

le cell anemia. In contrast to the limited studies that can be performed in humans, these animals provide an opportunity for rapidly exploring an expanded range of inquiry in an in vivo setting. As such, these sickle cell mice are likely to play an important role in furthering our understanding of the pathophysiology of sickle cell disease and in developing improved therapies for treating the more than 100,000 individuals born each year with this genetic disease.

Note added in proof: With a similar approach, we have also created mice that express exclusively normal human hemoglobin (HbA).

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6. Three DNA fragments were used to create transgenic mice: (i) 6.5-kb mini-LCR (Locus Control Region) [D. Talbot et al., *Nature* **338**, 352 (1989)], (ii) 1.5-kb Pst I fragment containing the human $\alpha 1$ -globin gene, (iii) 39-kb Kpn I fragment containing the human fetal (γ , γ) and adult (δ , β) globin genes in their normal genomic context [F. S. Collins, C. J. Stoeckert Jr., G. R. Serjeant, B. G. Forget, S. M. Weissman, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 4894 (1984)].
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8. C. Pászty et al., *Nature Genet.* **11**, 33 (1995).
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10. Genotyping was as follows. Polymerase chain reaction (PCR) conditions: 0.5 μ M each primer, 200 μ M deoxynucleotide triphosphate, 1 unit of Taq polymerase, 20- μ l reaction volume; 94°C (3 min); 35 cycles of 94°C (30 s), 58°C (30 s), 72°C (1 min). Sickle transgene, forward primer, $\delta 1$ (5'-GTATGGAGAGGCTCCAAC-3'), reverse primer, $\delta 2$ (5'-TCTGCCCAATCTTAGACAAAAC-3'). $\delta 1\delta 2$ PCR product, 480 base pairs (bp). Mouse α -globin genotypes (+/+), $Hba^{o1}/+$, Hba^{o1}/Hba^{o1} ; Hba^o allele: forward primer, Hba^o (5'-ATAGATGGGTAGCCATTAGATTCC-3'), reverse primer, Hba^{o1} (5'-CCGGGTATAATTACCTCAGGTC-3'). Hba^{o1}/Hba^{o1} PCR product, 461 bp. Also used previously published α -globin multiplex PCR (8). Mouse β -globin genotypes (+/+), $Hbb^{o1}/+$, Hbb^{o1}/Hbb^{o1} ; Hbb^o allele: forward primer, Hbb^{o1} (5'-AGATGTTTTTTCACATCTTTGAGC-3'), reverse primer, Hbb^{o1} (5'-AATGCCTGCTCTTACTGAAGG-3'). Hbb^{o1}/Hbb^{o1} PCR product, 398 bp. Also used PCR for part of region deleted in the Hbb^o allele: forward primer, $\beta del1$ (5'-TTAGGTGGTCTTAAACCTTTGTGG-3'), reverse primer, $\beta del2$ (5'-ACTGGCAGAGCATTGTTATG-3'). $\beta del1/\beta del2$ PCR was with Deep Vent (Exonuclease-) instead of Taq. Genotypes of sickle cell mice were confirmed by cellulose acetate gel electrophoresis of hemoglobins (Helena Laboratories, Beaumont, TX) [J. B. Whitney III, *Biochem. Genet.* **16**, 667 (1978)].
11. Sickle cell mice are fertile; however, females appear to have trouble feeding their pups and as a result many of the sickle cell mice we have produced thus far have come from sickle cell males bred with non-sickle cell females [Tg(Hu-minLCR $\alpha 1\gamma\gamma\beta\beta$) $Hba^{o1}/Hba^{o1}Hbb^{o1}/+$]. Interestingly, there was a fivefold increase in sickle cell newborn survival when sickle cell males were bred with non-sickle cell females (number obtained/number expected = 32/122) compared with when non-sickle cell males were bred with non-sickle cell females (number obtained/number expected = 4/82). One possible explanation for this is the presence of segregating "survival" alleles in the mixed genetic background (FVB/N, 129, DBA/2, C57BL/6, Black Swiss) of the breeding population. These alleles would be inherited at a higher frequency from sickle cell males than from non-sickle cell males. Another possible explanation involves the presence of fewer healthy non-sickle cell newborns in litters from sickle cell males. This might allow sickle cell newborns to compete more effectively for maternal attention and enable them to survive more readily. The following animal husbandry practices may influence the survival of sickle cell mice: Micro-Barrier Systems cages (17.8 $\times$ 27.9 cm) (Allentown Caging, Allentown, NJ), Bed-O-Cobs bedding (size, 0.32 cm) (Andersons Industrial Products, Maumee, OH), Nestlets nesting material (Ancare Corp., Bellmore, NY), and Purina 5008 food (PMI Inc.).
12. Globin chain synthesis was as described (8). Controls used were C57BL/6 (1.0 ± 0.02 ; $n = 3$) and $Hbb^{o1}/+$ β -thalassemic mice (1.38 ± 0.05 ; $n = 3$).
13. Blood was mixed (1:1) with a 2% sodium bisulfite solution [G. A. Daland and W. B. Castle, *J. Lab. Clin. Med.* **33**, 1082 (1948)] and wet mounts were prepared immediately. After 15 min, 80% of cells were completely sickled (60% of cells had a single domain or a few parallel domains, 20% had multisegmented holly leaf morphology).
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15. The increases (fold) in organ weights were calculated from organ weights expressed as a percentage of total body weight [sickle cell ($n = 4$) versus wild type ($n = 5$): kidneys, 2.5% versus 1.3%; heart, 1.0% versus 0.5%; spleen, 6.5% versus 0.5%].
16. Histological analysis was performed on four sickle cell and two wild-type mice, all 5 to 7 months of age.
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13 June 1997; accepted 18 September 1997

