REVIEWS

Biomedical Research on Nonhuman Primates: Results and Prospects

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The use of simian primates in experimental biomedical research reached its peak in the late 1950s and early 1960s. First studies in Russia (and, apparently, some of the first in the world) were undertaken in the late 19th century by I. I. Mechnikov who can be justly regarded as the founder of a new discipline, medical primatology. According to him, the rationale underlying the use of primates in biomedical studies is that the evolutionary proximity of monkeys to human beings permits reproduction and study of human diseases that cannot be examined on animals other than monkeys. Mechnikov generated the idea of setting up monkey colonies within natural habitats of various simian species — an idea that, rather unexpectedly, has acquired special importance in our days. Uncontrolled capture of monkeys in their habitats (particularly after poliomyelitis vaccine had been developed) and the contraction of the simian geographical range because of economic activities (deforestation, plowing up of savannas, etc.) led to catastrophic decline of natural populations of most simian species. Therefore, legislative acts restricting or prohibiting the export of monkeys from most of the countries containing their natural habitats were adopted. The reasons for imposing limitations on the import of monkeys are the risks of periodical outbreaks of infectious diseases dangerous for humans or domestic animals.

The impetus to writing this review was provided both by the data reported by other authors, by my own findings characterizing the biological norms for monkeys and the nosological profile of their diseases, and by the results of experiments conducted at the Institute of Primatology of the Russian Academy of Medical Sciences.

At present, many countries importing laboratory primates require information regarding the nursery or colony from which monkeys come from. Few countries import monkeys without indication of their origin. At the same time, few countries continue selling monkeys from natural habitats. Undoubtedly, trading of wild monkeys will cease completely in the next 3-5 years so that the only source of monkeys for experimental biomedical research, as well as for production purposes, will be specialized nurseries.

After the works published by Mechnikov, the main and, not infrequently, the only ground for the use of monkeys in experiments, was the *a priori* consideration that monkeys, because of their evolutionary, anatomical, and physiological similarities to man, should react in similar ways to environmental stimuli or pathogens. This thesis appears to be rather valid, but it should be borne in mind that different simian genera and species react in different ways to particular stimuli, so that the decision which simian species should be used in experiments must be made taking into account the available anatomical, genetic, physiological, biochemical, endocrinological, and other data characterizing various physiological systems of particular simian species which often differ from each other [38]. This makes it easier to choose particular primate species for particular experiments. Of much help in simian models of human diseases are comparative pathological studies characterizing the nosological profiles of spontaneous diseases in monkeys of different species and in human beings.

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It should be emphasized that, as demonstrated by comparative studies of simian and human diseases, the nosological profiles of these diseases are similar, as are their clinical and morphological manifestations. These manifestations, together with the experience gained in reproducing human diseases in various simian species, provide further evidence for the evolutionary kinship of human beings to monkeys and for classifying them as belonging to the single order of primates.

However, the selection of primate species for experimentation is still largely based on *a priori* considerations and is dictated by traditions, availability of particular species, and the number of studies conducted with a given species, which permits comparative analyses.

Studies carried out at the Institute of Experimental Pathology and Therapy (IEPT, Sukhumi) of the USSR Academy of Medical Sciences and later at the Institute of Medical Primatology (Sochi-Adler) of the Russian Academy of Medical Sciences led us to conclude that monkeys should be used in biomedical experiments if a) the problem is of global importance, b) no laboratory animals other than monkeys are suitable for a given study, and c) the monkeys intended for experiments have been bred in a nursery and do not belong to extinct species. It is obvious that experiments should be conducted observing the principles of humanity and taking the maximum possible care to protect the life of test monkeys.

In many situations monkeys are indispensable because the disease under study cannot be reproduced in other animals or the results obtained with other animals are not amenable to reliable interpretation.

