The role of the central laboratory animals house and of the laboratory animal scientist within a pharmaceutical company*)

The extent to which a laboratory animal unit can be centralized and the advantages and disadvantages of centralization become readily appreciable if one considers, for example, the facilities that have to be provided in a large pharmaceutical firm. Since the entire research establishment cannot, for various reasons, be centralized in one single complex, the laboratory animal units have to be sited accordingly. This has been done in our company in our multi-storey biology building in Basle, which houses the general pharmacology research groups conducting predominantly acute experiments. The central laboratory animal unit located in this building is run under conventional hygienic conditions. The animals are from our own SPF breed, or in certain cases purchased from reputable commercial suppliers (Table I) Strictly segregated behind hygienic barriers is the primate unit, in which up to 550 rhesus monkeys are kept for up to ten years, or even longer, for psychopharmacological investigations. This unit, opened in 1979, was so designed and constructed that it would be optimally suited for the study of the influence of psychotropic drugs on the social relations between individual animals in a community and at the same time meet the particularly critical conditions of accommodation and hygiene that have to be observed in keeping primates. Of the various primate species, the rhesus seemed the most suitable for such psychosociopharmacological investigations. The animals used in these experiments are exclusively monkeys that have

TABLE I

Multi-storey biology building with central laboratory animal unit
Occupancy: June 1967

Dimensions

Height	: 77 m	Normal area per storey	1,380 m²
Length	: 67 m	Total area	approx. 26,230 m²
Breadth	: 21 m		

Storeys	*Rooms on laboratory floors*
1 Basement	137 Laboratories
1 Ground floor	32 Laboratory animal rooms
11 Laboratory floors	22 Acclimatized rooms
4 Office floors	39 Service rooms
1 Machinery floor (air conditioning, etc.)	20 Offices

* Held at the Symposium of the Netherlands Society for Laboratory Animal Science (N. v. P.). "Centralization of Facilities for Animal Experiments", May 9—10, 1980 Nijmegen.

been caught in the wild state and display the full behavioural repertoire necessary to studies of this type. As a consequence of the attenuation or complete absence of the stimuli to which they are exposed in their natural habitat, animals bred in captivity either lose certain patterns of response entirely, or react in an inappropriate manner (*Jaekel*, 1980). In the primate unit, the rhesus monkeys are kept in single cages with an area of 0.8 m^2 and 1.2 m in height. The social-activity and observation cages have an area of 17. 2 m^2 and are 2.5 m high. The unit is in the way of bing a prototype: there were no models in existence for this sort of experimentation.

In another central unit, medium- and long-term toxicological investigations are carried on under strict SPF conditions. This unit is on the same premises as our animal breeding farm in Sisseln. The animals can be transferred direct from the breeding facilities into the toxicology unit, thus obviating the risks involved in transportation over long distances.

As the examples show, the three research units serve one common purpose, in so far as they are all designed for experimentation on animals: but the nature of the experiments and the conditions under which they have to be performed are quite different, and there would be little point in centralizing such heterogeneous experimental units (Table II).

Supply of laboratory animals

Our company has its own laboratory-animal breeding establishment, known by the name of Tierfarm Sisseln and situated about 30 km from Basle. The planning of this breeding unit began in 1959. The last of the buildings became operational in 1968. The whole complex, including a number of several-storeyed buildings covers an area of 14,000 m^2. The unit supplies most of the laboratory animals required by the experimental research sections of our company in a

TABLE II

Laboratory Animal Units

	Centralized	*Decentralized*
Advantages:	— Economy of building and installation costs and upkeep (air-conditioning plants, infrastructure)	— Elimination of long transport routes
	— Economy of operation (common use of operating materials)	— Smaller risk of infection
	— Better utilization of animal rooms through flexible occupancy	
	— Greater possibility for rational employment of trained personnel	
Disadvantages:	— Greater risk of infection	— Higher personnel costs

constant hygienic and genetic quality. The lay-out of the unit is follows: In the laboratory building are situated the isolator tract where the germ-free animals are reared and the special breeding quarters for small laboratory animals. The same building also accommodates the administration offices and the microbiological laboratory. The large-scale production of laboratory animals takes place in the two so-called SPF buildings, behind hygienic barriers. The service building houses the central auxiliary functions, stores, and the washing and incineration plants. Dogs are bred and raised in two separate sections. The unit has its own sewage plant.