TECHNICAL COMMENTS

Government Funding of Research and Development

In a Policy Forum, Robert M. May (1) uses bibliometric data from an Australian benchmarking study (2) to show that the United Kingdom had the most cost-effective science base among G7 countries (3), as measured by citations attracted per million pounds (per £million) spent. In doing so, May, who is the Chief Scientist of the United Kingdom, has established a baseline that raises the profile of quantitative studies in science policy and against which investigators can measure future performance. Part of May's analysis rests on the assumption

that there is a relationship between financial investment in research and development (R&D) and scientific impact, as measured by citations to papers published in the peer reviewed serial literature. Although it is reasonable to assume that there is such a relationship, we have two main concerns with May's analysis. First, he does not allow for a time lag between expenditure on R&D and the evaluation of a country's scientific impact. By taking this into account, we demonstrate that United Kingdom (U.K.) science is not the most cost-

effective of the G7. Second, we argue that it is incorrect to relate the citation performance of the national science system only to government expenditure, because private and overseas funders have made an increasingly large contribution to public domain U.K. science in recent years.

May estimates (1) return on investment for a single year (1991) based on the yearly average number of citations over the period 1981-94 (4). However, expenditure in 1991 will have little effect on citations before about 1997 because there is commonly a 4-year lag before papers emerge from the funded research and at least a further 2-year period before the citation peak is reached. The preferred analysis would be to compare expenditure figures for each year with citations achieved (say, 4 to 6 years later) and to track this over time. Because May takes

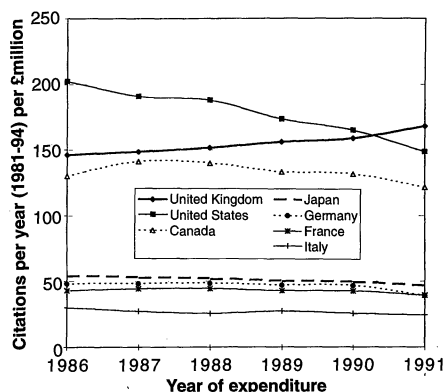


Fig. 1. Apparent cost effectiveness of the G7 countries' scientific output, as measured by the number of citations per year for 1981–94 per £million of government civil expenditure. As the numerator is constant, the cost effectiveness ratios are sensitive to the year of expenditure: A decline in government civil expenditure will result in an increase in apparent cost effectiveness, as illustrated for the United Kingdom.

average citation data as the numerator and a single funding year as the denominator, his analysis also becomes sensitive to the funding year selected. There is no "correct" funding year that one can use, but we would argue that an earlier year than 1991 would be better (5). We have therefore looked at government expenditures in the G7 countries for a range of earlier years (Table 1) (6) and compared these with May's citation data to calculate Apparent Cost Effectiveness (citations per £million).

