SYMPOSIUM*

THE INFLUENCE OF ANIMAL STRAIN SELECTION AND CONDITIONING ON BIOLOGICAL EXPERIMENTS AND ASSAYS

Chairman: W. LANE-PETTER, M.A., M.B., B.Chir.

Director, Laboratory Animals Centre, Medical Research Council Laboratories, Carshalton, Surrey

INTRODUCTION

THE method suggested in the British Pharmacopoeia for the biological assay of pertussis vaccine begins with the words:—"Healthy white mice drawn from a uniform stock . . .". As I have said elsewhere, the possession of a white coat is no more a guarantee of purity in mice than it is in those who use them.

In a paper by Elizabeth Russell, of the Jackson Memorial Laboratory in Bar Harbor, which appeared in the *British Medical Journal* (1955, **1**, 826–829), reference was made to work published in 1929 by Wright and Eaton, in which they listed four types of inbred strain difference. On re-reading the paper I do not think that these are very clear-cut types, but they do indicate that the differences may be *either* of the all or none variety; for example, BALB/c mice have white coats, C57B1 black, and CBA animals agouti: and DBA mice are unlike most other strains in being extremely susceptible to audiogenic seizures; *or* the differences may be graded; for example, the incidence of spontaneous mammary tumours will vary from the highly susceptible C_3H mice to the moderately susceptible DBA/1 and the insusceptible C57B1/6 strain. Gowan and Schneider, working independently in the U.S.A., have shown a grading from strains highly susceptible to mouse typhoid to those that are resistant. Russell in her paper mentions many other differences between strains; the nature of disease (for example, the same infecting organism may produce in one strain septicaemia, and in another an upper respiratory infection, and in another pneumonia): differences in the survival time after an infection; antibody production; cold tolerance; susceptibility to the vapour of chloroform (which will certainly kill male DBA/2 mice; DBA/1 mice are nearly as sensitive; C_3H are less so; BALB/c are less sensitive again; and most other strains are resistant to chloroform. This is a sex-linked difference, in that the females do not readily die from small amounts of chloroform vapour); sensitivity to hormones; content of hormones; reactions to the removal of endocrine glands; enzyme activity; blood picture; and longevity.

As these differences between strains exist also in other species of laboratory animal, why is it that inbred strains are not more commonly used? The reasons that have been advanced against the use of inbred

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strains, I think, are four. (1) It has been said that the differences are not great enough to be of any practical interest. That is not true; the differences in many cases are very large. (2) They are said to be difficult to breed. That again is largely untrue. Many inbred strains have a productivity that compares reasonably well with the productivity of non-inbred strains. Even under the far from ideal conditions that we have at Carshalton, we find that the best of our inbred strains are not much less productive than the best of our non-inbred strains. (3) The technique of inbreeding is laborious, and (4) if colonies of inbred strains are established in different places, genetic divergence will arise between them. These two reasons I think are valid. To maintain an inbred colony, a good deal of technical competence is needed; and divergence does occur.

These difficulties have interested the Laboratory Animals Centre for some years, and we have suggested that if primary colonies of various strains are kept in one place and constantly controlled, genetically and from the points of view of health and specific responses, they are capable of producing a relatively small number of animals, which can be used for limited sub-cultivation to produce the large numbers required for experimental purposes. We have suggested that foundation stock from such primary colonies may be sub-cultivated elsewhere for up to about three generations, and that brother $\times$ sister mating for those three generations can be ignored. To avoid going beyond the three generations which can reasonably be regarded as a useful limit of sub-cultivation, the first generation should be distinguished by putting a green label on the box, the second generation by a yellow label, and the third by a red label. Animals from a red label box should never be used for breeding. We call this "traffic light sub-cultivation", and in practice it works well. It relieves the sub-cultivator of the need to study inbreeding techniques, and avoids tedious and troublesome quality control. The feedback of information about specific responses of mice sub-cultivated in this way would add greatly to our knowledge of inbred strains.