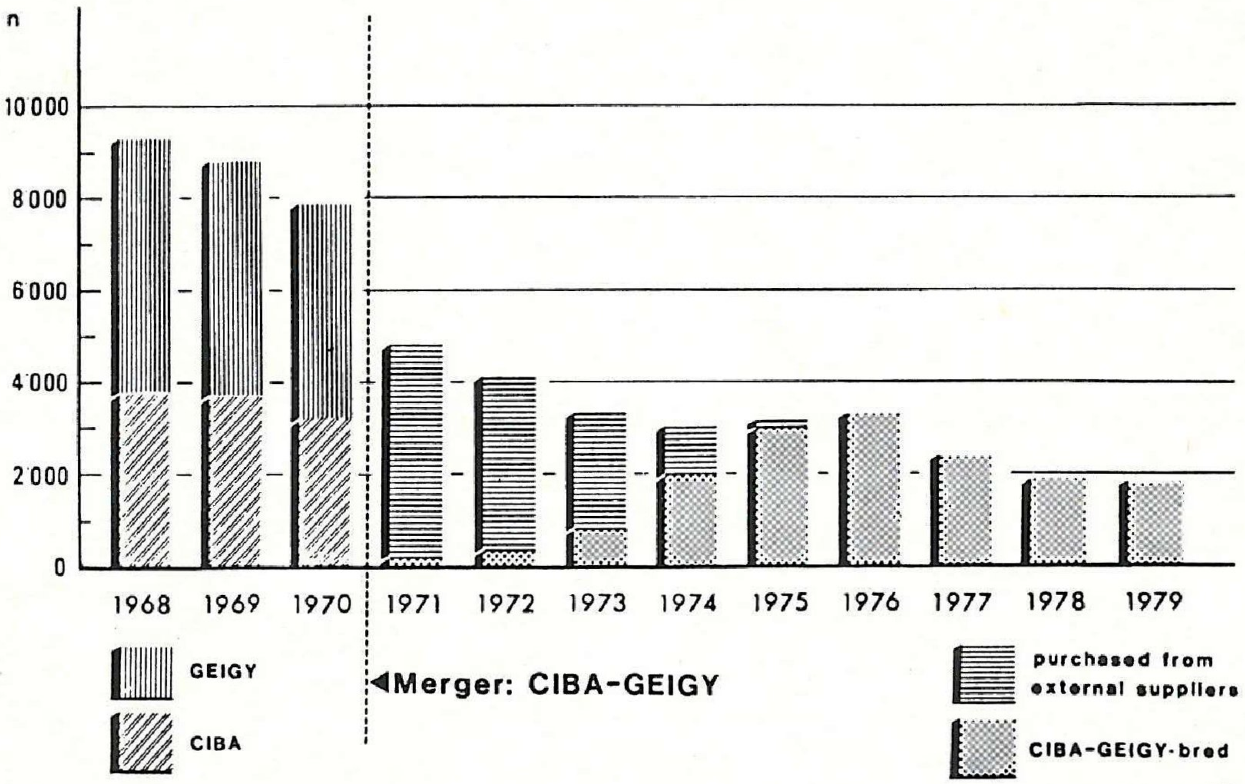
Considering that there are somewhere in the region of 200 inbred strains and about 600 mutants of mice and 100 inbred strains of rats as well as numerous strains and mutants of rabbits and guinea-pigs, it is evident that the breeding unit has to limit its production to selected strains, either those in greatest demand or special strains otherwise difficult to obtain. Any special strains required sporadically or additional supplies needed at short notice are purchased from commercial sources. In principle, all the animals bred in the unit are intended for our own use. Other institutes are only supplied if they happen to be collaborating in a given research project. The breeding unit is run by two scientists with the help of a staff of some 70 persons.