A large proportion of such situations occur in the area of communicable diseases, for none of the animals other than monkeys can be used to produce infectious diseases similar to those that are so numerous in man. A good case in point is poliomyelitis. Thanks to the use of monkeys, the etiology, pathogenesis, and immunology of poliomyelitis are now well known and the question of eradicating this disease has been raised. Only monkeys and man have proved to be susceptible to the three types of poliovirus. Studies of immunity using the method of cross neutralization *in vivo* carried out in Sukhumi by Drs. M. P. Chumakov and M. K. Voroshilova in collaboration with the workers of the Biomedical Research Station of the USSR Academy of Medical Sciences (similar studies were under way in the USA at that time) identified three immunological types of poliovirus, showed a high susceptibility of monkeys to all these types, and shed more light on the epidemiology and pathogenesis of poliovirus infection. Experiments with monkeys subsequently identified poliomyelitis-like Coxsackie viruses, including the previously unknown enterovirus Coxsackie type 71.

The use of laboratory primates (currently of green monkeys) continues to ensure the production of oral live poliomyelitis vaccine; thus, a vaccine strain of the virus is cultured on green monkey kidneys, and monkeys are then used to check the safety (residual neurovirulence) of prepared vaccine. This requires a relatively large number of monkeys to be killed for obtaining primarily trypsinized kidney cell cultures and determining the residual neurovirulence. Whereas primarily trypsinized monkey kidney cultures can be replaced by transplantable cell lines (which will decrease the number of killed monkeys), no alternative exists as yet to checking the neurovirulence of each vaccine series.

There is no alternative to the use of primates for investigating etiology, pathogenesis, epidemiology, and vaccine-based prevention of several infectious diseases.

Two of the most striking examples are hepatitis A and hepatitis B. Although hepatitis A and hepatitis B viruses are members of two different families, those of enteroviruses and hepadnaviruses, respectively, they are traditionally mentioned together here. In the literature, many cases of hepatitis B among people contacting chimpanzees or virus carriers have been described, as have been cases of hepatitis B among chimpanzees after their contact with human patients or virus carriers.

The use of primates is associated with the studies by Deinhardt *et al.* [32,33], where the etiology of hepatitis A was elucidated. Although the hepatitis A virus (HAV) had not yet been isolated and characterized in tissue culture by that time, Deinhardt's experiments indicated that hepatitis A is of viral nature. Interestingly, sera from people who had sustained hepatitis A neutralized the virus subsequently isolated from monkeys with hepatitis.

Studies performed at the IEPT showed that macaques of various species, hamadryas baboons, and green monkeys are highly sensitive to HAV, which causes enzootic outbreaks among monkeys in a nursery, especially in recently imported monkeys with compromised immunity, which is associated with stress consistently experienced by all imported animals. Macaques proved to be susceptible to infection by materials from human patients with hepatitis and by cultured hepatitis A viruses. The question of whether hepatitis A is caused in monkeys and humans by the same virus remains open. Viruses inducing spontaneous hepatitis A in monkeys are virtually indistinguishable by the classical immuno-

logical methods. In our view, hepatitis A is caused in monkeys and humans by the same virus, although the possibility of existing simian and human "twin" viruses almost identical in their antigenic structure and pathogenic range cannot be excluded. The simian model of hepatitis A developed at the IEPT, irrespective of the causative virus, is indispensable in the testing of experimental vaccines against hepatitis [8,41]. This model allowed us to solve a number of important problems regarding the pathogenesis and epidemiology of hepatitis A and, in particular, to demonstrate extrahepatic localization of HAV and the possibility of HAV replication in the oropharynx. Perhaps one of our most important findings during periodic examinations of HAV-infected monkeys over a period of two years was that hepatitis A may take a chronic form. The acute form of hepatitis involving virus excretion in feces, elevated alanine aminotransferase levels, and morphological changes in the liver lasted up to 3 or 4 months, while the chronic form persists for almost 2 years and is characterized by remissions alternating with exacerbations, and excretion, throughout that period, of the virus that retained its pathogenicity. This finding is of considerable epidemiological importance, compelling us to revise our views regarding those who are recovering from this disease [8,27,41].

