Inbred Mice in Research

by
MICHAEL F. W. FESTING
MRC Laboratory Animals Centre,
Carshalton, Surrey

Very few inbred strains of mice are used in cancer and immunological research. Should there be more?

THERE are now more than 200 inbred strains of mice maintained in the world[1]. Most of them are only maintained in one or two laboratories, usually where they were first developed, but a few strains have a wider distribution. Thus there are now thirty strains which are held at more than five centres throughout the world.

Inbred strains of mice are widely used in both cancer research and immunology, and it is therefore worth asking: is full use being made of available genetic material, or are research workers tending to concentrate on only a narrow spectrum of inbred strains and ignore new genetic materials as they become available?

With a view to answering this question, I have surveyed published work to determine the use of inbred strains in cancer and immunological research during two periods. The data came from the *Subject–Strain Bibliography of Inbred Strains of Mice*, which is produced by Miss J. Staats of Jackson Laboratory, Bar Harbor, Maine[2]. The number of papers surveyed in the early (1953–55) and recent periods (1965–66) was as follows:

	No. papers surveyed	
	Cancer	Immunology
Early period (1953–55)	418	47
Recent period (1965–66)	513	339

giving a total of 1,307 papers.

Seventy-two different inbred strains were used in the 418 early cancer papers, and sixty-nine different strains in the recent cancer papers, but only thirty-one strains were common to both the early and recent work. In immunology thirty-two different strains were used in the early work, and fifty-seven in the recent work, with twenty-one strains common to both periods.

I then made a more detailed examination of the twelve most commonly used strains in each discipline. The percentage use of these strains is listed in Table 1. In all cases, the top twelve strains accounted for more than 78 per cent of the total use of inbred strains in each discipline.

In cancer research strain C3H was easily the most popular strain, accounting for approximately 20 per cent of all occasions when inbred strains were used. A remarkable feature of the results is the relative stability of the strains used during this 12 years. Thus eleven of the twelve most popular strains in 1953–55 were still among the top twelve strains in 1965–67.

In view of the number of inbred strains of mice available, and the number of new lines constantly being developed, it seems rather surprising that there should be such stability in the use of inbred strains in cancer research. The average "age" of the strains (that is, the time since the strain was first developed) is now 44 years.

Is it a good thing that more than 80 per cent of cancer research in inbred mice is being carried out on so few strains? It has been said that the development of inbred strains has constituted probably the greatest advance in all cancer research[3], but if the strains most widely used today were developed more than 40 years ago, has genetics and the development of the new genetic materials no part to play in future cancer research? Immunologists are now making full use of genetic methods. The congenic resistant strains developed by Snell and others are already having a considerable impact on immunological research with mice. It is true that in most cases the mode of inheritance of cancer has proved to be complex, but there is at least one report of a major gene effect influencing the susceptibility of inbred mice to induce lung tumours[4].

Priority should surely be given to the development of congenic cancer strains, as suggested by Murphy[5]. Some of the more recently developed inbred strains are also showing great promise. Thus strain SJL/J has revealed some close replicas of Hodgkin's disease, and a wide range of tumours has been revealed by crosses[6].

In addition to the new material which is being developed as a result of inbreeding, selection within non-inbred strains could possibly produce new strains which develop their tumours at a much earlier age than present stocks. Falconer and Bloom[7] have shown the feasibility of this approach. Such strains would have many practical advantages, for the long latency required for the development of most tumours slows down the rate of research. These developments are, however, useless if most cancer research workers feel that they have so much investment in the "top twelve" strains that they are unable to look at new material as it becomes available.

In immunological research, strain C3H was again the most popular single strain although in recent work, crosses and congenic resistant lines have been increasingly used.

There was considerably less stability in the strains used in immunological research, although nine of the twelve most popular strains in 1953–55 were still among the twelve most popular in 1965–67. The most important changes were an increased use of crosses and of the recently developed "congenic resistant" strains. These latter strains have been developed as specialist lines for immunological research, and are important.

Table 1. PERCENTAGE USE* OF THE "TOP 12" INBRED STRAINS OF MICE

Cancer			Immunology		
Strain	1953–55	1965–66	Strain	1953–55	1965–66
C3H	19·3	21·3	C3H	11·0	10·7
C57Bl	11·6	10·2	BALB/c	11·0	5·4
Crosses	10·6	15·9	A	10·4	10·0
A	9·6	6·7	C57Bl	9·8	7·5
DBA/1	6·3	1·4	C57BR	6·7	—
BALB/c	5·4	10·7	CBA	5·5	6·8
AKR	4·5	4·7	C57Bl/6	4·9	6·5
DBA/2	3·1	4·8	AKR	4·3	2·2
C57Bl/6	3·0	3·9	C57L	3·7	—
RIII	2·6	1·4	DBA/1	3·7	1·0
CBA	2·4	3·1	DBA/2	3·7	4·3
C57Br	2·0	—	CFW	3·7	—
C58	—	1·5	Crosses	—	20·8
			CR strains†	—	10·2
			C57Bl/10	—	2·7
Total	80·4	85·6		78·4	88·1

* Number of times that the strain was used per 100 times that an inbred strain was used.
† Congenic resistant strains. One group of CR strains differs from another by only a single histocompatibility gene.

In conclusion, the extreme concentration of cancer research on a very few inbred strains of mice, all of which were developed more than forty years ago, may not be completely justifiable. A careful and systematic look at other material already available, and the further use of genetic tools to provide new and possibly more useful strains could give added stimulus to cancer research.

[1] Staats, J., *Cancer Res.*, **28**, 391 (1968).
[2] Staats, J., *Subject-Strain Bibliography of Inbred Strains of Mice*. Published as supplements to *Mouse News Letter* (1953–66).
[3] Heston, W. E., in *Methodology in Mammalian Genetics* (edit. by Burdette, W. J.) (Holden-Day, San Francisco, 1963).
[4] Bloom, J. L., and Falconer, D. S., *J. Nat. Cancer Inst.*, **33**, 607 (1964).
[5] Murphy, E. D. in *Biology of the Laboratory Mouse*, second ed. (edit. by Grea, E. L.) (McGraw-Hill, New York and London, 1966).
[6] Dickie, M. M., *J. Nat. Cancer Inst.*, **15**, 791 (1954).
[7] Falconer, D. S., and Bloom, J. L., *Brit. J. Cancer*, **16**, 665 (1962).