

Relevance of Animal Studies to Human Disease¹

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Summary

Increasing restrictions on the experimental use of human subjects and the difficulties of either evaluating or controlling human subjects over long periods of time suggest the need for increasing use of experimental animals, especially in the study of chronic disease. Experience appears to provide the only guideline for the selection of the most useful species in any particular field. It should be recognized that the species that are most susceptible or those that most nearly approximate the lesion found in man are not necessarily the only useful species. Differences in susceptibility or metabolism provide opportunities for identifying significant parameters in man. We tend to be locked into the use of a few experimental species for no obvious logical reason and have not yet begun to utilize the potential of the diverse species available. Whatever the experiment, diet remains an environmental variable that should be considered in the design and evaluation.

It is obvious that one is very fortunate, or unfortunate, to find that his subject matter has been dealt with by another eminent author. Fortunately for me a recent article in *Lancet* (1) has dealt with "Animal Models in Cancer Research" and I must, of necessity, quote extensively from this article. The author states:

"It is now quite clear that the best model for human cancer is *Herringus rufus*. All known chemicals are carcinogenic in this animal—a happy finding since it is now possible to reconcile all the theories of carcinogenesis advanced in the last century. The tumours can be caused to regress completely by a nutritious diet, surgery, radiotherapy, chemotherapy, endocrine therapy, and even by immunotherapy (although in this instance the fish die).

"The histology of the tumours is identical to that in man but, if necessary, it may be different. Although the red-herring lives only two years, correction factors can be applied such that a herring aged 18 months is equivalent to a human being aged 20–70 years: the incidence of tumours is then found to be the same as, or different from, that in man.

"Work on tissue-culture of *Herringus* explants has yielded results of great value in spite of the fact that they are intrinsically worthless since there is an instantaneous transformation of all cells to fibroblasts.

"All known D.N.A., R.N.A., and polystyrene viruses are oncogenic in all organs in this species. Interestingly enough, tumours develop at the same

rate in the total absence of virus, which is a splendid demonstration of the oncogene theory in everyday life. The genes have a poisson distribution in this species.

"Almost all molecular biologists who are still mobile now work on *Herringus*. It has been calculated that the cells of this creature contain only 10²² chemical substances. It follows that, once these have been identified, synthesized, and their interactions elucidated, all known diseases can be cured and several new ones invented. This should be of great encouragement to the clinicians who are frankly bored to the teeth with the diseases they see today."

He further points out that:

"The Department of Sickness and Insecurity has appointed 32 new herringorufologists to exploit this advance. Asked about the relevance to human cancer, a spokesman for the new group has stated that man is a very poor model for the red-herring. He pointed out that vast sums of money were spent fruitlessly on the treatment of cancer and that it would be better to redeploy these resources to the rufologists. Most hospitals could be converted to the new science simply by filling them with sea-water."

The original reports of the work quoted have appeared in such eminent journals as *Thanatology Newsletter*, the *Journal of Ephemera*, and *Fische Wissenschaft*.

In a more serious vein, we all understand that the best model for man is man. One cannot expect another species to duplicate everything that characterizes man; if it did, it would be a man. This sometimes leads to a denigration of the value of experimental animals. The authors of such statements fail to consider the limitation of man as an experimental species. The past history of human subjects can only be vaguely known; they are heterogeneous from the genetic and environmental point of view; they cannot be accurately controlled with regard to diet or other variables for extended periods of time; they are long lived and experimental control will be short, relatively speaking. Quantitative data with regard to nutritional requirements, for example, obtained directly with man as the subject are usually very poor. Considering the increasing limitations upon what can be done ethically with human subjects, it appears that there will be increasing need for study with experimental animals.

The case for experimental animals apparently does not need to be greatly emphasized for this group. Dr. Goldsmith, for example, has pointed out that patients with cancer of the pancreas cannot be identified prior to the development of the disease (3). Since the disease itself may change the metabolic characteristics of the subject, the only apparent way to study the antecedents of the disease or the factors that may modify susceptibility is through

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animal models. It is probably generally true that animal models are most useful for investigations of chronic diseases.