One of the viral diseases that can be studied only on pig-tailed monkeys is AIDS. Although chimpanzees and gibbons are also potentially suitable for this purpose, these animals are among the rare and specially protected species to be considered for such use. Infecting two subspecies of pig-tailed monkeys (*M. nemestrina nemestrina* and *M. nemestrina leonina*) with HIV-2 virus (or with the related SIV virus) and then with HIV-1 led to a disease that was characterized as AIDS both clinically and virologically. For the infection, virus isolates precultured on peripheral blood cells from various simian species were used, and it was found that the virus failed to replicate in *M. rhesus* or *M. fasicularus* cells, but did replicate well in *M. nemestrina* and human cells. The virus passaged through a blood cell culture was able to induce disease following the introduction of cultured and filtered materials. It should be noted that cultured virus isolated from infected monkeys could be passaged on human $CD4^+$ lymphoid cells. Monkeys infected with cells from such cultures were found to develop seroconversion to the antigen gp110/120 and p24 in 3 to 4 weeks. In other experiments, HIV-1-infected *M. nemestrina* were observed to develop a strong antibody response to proteins of the *gag* and *env* genes, although the titer of virus-neutralizing antibodies remained low. First clinical manifestations in the form of pronounced adenopathy were seen as early as after 2 weeks. The HIV-1-infected monkeys were followed up for about 2 years and the virus could be isolated from their blood throughout this period, although clinical manifestations of the disease were then confined to lymph node enlargement and depressed immunity with a characteristically changed ratio of helpers to suppressors (CD4/CD8).

By contrast, pig-tailed monkeys infected with HIV-2 developed a severe disease with clinical and morphological changes characteristic of AIDS (marked $CD4^+$ depression, anemia, opportunistic infections, and encephalitis with syncytial cells in the brain) with a mortality rate of approximately 50%.

Thus, three primate species (chimpanzees, gibbons, and pig-tailed monkeys) are now known to be sensitive to HIV-2 and HIV-1 (the causative agents of AIDS in man) and are suitable in principle for evaluation of vaccines, prevention, and therapy of AIDS. However, since chimpanzees and gibbons cannot be used in such experiments, pig-tailed monkeys are the only simian species available so far for the investigation of this disease.

Among the diseases for which primates remain the only animal models is measles to which many lower simian species and virtually all higher ones are susceptible. Monkeys are susceptible not only to experimental infection but may also become infected "spontaneously" as a result of contact with diseased human beings during virus excretion into the environment. We have periodically observed and described outbreaks of measles in some areas of the Sukhumi Nursery, usually associated with contacts of monkeys with children who were in the prodromal period of measles. Outbreaks, which often involve large numbers of animals, usually end favorably after a period of time characteristic for human disease. After the recovery, animals develop sustained immunity. It is only after several years, with the accumulation of measles virus-sensitive animals of a new generation, that conditions for further outbreaks are created. Clinical and pathomorphological manifestations of spontaneous and experimental measles which we observed in monkeys (and which have been described in detail by Shroit [29]) are virtually identical to those seen in man.

Experiments with monkeys led to the success of the development of effective preventive vaccine against measles. In this country such studies were initiated by Sergiev and his colleagues in collaboration with workers of the Sukhumi Biomedical Station of the USSR Academy of Medical Sciences [19,20].

Studies of "spontaneous" intestinal diseases, which are common among monkeys in captivity,

have revealed their infectious nature and, in particular, their association predominantly with *Shigella flexneri*, less frequently with *S. sonnei*, and sometimes with *Salmonella*, *Yersinia*, enteropathogenic *Escherichia*, or other opportunistic enterobacteria. These observations initiated experimental studies of dysentery on monkeys that resulted in the development of a model which was successfully used to test novel therapeutic schemes and methods, new antibiotics and chemotherapeutic agents, as well as antidysentery vaccines of various generations (corpuscular, chemical, ribosomal, and live vaccines from spontaneous or streptomycin-dependent mutants).

Infections worth mentioning in this review include malaria, a severe disease in many parts of the world where the availability of an animal model (spontaneous or experimental) makes it possible to test methods for treating malaria, especially malaria induced by drug-resistant *Plasmodium* strains.

Of interest in this respect is the malaria model produced through infection of night monkeys (*Aotus trivirgatus*) with *Plasmodium vivax*. The similarity of several plasmodial species causing malaria in monkeys to those causing it in man (*P. vivax*, *P. cynomolgi*, *P. malariae*, and *P. brasilianum)* permits extrapolation to man of the data obtained on monkeys. For example, the finding that *P. cynomolgi* develops in the liver of monkeys stimulated studies on the developmental cycle of *P. vivax*, which showed that it can also develop in the human liver.