Our sensitivity analysis (Fig. 1) shows that the United Kingdom moved into first position ahead of the United States only if expenditure in 1991 is used as the denominator. This is because, in contrast to the situation in other G7 countries, U.K. government civil expenditure on R&D has been steadily falling in real terms (7). This might have been expected to have led to a decline in U.K. scientific output. In practice, the reduction in government expenditure has largely been made up by an increase in funding from other sources, including private nonprofit funders such as charities, and the part of spending by industry and foreign sources that is for research in the public domain (that is, which leads to research publications in the open literature).

The importance of nongovernment funders varies with the field of science. In particle physics, government support dominates, while in biomedical science, private funders play a bigger role. Biomedical science represents one of the United Kingdom's great strengths, with outputs increasing from 23,354 papers in 1988 to 29,391 papers in 1994 (8). Research charities have played a key role in the growth

Table 1. Government funding of R&D for civil objectives in real terms (adjusted to 1991 prices in £billion) and, in italics, as a percentage of gross expenditure on R&D (GERD), 1986–91, for the G7 countries (4).

Country	R&D funding per year					
	1986	1987	1988	1989	1990	1991
U.S.A.	12.44	13.20	13.41	14.52	15.27	16.93
	<i>13.4</i>	<i>14.0</i>	<i>14.0</i>	<i>14.9</i>	<i>15.4</i>	<i>16.5</i>
Germany	6.44	6.45	6.40	6.62	6.66	7.95
	<i>35.9</i>	<i>33.7</i>	<i>32.6</i>	<i>32.2</i>	<i>32.5</i>	<i>35.2</i>
Japan	5.40	5.55	5.65	5.86	5.95	6.32
	<i>18.0</i>	<i>17.4</i>	<i>16.4</i>	<i>15.6</i>	<i>14.8</i>	<i>14.8</i>
France	5.33	5.16	5.14	5.34	5.36	5.81
	<i>42.0</i>	<i>39.0</i>	<i>37.7</i>	<i>36.7</i>	<i>35.3</i>	<i>36.5</i>
Italy	3.51	3.86	4.09	3.85	4.09	4.31
	<i>57.8</i>	<i>59.0</i>	<i>59.5</i>	<i>53.3</i>	<i>53.5</i>	<i>52.5</i>
U.K.	3.21	3.16	3.09	3.00	2.95	2.79
	<i>26.4</i>	<i>25.6</i>	<i>24.7</i>	<i>23.2</i>	<i>22.8</i>	<i>22.5</i>
Canada	1.77	1.63	1.65	1.73	1.75	1.90
	<i>40.2</i>	<i>36.7</i>	<i>37.3</i>	<i>37.8</i>	<i>36.7</i>	<i>37.9</i>

in numbers of research papers in this field. Over the period 1988–94, there was a 60% increase in the number of funding acknowledgements to U.K.-based charities in that country's biomedical literature. By 1994 charities were the acknowledged funding source on about 25% of national U.K. biomedical science publications. In comparison, the growth in the number of papers acknowledging support from the main government funding agency, the Medical Research Council, was only 5% over the same period. Despite this growth in charity output, the United Kingdom's world share of publications in biomedicine has declined marginally (9), mainly because of more rapid growth in other countries. Without the contributions of charities, it is clear that the United Kingdom's international position in biomedical science would be worse than it is now.

It is doubtful that the increase in private sources of funding is sustainable indefinitely. So, if government funding continues to decline, it is likely that there will be a reduction in the United Kingdom's gross scientific output and impact. Given the evidence that a strong, locally funded science base is important for technology innovation in industry (10), our results would argue for a sustained or increased commitment by government funding to science in the United Kingdom.