It seems equally obvious that some animals are better models for the investigation of certain diseases than others. In the nutritional field, it would seem clear that studies on vitamin C are more appropriately done with guinea pigs or primates that require the nutrient than with species that do not. The chick, like man and unlike the rat, requires folic acid and in spite of obvious metabolic and anatomical differences from mammals may often be the species of choice. One may argue, of course, that nonhuman primates are the nearest relatives of man and therefore the most appropriate experimental species. These advantages, of course, must be weighed against cost, the number of animals available, the state of knowledge of their nutritional needs, etc. It must also be realized that a monkey is not a monkey. Although it is as yet a relatively unexplored field, various species of monkeys have differing metabolic characteristics (2) which make them more or less useful in the laboratory for specific studies.

Experimental models may be exploited in 2 ways. Using nutrition as the example again, one may find a general similarity in the way species respond. For example, the vitamin A requirements of various species differing greatly in size appear to be proportional to body size. Thiamine requirements, on the other hand, appear to be more closely related to metabolic rate. If such relationships are demonstrable for all species studied, there is considerable justification in applying them to man. One may only need to demonstrate that the human species does not differ markedly from the general rule. This is a great advantage since the quantitative estimates of nutritional requirements obtained directly from studies with man are poor; estimates obtained with animals are usually more accurate.

In contrast, when species variation is obvious these differences can be utilized to explore the metabolic variations that cause them. An example would be the difference in the way that nonhuman primates differ in their response to dietary fat and cholesterol (2). Some species appear to be better models for some of the variants in human lipidemias than others and it is clear that the metabolic differences can be studied in greater detail in the experimental animal.

It is unfortunate, however, that we tend to get "locked into studies" with some species for no very logical or apparent reason. Those with a nutritional orientation tend to study rats. This is not because rats are necessarily a good model for man. Indeed, the very characteristics that have made the rat so attractive for nutritional studies contrast with those found in man.

The young rat weighing 50 to 60 g will grow some 5 to 6 g/day, a rate of about 10% of his body weight per day. He continues to grow rapidly until reaching a weight of 200 to 300 g. This results in a great dilution of the body stores of nutrients and makes it very easy to produce a variety of nutritional deficiencies. In contrast, a child of 4 to 5 years of age also grows about 5 g/day but weighs 20 kg. The growth rate is negligible compared to the body size.

One can demonstrate that as much as 95% of the total protein eaten by a young rat is directly deposited as new tissue protein. This contrasts to the inefficient use of dietary protein by the growing child. Similarly, the energy needs of the young rat are tremendous, relatively speaking, compared to those of the growing child. Because the rat is growing so rapidly his food intake must be highly correlated with his rate of growth or, stated the other way, if he does not grow for any reason, his food intake must decrease markedly. In view of the demonstrated effects of food limitation on susceptibility to cancer, these differences in the way food is handled by the rat and man should be borne in mind.

The rat is a poor model for many studies on cholesterol and lipid metabolism since plasma lipid levels are usually only minimally affected by modifications of dietary fat and cholesterol, factors that have marked effects in man. Fundamental differences in gluconeogenic pathways of various species have been pointed out (4) suggesting that the rat is a less than adequate model for several metabolic diseases of importance.

As a contrast to the rat, the gerbil readily develops circulating cholesterol levels approximating 300 mg/100 ml when fed a cholesterol-free diet containing coconut oil and levels approximating 100 mg/100 ml when fed a highly unsaturated oil (5, 8). This species, in contrast to most laboratory species, readily develops an inositol deficiency under certain dietary conditions (6, 7). The relevance of these findings to the human problem remains somewhat in doubt since it appears that the circulating lipoproteins present a dissimilar pattern than that seen in man (J. A. Marlett and D. M. Hegsted, unpublished data).

The point I would emphasize is that generally speaking we have made little use of the abundant biological material available. Comparative nutrition or comparative biology, in general, is an infant science. In many ways comparative biology offers the same kind of "natural experiments" that we observe by comparing populations. Biological diversity offers advantages and we should get out of the rut that we are in.

The utility of the mouse in genetics and toxicity studies is obvious to all. Because it does not grow very fast or get very large, it is more difficult to develop nutritional deficiencies in the mouse than in the rat and there are other technical difficulties in their management. We know much less about the nutrition of the mouse than of the rat. It must be clear in the cancer field that genetic or host factors must have a very important effect upon susceptibility, yet we persist in utilizing rats that are essentially undefined genetically. We specify the laboratory or strain of origin but we are uncertain how meaningful this is. There is a crying need for the development of defined strains of varying susceptibilities to whatever disease we happen to be interested in.