In this brief review it is impossible to describe all nosological forms of human infectious diseases that have been successfully modeled on monkeys, and for this reason only a few examples are listed above.

In concluding the discussion of the use of monkeys to study infectious diseases, we would like to stress the desirability, and in some cases the necessity, of utilizing monkeys to examine diseases of unknown but apparently infectious nature. A good case in point is the research by Gajdusek that established the "infectious" nature of kuru and led to the discovery of a previously unknown class of pathogens — slow viruses [34-36]. This research was preceded by investigations carried out by L. A. Zil'ber and his colleagues together with workers of the Biomedical Station for Investigation of Amyotrophic Lateral Sclerosis. In these studies, rhesus macaques inoculated with brain tissue from people who died of lethal amyotrophic lateral sclerosis were found to develop neurological symptoms resembling those in human patients after 4-4.5 years. Subsequent inoculations of brain tissue from diseased monkeys proved to be positive in three successive passages. Unfortunately, the death of Zil'ber prevented the continuation of these highly interesting studies.

One line of research undertaken at the Institute of Experimental Pathology and Therapy on the initiative of N. N. Petrov, L. M. Shabad, and L. A. Zil'ber shortly after the creation of the nursery was experimental oncology. It is of interest that the view prevailed in the literature in the late 1940s and the early 1950s that these spontaneous tumors occurred rarely in monkeys and these were therefore classed among animals with low incidence of cancer. Attempts to trigger tumor growth in monkeys using carcinogens that consistently induced neoplasms in classic laboratory animals (mice and rats) were unsuccessful. A breakthrough came in experiments conducted by N. N. Petrov, N. A. Krotkina, A. V. Vadova, and Z. A. Postnikova who reproduced malignant bone tumors in monkeys using a chemical or radioactive carcinogen (methylcholanthrene or radium ore). The tumors produced in monkeys by Petrov *et al.* had a long latent period between carcinogen injection and tumor occurrence [18]. The first ever production of tumors in monkeys met with a warm response, and the authors were awarded the Mechnikov Prize of the USSR Academy of Sciences. Concerning the prolonged latent period, it could be explained by the long life cycle in primates. A shortening of the latent period was achieved by R. A. Mel'nikov and E. M. Barabadze in experiments where monkeys were administered an increased dose of radioactive silver (^{110}Ag). In their experiments, monkeys developed tumors as a result of radiation necrosis of the mandibular bone and buccal soft tissues after sequestration of the latter together with the wire of radioactive silver. Subsequently, squamous-cell carcinoma of the tongue also occurred, in parallel with the formation of mandibular sarcoma, in tissues adjacent to the ulcer [13].

Thus, although Petrov's experiments did not add to our knowledge of the etiology and pathogenesis of neoplasms, they did demonstrate that tumors can be produced experimentally in monkeys and that these animals are susceptible to carcinogenic action of methylcholanthrene and radioactive substances (facts which became known from experiments with many laboratory animals and even from occupational diseases occurring in people).

Very interesting data came from studies in which the action of oncogenic viruses on laboratory primates was examined. It was known by the 1950s that there are oncogenic viruses inducing neoplasms in chickens and mammals such as mice, rats, cats, and cattle.

Retroviruses of the C type induced sarcomas in chickens and leukemias and lymphomas in rodents, cats, and cows. Only in primates were these virus-associated neoplasms not known.

In 1950, L. A. Zil'ber *et al.*, and, independently, G. Ya. Svet-Moldavskii *et al.*, showed that the Rous sarcoma virus of chicken is not strictly specific and can induce neoplasms in rodents, thus overcoming the "species barrier." Shortly after these studies, the possible oncogenicity of the Rous sarcoma virus for various species of laboratory primates began to be investigated on Zil'ber's initiative. Almost at the same time, similar experiments were staged on rhesus macaques by S. Monroe and W. Windle at the Puerto-Rican Primatological Center [39]. Experiments carried out at the IEPT in Sukhumi by L. A. Zil'ber, F. I. Adzhigitov, and I. B. Obukh showed that Rous sarcoma virus-containing materials are highly oncogenic for several primate species, and found that tumors arise not only in newborn but also in juvenile monkeys. Specific feature of the tumors occurring in monkeys inoculated with Rous sarcoma virus was their well-defined dependence on immunity, which was manifested in partial or complete tumor regression. The proportion of regressing tumors varied from one experiment to another, possibly because of different characteristics of the virus materials used [1,4,5,17].