Altogether about 70 % of the laboratory animals required by CIBA-GEIGY are bred in Sisseln.

The role of the Laboratory Animal Scientist

The principal task of the Laboratory Animal Scientist is to provide the experiments with suitable laboratory animals, offer expert advice and see to it that the necessary equipment is available. In addition to these responsibilities, it is

TABLE III Number of cats used annually by CIBA-GEIGY Basel.



also his duty to optimize experiments on animals. This can be achieved by various means, e.g. by improving the quality of the laboratory animals. In this way, the predictive value of the experiments can be enhanced and, in the long run, the costs reduced. The cat affords a good example of this.

The number of cats used annually in our firm over the last twelve years is shown in Table III. The maximum was in 1968, with a total of 9,385 cats used in experiments by the two then still independent companies, CIBA and GEIGY. At that time, cats could only be obtained from external suppliers.

The rate of losses before experiments was between 20 % and 50 % and was unrelated to the season and the age and sex of the animals. The main causes of death were enteritides and respiratory infections. Deaths occurred within the three weeks of delivery. The number of animals that died during experiments or were sacrificed after experiments that failed to produce results of any practical or theoretical value is indeterminable. Our observations are confirmed by the outcome of a survey conducted by *Soave* (1974), who quoted similarly high death rates among cats purchased from commercial sources.

In 1971 began the first deliveries of cats from our own SPF cat colony, after a planning and establishment phase of six years' duration (*Hurni*, 1980).

Since 1976 we have been able to produce all the cats we need without having to rely at all on purchases from outside suppliers. Our annual requirements, originally estimated at 6,000 cats, can now be fully covered by fever than 2,000. This considerable reduction in the number of cats used can be ascribed to the following factors:

a) Intercurrent losses before, during and after experiments have been practically eliminated.
b) The excellent quality of the animals has made it possible to carry out chronic experiments and, in many cases, dispense with acute experiments.
c) The sense of responsibility of the experiments of equal predictive value can be performed on hierarchically lower animals, even if the technical difficulties involved may sometimes be greater.
d) The integration of two formerly independent research groups through the merger of CIBA and GEIGY.

The cats are bred an SPF environment. After their delivery to the research laboratories, however, the conditions under which they are kept, and under which the experiments are performed, are conventional, although various hygienic precautions are taken: e.g. entry to the animal quarters and laboratories is prohibited to unauthorized personnel. Unless the nature of the experiments calls for other measures, the cats are housed in communal cages. Even cats with electrodes implanted in their skulls can be kept in this wey without difficulty.

Another means of optimizing experiments is the introduction and propagation of new species: for example, it is preferable to use monkeys reared in captivity as laboratory animals instead of imported animals trapped in their natural habitet, not noly from the point of view of the protection of wild life and the preservation of the species, but also because of the supply problem and the risk of transmitting infections to man. It would be hard to imagine any scientist ever going to the lengths of catching his own mice and rats, keeping them in quarantine, and treating them so as to be able to use them for biomedical research. Quite the contrary, there has even been a demand for the exclusive of animals of "pro analysi" (*Hurni*, 1964). As far as concerns the supply of primates, however, we have still not evolved beyond the primitive status of the collectors and hunters.

The practice of obtaining rhesus monkeys by trapping them in the wild came to a sudden end in 1978, when Desai, then the Prime Minister of India, placed a ban on their exportation. In point of fact, this measure was motivated more by religious sentiments than by the desire to protect wild-life: the monkey is a holy animal and the monkey god, Hanuman, has his place in the Hindu panteon. Other countries with other indigenous species of monkeys followed suit, or imposed stricter conditions on the exportation of primates, to forestall the use of alternative species as laboratory animals.

Incidents like the fatal infections with B-virus and the Marburg Agent are proof enough that working with wild monkeys is not without its dangers, and for this reason the authorities had to issue regulations to prevent the transmission of infectionse from monkeys to human beings (Berufsgenossenschaft, 1968; *Dollinger*, 1979).