Another weakness in much of the experimental work is that we often make the conditions so extreme that they are of doubtful relevance. We often do studies with animals severely limited in one nutrient or another. This may be a useful screening device, but there is no reason to believe that one can then extrapolate the findings to modest limitations

or excesses in intake found in human populations. Similarly, in the administration of carcinogens we are fundamentally interested in diseases with a relatively low prevalence but we usually do not have the patience, money, or facilities to work at low prevalence rates with animals. I recall to you the general impression that the rabbit fed with cholesterol is a poor model. The fact is that the animal model may not be so bad, but that the cholesterol levels which were fed were so high they obviously had little relevance to the human experience. Since susceptibility to any disease represents a combination of host-environment-agent, one can overwhelm one or the other under certain experimental conditions. It may take a miracle to demonstrate nutritional influences if the level of carcinogen is inappropriate.

Finally, I wish to comment on the general field of diet and toxicology and carcinogenesis. Sufficient examples are available to demonstrate that the outcome of some experiments may be determined by the nature of the diet fed as well as the nature of the toxic material under test. Yet in many experiments there is not enough information available to even allow a duplication of the experimental conditions. A "normal rat diet" is usually a complex mixture of materials of unknown and variable composition formulated by a commercial company. Such diets are formulated to a considerable degree on the basis of the cost of materials available.

The fact that a diet will produce good growth or reproduction in a laboratory species is important, of course, but does not mean that the nutritional variables, of importance to the outcome of the experiment, are under control. A normal rat diet is very low in fat compared to most diets consumed by man and very much higher in protein. A normal diet for guinea pigs or rabbits is very high in fiber; a normal diet for a dog may or may not be very high in protein.

The diet is an environmental factor in all biological studies. Animals have to be fed something. We obviously do not know enough at this time to decide what diet is "best," if any such exist. Rather, we ought to begin specifically to investigate the role of dietary factors. It is rather frightening

to contemplate the possibility that the results of the extensive testing programs may be erroneous because of unexplored dietary effects. We should also make some move toward developing diets which are at least reproducible from the dietary point of view.

The need for experimental animals in all kinds of biological research seems to me to be so well demonstrated that it requires no justification. Ethical and other restrictions continually limit experimentation with human subjects; one can only anticipate that the need for appropriate research with animals will increase rather than decrease.

The term "animal model" is often used inappropriately to imply that only work with species that duplicate the human condition is useful. Rather, we should recognize that there is both a unity in metabolic patterns of animals and a diversity and that both can be exploited for further understanding of the processes under investigation. It is only required that we be intelligent enough to utilize the experimental material available and to correctly interpret the findings.

References

1. Anonymous. Animal Models in Cancer Research. *Lancet*, 2: 1506, 1974.
2. Corey, J. E., Hayes, K. C., Dorr, B., and Hegsted, D. M. Comparative Lipid Response of Four Primate Species to Dietary Changes in Fat and Carbohydrate. *Atherosclerosis*, 19: 119-134, 1974.
3. Goldsmith, E. I. Formal Discussion of "Cancers of the Pancreas and Biliary Tract: Epidemiological Considerations," *Cancer Res.*, 35: 3447-3449, 1975.
4. Hanson, R. W. The Choice of Animal Species for Studies of Metabolic Regulation. *Nutr. Rev.*, 32: 1-7, 1974.
5. Hegsted, D. M., and Gallagher, A. Dietary Fat and Cholesterol and Serum Cholesterol in the Gerbil. *J. Lipid Res.*, 8: 210-214, 1967.
6. Hegsted, D. M., Hayes, K. C., Gallagher, A., and Hanford, H. Inositol Deficiency: An Intestinal Lipodystrophy. *J. Nutr.*, 103: 302-307, 1973.
7. Kroes, J. F., Hegsted, D. M., and Hayes, K. C. Inositol Deficiency in Gerbils: Dietary Effects on the Intestinal Lipodystrophy. *J. Nutr.*, 103: 1448-1453, 1973.
8. Seiler, M. W., Hamilton, M. A., Lauris, V., Herrera, M. G., and Hegsted, D. M. Hyperlipemia in the Gerbil: Effect of Diet on Serum Lipids and Hepatic Glucokinase. *Am. J. Physiol.*, 221: 548-553, 1971.

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