Sometimes, the tumors were of mixed morphology, with some of their areas being characterized as fibrosarcomas and others as rhabdomyosarcomas. In approximately 50% of the cases they appeared as myosarcomas [10].

Thus, the studies described above demonstrated not only the ability of oncogenic viruses to overcome species and class barriers (avian viruses are pathogenic for mammals) but also that several members of the highest order of the mammalian class (primates) are sensitive to the virus.

Considerable progress was made in examining the possible viral nature of lymphoproliferative diseases and of malignant lymphomas.

Monkeys injected subcutaneously or intraperitoneally with fresh heparinized blood from patients with various forms of leukemia (in some instanced pooled blood from several patients was used) developed malignant B-cell or T-cell lymphomas associated with two virus types: EBV-like herpesvirus and the C type T-lymphotropic virus. Oncornaviruses of the C type were detected in plasma, saliva, urine sediments, and in cells of 2-day cultures. The viruses were not identified and differed immunologically from known avian and mammalian viruses. The virus was tentatively designated as "plasma" virus and subsequently was identified as STLV-1. Studies carried out over many years demonstrated the existence of two subfamilies of oncogenic primate viruses: a subfamily of EBV-like herpes viruses (*m. arctoides* herpes virus, HVP of baboons, and HVGM of green monkeys) and HTLV-1/STLV-1 subfamily. These findings were confirmed by other researchers. Virological and immunological studies using a baboon model of an outbreak of virus-associated malignant lymphoma demonstrated the possibility not only of horizontal spread of HTLV-1/STLV oncogenic viruses, but also of horizontal spread of the disease. A lymphoma outbreak resulted in the death of about 400 hamadryas baboons, which amounted approximately to 10% of the total number of animals kept in the nursery. That lymphomas are linked etiologically with viruses was evidenced both by the dynamics of antibodies to STLV-1 and EBV-like virus (HTP) and by the monoclonal character of STLV-1 integration into the DNA of lymphoma cells in baboons, as well as by the polymerase chain reaction with primers to the *env* and *tax* fragments of STLV-1. Molecular biological studies and comparison of sequenced *env* and *tax* fragments of the STLV-1 detected in a flock of increased risk for lymphoma and in lymphoma-affected animals (STLV-1L) with the virus detected in a control "forest" flock (STLV-1N) revealed different degrees of their homology with HTLV-1 virus and with each other. Thus, three STLV-1 viruses with different homologies in the areas of *env* and *tax* genes were shown to exist in a flock of baboons [11,12,26,30,31].

Since monkeys with lymphoma are found to have only one variant of STLV-1 retroviruses, its oncogenicity is presumably associated with characteristics of its molecular biological structure.

Given the high sensitivity of monkeys to a number of oncogenic viruses, it seems advisable to study on monkeys human neoplasms whose viral nature is highly probable, such as Kaposi's sarcoma, which is possibly linked with HHV-8 virus, and uterine and rectal tumors possibly linked with type 16 and type 18 papilloma viruses.

Studies traditionally conducted on monkeys include those of brain functions, higher nervous activity in health and disease, neuroses, stress, and complex forms of behavior, since the results of such studies can be extrapolated to man after minor corrections [3,7,23,24,28]. Systematic monthly reviews in the *Current Primate References* indicate that most studies on primates deal with the nervous system and psychology. Judging from the number of publications cited in the sections on pharmacology, toxicology, and some others (concerned in one way or another with the physiology and pathology of the nervous system), the number of studies on primates published monthly outside this country amounts up 50% of the total number of publications devoted to the use of primates in other experiments.