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1. R. May *Science* **275**, 793 (1997).
2. May's Policy Forum was derived in part from a benchmarking study [*The Quality of the UK Science Base* (Office of Science and Technology, U.K. Department of Trade and Industry, London, 1997)], which in turn draws heavily on an analysis of Australian research [*Australian Science: Performance from Published Papers* (Australian Government Publishing Service, Canberra, 1996)].
3. The G7 countries are Canada, Germany, France, Italy, Japan, the United Kingdom, and the United States.
4. In (1), the citation period is given as 1981–84 [table 1 in (1)], but in the U.K. report and in the Australian study [(2), tables 5 and 2.1, respectively] it is given as 1981–94. We have assumed that the dates in May's Policy Forum are a typographic error.
5. One way of estimating which funding year is relevant is to analyze the age distribution of articles cited in a leading general science journal. For the 1994 editions of the journal *Nature*, the median age of papers cited is 3 to 4 years. If the age distribution of papers cited in 1994 is similar to the age distribution of papers cited in all previous years back to 1981, then the median year of publication, for papers cited in *Nature* between 1981–94, is 1985/6. The research reported in the cited papers would plausibly have been funded several years previously. Therefore, if *Nature* is representative of science in general (spanning many disciplines), it is most reasonable to compare funding in the early to mid 1980's with citations achieved during 1981–94.
6. Figures for government civil expenditure on R&D and Gross Expenditure on R&D (GERD) for 1986–91 were taken from Table 7.7 and 7.2, respectively, from the government report *Science, Engineering and Technology Statistics, 1996*, Her Majesty's Stationery Office, London, where published (1996). The figures were adjusted to 1991 prices with the use of GDP deflators presented in footnote 2 of Table 2.2 of the same publication.
7. Government civil expenditure on R&D continued to decline in the United Kingdom to £2.65 billion (1991 prices) in 1994 (4).
8. J. Anderson *MRC News* (Autumn/Winter 1996), pp. 14–16.
9. *Science & Engineering Indicators 1993* (National Science Foundation, Washington, DC, 1993), appendix table 5–23, and *The European Report on Science and Technology Indicators 1994* (European Commission Publications, Luxembourg, 1994), table I.11.B.
10. J. Anderson, N. Williams, D. Seemungal, F. Narin, D. Olivastro, *Technology Anal. Strategic Manage.* **8**(2), 135 (1996); F. Narin and D. Olivastro, *Proceedings of the Sixth Conference of the International Society for Scientometrics and Informetrics*, Jerusalem, Israel, 16–19 June 1997, pp. 305–312.
11. We are grateful to J. Anderson and D. Seemungal for helpful discussions and to R. Cottrell for performing some of the analysis. Funded by the Wellcome Trust.

27 May 1997; revised 15 July 1997; accepted 13 August 1997

Response: First, in that part of my Policy Forum which focused on the ratio of outputs (measured by papers or citations) to inputs (in terms of funding), I emphasised the marked—more than twofold—differences between such ratios for the United States, United Kingdom, and Canada (along with other countries such as Switzerland and Sweden) compared with the other four of the G7 nations (1). Although readers may have misperceived my message as one of U.K. chauvinism, the intent was to air some tentative speculations on the reasons for these differ-

ences in "cost effectiveness," which have sparked discussion and controversy (2). The main feature of figure 1 in the comment by Grant and Lewison is to confirm that these marked differences among the G7 have persisted over the extended interval 1986–91; the gap is so marked that the key to the figure is inserted between the top three lines and bottom four.

Second, Grant and Lewison correctly observe that my "output/input" calculations are rough, in two respects: Government civil expenditures on R&D are an unsatisfactorily coarse measure of what produces the output of the "science base"; and there are time lags between inputs of relevant funding and outputs of papers or, even more, citations. But, having made these telling points, Grant and Lewison do not pursue them. Instead, they repeat my rough calculation, dividing the average citations over the span 1981–94 by total

government civil R&D spends for a range of years, with the conclusions noted above.

Taking on board Grant and Lewison's constructive criticisms, I have made better estimates of "output/input" ratios (Tables 1 and 2). The first problem is how to measure "input." Government civil spend on R&D includes both too much and too little: too much in that it includes money spent on R&D to underpin policy, which does not typically lead to publications as might be counted by the Institute for Scientific Information (ISI); too little in that support for the "science base" from charities and "business enterprise" (industry, and so forth) are omitted. But consistently collected data about appropriate expenditure are not easily compiled. The Organization for Economic Cooperation and Development (OECD) publishes statistics for expenditure on R&D performed in higher education (HERD) (3), which is probably a better measure of "input" than total government civil R&D spend; but although roughly 80% of the U.K. scientific papers come from universities (including teaching hospitals), such patterns vary from country to country. A better "input" measure is arguably the total "science base" expenditure on R&D (SBRD), defined as all R&D carried out in universities and nonprofit making institutions, irrespective of funding sources, including intramural government funded civil R&D, mostly at government research establishments. The U.K. Office of Science and Technology has put together estimates of such expenditure for several countries, drawn from published OECD statistics on the breakdown of national gross expenditure on R&D (GERD) data, but these numbers arguably also suffer from problems of comparability owing to national structural differences, although possibly less so in aggregate than the OECD HERD numbers (4). The second, and easier, problem is how to take account of time lags between inputs and outputs. If the output is scientific papers, I divide the total papers (5) published in any one year by the input (HERD, or SBRD, or total government civil spend) 3 or 4 years earlier. If the output is citations, then one correspondingly counts citations to the papers in question.