For special purposes, such as the psychopharmacological investigations in rhesus monkeys already mentioned, there may be no alternative to the use of imported wild monkeys, if it is their natural behavioural patterns that are to be studied. Conceivably, however, monkeys bred in captivity could also be used, provided they have been reared in a tribe. With various smaller species of primates, e.g. the marmoset (*Callithrix jacchus*), this can now be done. As long ago as 1960, it was already evident this species was suitable for the evaluation and development of pharmaceuticals and for

TABLE IV.

	Animal Experiment		
	Pharmaceutical industry	Basic research	University
Experiments	Experienced specialist	Experienced specialist	Beginner (student)
Experiment, project	Established	Variable, new areas	Established (curriculum)
Duration of project	Long-term	Medium- to long-term	Short- to medium-term
Scope of project (number of animals)	Large	Small to large	Small
Laboratory Animal Scientist	Indirectly involved in experiment	Indirectly involved in experiment	Directly involved in experiment
Directly involved in the new experimental model			

studies to elucidate the aetiology of virus infections (*Deinhardt et al.*, 1967; *Hiddleston* and *Siddall*, 1978). Presumably the marmoset was selected for the following reasons:

— smallness and ease of handling
— breedable under laboratory conditions
— short maturation time
— small amounts of trial substances suffice
— sensitivity to various human viruses
— relative insensitivity to Mycobacterium tuberculosis.

It is now up to the laboratory animal scientist to convince experiments of the need to decide on an alternative species and of the need for their active collaboration in this task (Table IV).

Scope of animal experiments

According to a statistical survey, 321,000 laboratory animals were used in 1972 in universities and state-run teaching and research institutes in Switzerland. The survey was based on the data furnished by 113 of the 135 institutes in which laboratory animals are used (*Weihe et al.*, 1974). In the same period, three times as many animals were needed by CIBA-GEIGY.

What is the explanation for the enormous number of laboratory animals required by one single industrial enterprise?

In the pharmaceutical research and development departments of our company there are some 120 scientists working in about 50 different research groups that need laboratory animals and a further 40 engaged in basic research and oecotoxicological studies, for which animals are likewise indispensable.

CIBA-GEIGY ranks fourth among the pharmaceutical manufacturing firms throughout the world and produces about 3.2 % of the drugs sold in the world market. Roughly the same percentage of the innovative achievements of the research-based pharmaceutical industry originate from the CIBA-GEIGY laboratories. The number of trial compounds subjected to thorough investigation there between 1955 and 1978 was no less than 75,000.

To a large extent, the number of laboratory animals used reflects the growing concern for the safety of drugs on the part of manufacturers and consumers, and also of the legislature, which by imposing appropriate regulations on the manufacture of drugs and, to an in creasing degree, chemical in general seeks to insure against the risk of accidents and side-effects occurring (*Bruhin* and *Gelzer*, 1980).

The mass use of laboratory animals inevitably entailed by this trend, however, is in direct conflict with the growing public awareness of the need for the protection of animals and of their right to live (*Stern*, 1979; *Hoff*, 1980).

The consequence of this is the periodic dissemination of alarming reports in the mass media, public campaigns and growing pressure on the legislature to restrict experiments on animals (*Hammans et al.*, 1980).

Under the banner of anti-vivisection, fanatical animal protectionists keep up an incessant barrage of vituperation on all levels from the sensational tabloi press to the university lecture hall: animal experiments are descried as sheer barbarism and patent nonsense: a mere outlet for the lust for power of sadistic scientists (*Ruesch*, 1976; *Stiller*, 1976).

As one who experiments on animals, the laboratory animal scientist is thus exposed to public criticism. He is duty-bound to call himself constantly to account in order to safeguard against any risk of pursuing laboratory animal science as an end in itself; and he must, by the same token, spare no effort in the active search for alternative methods that will help to reduce experimentation on animals to the absolute minimum (*Merkenschlager* and *Wilk*, 1979).