The data obtained at the Biomedical Station and later at the IEPT suggest that the most promising

neurophysiological studies on primates should include those on stress and neuroses and the associated somatic diseases and also those on their complex forms of behavior. Such studies, initiated by S. D. Kaminskii [6], V. Ya. Kryazhev [9], N. Yu. Vaitonis [2], and N. A. Tikh [22] at the Subtropical Branch of the All-Union Institute of Experimental Medicine and continued by L. N. Norkina [16], and D. I. Miminoshvili [14,15], G. M. Cherkovich [25], V. G. Startsev [21], and others at the Biomedical Station, identified the most traumatic situations and influences leading to pathological deviations of higher nervous activity and to neuroses.

Attempts to use the classic Pavlovian methods (effective in dogs and other animals) for the study of neuroses by creating errors, overstrain, and excitation and inhibition processes or remaking signal meanings of stimuli using unnatural stimuli met with little success in monkeys. Neuroses could be effectively produced when natural stimuli of great biological significance (sexual, defensive, disruption of the herd hierarchy, distortion of the normal diurnal rhythm of physiological functions) are employed [14-16,25-37]. Developed neurosis was complicated by somatic disorders such as blood pressure elevation leading to essential hypertension and coronary insufficiency complicated by myocardial infarction in severe cases. Published reports and our observations showed surprising similarities between normal electrocardiograms in monkeys and man. The only differences were a very high heart rate (up to 200 beats/min or more) and a virtually complete absence of the vagus tone (absence of respiratory arrhythmia and of a reaction to atropine) in monkeys. However, telemetric ECG recordings that require neither fixation of the monkeys nor the presence of researchers near them and so remove emotional tension, showed normal ECG and vagus tone parameters close to those observed in man [25,37,38].

Of particular interest are endocrinological studies in various primate species. This interest is due to many factors, but primarily to the similarities between monkeys and human beings in the pluriglandular regulation of physiological functions, in biochemical and immunological characteristics of a number of hormones, and in the presence of an ovarian-menstrual cycle which occurs only in the primates and is absent in all other mammalians.

These similarities provide the basis for extensive use of monkeys in studies on the physiology of reproduction and various methods of contraception.

Recent studies have demonstrated an important role of the adrenal androgens dehydroepiandrosterone (DHA) and its sulfate (DHAS) in preventing the development of atherosclerosis, diabetes mellitus, neoplasms, and other pathological conditions. It has also been shown that only primate adrenals secrete these compounds in considerable amounts, which undergo dramatic reductions in the process of aging. In view of this, of great interest are investigations conducted on lower primates into the role of DHA and DHAS in the mechanisms of aging and of age-related diseases (cancer, prostatic adenoma, atherosclerosis, etc.).

Of much interest are also the recently initiated studies on xenotransplantation of the insular apparatus from pigs to monkeys, for such studies are directed, in the final analysis, at the treatment of diabetes.

In our early publications describing endocrinological studies on primates, we considered the possibility of utilizing primates for testing contraceptives and noted that the best animals for this purpose are chimpanzees. However, whereas the use of chimpanzees in the past involved great difficulties because of legislative restrictions, high costs of these animals, and problems of their maintenance, chimpanzees are now becoming practically inaccessible for experimentation. Of the lower primates particularly suitable for the above-mentioned studies are hamadryas baboons whose functional system of reproductive hormones has been well studied and which show clearly defined external manifestations of sexual cyclicity. Moreover, baboons are still available for study.

Monkeys are indispensable in the testing of a number of pharmacological preparations, notably psychomimetics, since certain neurotropic drugs produce different effects in monkeys and other animals such as dogs but similar effects in monkeys and humans, although there exist marked differences between the actions of some neurotropic compounds on different simian species.

Clearly, drugs intended for more or less prolonged use by pregnant women should be tested for teratogenicity on pregnant monkeys at various stages of pregnancy.

One of the most important uses of laboratory primates is the development of models of human diseases to study their pathogenesis, prevention, and treatment and for testing new drugs.

It should be noted in conclusion that the use of primates for experimental purposes has been subjected to severe attacks by members of animal protection movements. Although their protests are not infrequently justified, the use of primates is *a sine qua non* in a number of instances. By adhering to the principles of primate utilization set out at the beginning of this review, we appear to satisfy their demands in large measure. The experimental use of monkeys bred in a nursery is an indirect way of preserving monkeys in their natural habitats.

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