarian and at least one person not affiliated with the institution[6]. Therefore, long delays resulting from a single national committee, as the sole licensing body for all animal experiments involving large animals in the country does not augur well and cannot, by any stretch of imagination, be said to be in conformity with American norms of keeping animals in healthy conditions.

Alternative regulatory regimes

The basic aim is to delink drug research from the purview of CPCSEA and empower the concerned departments to approve animal experimentation, for which an animal ethics committee could then be set-up accordingly. If the intention of the CPCSEA is really to adhere to American norms, then it should facilitate all clearances at the institutional level. Institutions and researchers engaged in biomedical science might do well to re-examine their own procedures for regulating animal-based research. Strict self-policing might be the best way to avoid governmental initiatives, like the CPCSEA[7].

The legal framework – Unreasonable conditions

According to Rule 5 (c) a research establishment, on obtaining registration would have to comply with the 'conditions' imposed by the CPCSEA. Also Rule 8 (c) specifies that the CPCSEA, while granting permission for conducting experiments on animals, may put in conditions to prevent unnecessary cruelty to animals. Now what would and should be the tests of validity of such conditions? Can the statutory authority go to any length?

The condition must be *reasonable*, which means that it must 'fairly and reasonably relate' to the permitted activity or the fulfillment of the purposes of or the policy behind the legislation and not be used for an ulterior object.

Therefore the conditions imposed can only go to the extent of preventing *unnecessary* cruelty to the experimental animals. This is the stated purpose behind the rules and any measure, which tries to prevent cruelty by putting an end to animal research altogether, is unreasonable. The Prevention of Cruelty to Animals Act, 1960 clearly enunciates only one ground under which the CPCSEA may

be vested with the power to prohibit experiments on animals altogether – that is, if conditions imposed by the CPCSEA are not being complied with. However, unilateral measures, which will practically stop scientific research without fulfilling the test under Section 19, are against the letter and spirit of the Act. If the Court finds a condition to be *ultra vires* or unreasonable, it will strike down the condition, so that the permit will operate free of the invalid limitation. Therefore, the near-ban on import of laboratory animals for experimentation under Rule 10 (e) is clearly without jurisdiction.

The rules framed by the Ministry of Social Justice must relate to the permitted activity, which is scientific research. Therefore, if the purported exercise of the powers by the statutory authority is to prevent suffering of animals without due regard to scientific research needs, then such rules do not have the necessary nexus and thus should be struck down.

The *Doctrine of Reasonableness* emerging out of the English cases in *Wednesbury*[8], *Padfiled* and *Anisminic* has been cited with approval in many Indian decisions[9]. In the Liberty Oil Mills case, the court reiterated the principles that the action will be patently without jurisdiction, if it is not based on any relevant material whatsoever. If the authority declines to consider the representation, or if the authority after consideration of the representation eschews relevant considerations and prefers to act on irrelevant considerations or from an oblique motive, or the decision is such as no reasonable man properly directed on the law would arrive at based on the material facts, it will be open to the party to seek the intervention of the Court at that stage. Therefore if the CPCSEA minutes reveal a lack of understanding of the scientific merit of the experiment and the decision to disallow the same is taken on grounds which were without going into detailed considerations, then the same decision of the authority can be successfully challenged in a court of law.

In the J. R. Raghupathy case, the Supreme Court again emphasized the principle that the statutory authority must act in good faith, must have regard to all relevant considerations and must not be swayed by irrelevant consideration, must not seek to promote purposes alien to the letter or to the spirit of the legislation that has given it power to act, and must not act arbitrarily or capriciously. In light of this authoritative ruling of the Supreme Court, it is evident that the CPCSEA rules are alien to the letter and spirit of the legislation giving it power to exercise authority. Nor, where a judgment must be made that certain facts exist, can discretion be validly exercised on the basis of an erroneous assumption about those facts. This observation reflects the acceptance of the Wednesbury unreasonableness as subsequently modified and refined by the Indian judiciary.

It was found that the National Institute of Nutrition, Hyderabad was violating the rules framed under the Prevention of Cruelty to Animals Act, 1960. Their primate house is neither registered nor recognized due to lack of facilities, according to the rules under the Act. The CPCSEA secured the release of monkeys from the animal house and set them free in the wild. It is submitted that under Section 20 of the Act, the penalties for non-compliance do not include setting experimental animals free in the wild. Subsequent clarification by the Ministry of Social Justice that the chances of survival of animals in the wild are excellent, betrayed an understanding of the law and the scientific merit behind their action.

Concluding remarks

The specific provisions of the Rules, which have brought biomedical scientists on the one hand and the CPCSEA on the other, on a confrontational course are as follows:

(1) The rules authorize a single national committee as the sole licensing body for all animal experiments involving large animals in the country.
(2) The rules envisage prior approval for each individual experiment separately.
(3) The rules implicitly prohibit acquiring all experimental animals from non-Indian sources.

Having looked at the rules proposed by the CPCSEA and the evident attempt to pursue an agenda alien to the legislation guiding its conduct, it is clear that these rules are unreasonable. Further, the delays, which would be caused to scientific research, would prove expensive for the nation in the coming years. For instance, the disruption of an Indian biotech concern's trial of the anti-cancer drug at the National Institute of Nutrition by animal-rights activists is likely to have benefited its MNC competitor in the same segment.

Therefore, if the Union Government, for whatever reason, is not willing to change the rules to establish a much-needed balance between the lopsided rules and the legitimate concerns of the scientific community, then the courts may well be the last bastion which the scientists would have to storm.

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