References

Berufsgenossenschaft der Chemischen Industrie, 1968. Richtlinien für die Verhütung von Infektionen des Menschen durch Affen. Richtlinien Nr. 21, Verlag Chemie GmbH, Weinheim/ Bergstr.

Bruhin, H. und *J. Gelzer*, 1980. Why experiments on animals are indispensable in research, with special reference to drug development. Animal Regulation Studies (in press).

Deinhardt, J. B., J. Devine, M. Passovoy, R. Pohlman and *F. Deinhardt*, 1967. Marmosets as laboratory animals. Lab. Animal Care, 17: 11—29.

Dollinger, P., 1979. Rules governing the import, quarantine and husbandry of primates in Switzerland. Primate Report, No. 5: 6—8.

Hammans, et al., 1980. Durchführung von Tierversuchen bei Arzneimitteln und Chemikalien. Kleine Anfrage im deutschen Bundestag vom 30. 1. 1980. Drucksache 8/3627, Thesée Druck KG, Bonn.

Hiddleston, W. A. and *R. A. Siddall*, 1978. The production and use of Callithrix jacchus for safety evaluation studies. In: Neubert, D .et al. (Editors), Role of pharmacokinetics in prenatal and perinatal toxicology: 289—297. Georg Thieme Publishers, Stuttgart.

Hoff, C., 1980. Immoral and moral uses of animals. New England J. Med., 302: 115—118.

Hurni, H., 1964. Zucht und Haltung von Laboratoriumstieren. In: Weihe, W. H. (Editor), Die Umwelt der Versuchstiere und ihre Standardisierung im biologischen Test. Intern. Zschr. Vitaminforschung, Beiheft Nr. 9: 15—26.

Hurni, H., 1980. SPF-cat breeding (in preparation).

Jaekel, J., 1980. Affen, Spiegel der Menschen? Ciba-Geigy Magazin, 10, Nr. 1: 8—13.

Merkenschlager, M. und *W. Wilk*, 1979. Gutachten über Tierversuche, Möglichkeiten ihrer Einschränkung und Ersetzbarkeit. Schriftenreihe Versuchstierkunde, Helf 6: 49—53. Verlag Paul Parey, Berlin und Hamburg.

Ruesch, H., 1979. Die Fälscher der Wissenschaft. Edition Hirthammer, München.

Soave, O. A., 1974. Mortality of cats in a research institution: a five-year study. La. Anim. Sci., 24: 99—100.

Stern, H., 1979. Tierversuche in der Pharma-Forschung. Kindler - Verlag, München.

Stiller, H. und *M. Stiller*, 1976. Tierversuch und Tierexperimentator. Eigenverlag, Hannover.

Weihe, W. H. und *P. Joller*, 1974. Der Versuchstierbedarf, der Stand der Tierhaltung und der Tierpflege an den schweizerischen Universitäten und staatlichen Lehr- und Forschungsanstalten. Wissenschaftspolitik, Mitteilungsblatt der schweizerischen wissenschaftspolitischen Instanzen, Nr. 4: 445—482.

Sammanfattning

Författaren beskriver uppfödning samt den experimentella verksamheten vid Ciba-Geigy, som storleksmässigt ligger på 4:e plats bland samtliga läkemedelsindustrier. Författaren konkluderar att verksamheten inom de olika disiplinerna på en läkemedelsindustri är så olika att de skulle vara små fördelar med att centralisera djurverksamheten.

Författaren beskriver sedan uppgifterna för laboratory animal scientist, som förutom att arbeta för att förbättra djurkvalitén även skall ge expertråd under experimenten och därigenom se till att djuren utnyttjas på ett riktigt och optimalt sätt. Författaren ger även exempel på hur en förbättrad djurkvalité medfört minskat behov samt förändrad försöksinriktning. *K. G.*

Author's address:
Dr. H. Bruhin
Department Forschung
Division Pharma der CIBA-GEIGY AG
CH-4002 BASEL