I have calculated (Table 1) the ratios between outputs of scientific papers, in 1993 and 1996, to inputs of HERD or SBRD expenditures 3 years earlier, for an admittedly arbitrarily chosen set of countries (the G7 plus Switzerland, Sweden, and the Netherlands). The output in cita-

tions to the papers published in 1993 and in 1996 is also presented (Table 2) (obviously, 1996 papers have on average accumulated fewer citations than 1993 ones). The patterns in these two tables are striking and fairly stable over the 3-year interval of inputs, 1990–93.

The second part of the comment by Grant and Lewison underlines the important contribution made by charities to the U.K. "science base," especially in biomedical areas. I strongly endorse their views. In the U.K. in 1993, funding from the Wellcome Trust and other charities accounted for roughly 10% of the total "science base" income, a higher proportion than for any other country listed (Tables 1 and 2). Similarly, business enterprise support also accounts for about 10% of the total U.K. "science base" expenditure, again a higher proportion than for other countries listed (Tables 1 and 2).

Any attempt to compare output/input ratios among countries, whether by scientific papers or by citations, is bedeviled by all manner of difficulties in compiling truly comparable statistics and by ineluctable biases inherent in counting papers or, even more, citations (6). Even so, some of the differences in such crude measures of the cost efficiency of research among the G7 and other countries (Tables 1 and 2) are so large as to defy explanation as statistical artifacts. These patterns deserve more attention than they have so far received (7).

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REFERENCE AND NOTES

1. R. M. May, *Science* **275**, 793 (1997), first column on p. 796.
2. G. R. Barreto, *ibid.* **276**, 882 (1997); S. Bauin, *ibid.*, p. 883; I. Gómez, M. Bordons, J. Camí, *ibid.*, p. 884; S. Herskovic, *ibid.*, p. 884; R. M. May, *ibid.*, p. 885.
3. *Main Science and Technology Indicators* (Organization for Economic Cooperation and Development, Paris, 1997).
4. These estimates, and accompanying discussion, will be published soon. I will also display them on the website: www.open.gov.uk/ost/osthome.htm
5. The papers, and citations, are for the 20 fields of science, engineering, and medicine used in the Australian study and in the partly derivative OST study: See reference 2 of the comment by Grant and Lewison.
6. See the lengthy notes 6 and 7 in (1).
7. I thank J. Grant, G. Lewison, and J. Anderson of the Wellcome Trust for their helpful collegiality and courtesy, and R. Dowdell, K. Root, D. Barker, and T. Quigley of OST for their help with Tables 1 and 2.

13 June 1997; revised 22 September 1997; accepted 26 September 1997

Table 1. Papers per £million spent. Ratio between output of papers (5) to input of SBRD or HERD expenditure 3 years earlier (3, 4). Ratios are given at two time points: 1993/90 and 1996/93.

Country	Ratio for 1993/1990		Ratio for 1996/1993	
	SBRD	HERD	SBRD	HERD
Canada	16.4	28.4	14.3	24.0
France	9.3	18.4	9.1	16.5
Germany	9.8	17.2	7.9	14.1
Italy	7.8	14.8	8.5	16.4
Japan	4.9	8.0	7.0	7.0
Netherlands	13.5	22.9	13.1	22.2
Sweden	15.4	16.9	16.7	18.7
Switzerland	17.9	21.4	15.3	17.9
United Kingdom	18.0	29.8	17.5	28.6
United States	11.3	16.4	10.1	15.2

Table 2. Citations per £million spent. Similar to Table 1, except the outputs are citations to papers published in 1993 and 1996. The latter have, on average, many fewer citations.

Country	Ratio for 1993/1990		Ratio for 1996/1993	
	SBRD	HERD	SBRD	HERD
Canada	106	183	4.7	7.9
France	57	113	2.5	4.6
Germany	63	111	2.5	4.5
Italy	44	84	2.1	4.1
Japan	26	42	1.5	1.5
Netherlands	101	172	4.5	7.6
Sweden	112	123	5.4	6.1
Switzerland	164	196	7.1	8.4
United Kingdom	130	215	6.2	10.1
United States	96	139	4.1	6.2