Fortnightly Review

Neonatal screening for sickle cell disorders: what about the carrier infants?

Linda Laird, Carol Dezateux, Elizabeth N Anionwu

The recessively inherited sickle cell disorders affect about 6000 people in the United Kingdom, mainly those of Afro-Caribbean origin.¹ The 1994 recommendation for universal antenatal and neonatal screening for haemoglobin disorders in districts where the antenatal population comprises 15% or more ethnic groups at risk for the sickle cell disorders¹ has provided renewed impetus to review local screening policies. While the objective of preconceptional and antenatal screening for haemoglobin disorders is to maximise reproductive choice, the aim of neonatal screening is the early detection and treatment of infants with a clinically important haemoglobin disorder in order to reduce early childhood mortality and morbidity.^{1,2}

However, neonatal screening, unavoidably, also detects infants who, although without a disorder themselves (unaffected infants), are carriers of one haemoglobin variant gene. Depending on local ethnic composition, as many as 1 in 32 of all infants born may be a carrier,^{3,4} and neonatal screening may identify 17 to 100 times more carrier infants than infants with a disorder (affected infants).¹ Currently, two thirds of Britain's haemoglobinopathy counselling centres offer information and counselling to parents of carriers detected during neonatal screening, although the timing and nature of follow up vary widely among centres.⁵ This variation in practice highlights existing uncertainty about policies for responding to a screening result that indicates a presumptive carrier status. We review the potential benefits and risks arising from neonatal detection of carriers of sickle cell disorders and consider the policy options available.

Department of Epidemiology and Biostatistics, Institute of Child Health, London WC1N 1EH

Linda Laird, *senior registrar in public health medicine*
Carol Dezateux, *senior lecturer in paediatric epidemiology*

Department of Clinical Genetics and Fetal Medicine, Institute of Child Health
Elizabeth N Anionwu, *senior lecturer in community genetic counselling*

Correspondence to:
Carol Dezateux.

BMJ 1996;313:407-11

Potential benefits and risks of neonatal detection of carrier status

It has been suggested that, without expert counselling, routine notification of parents whose infants are heterozygous is of no immediate value and may cause unnecessary anxiety.⁶ These views, however, may not reflect those of parents or self help groups.^{7,8} Professionals disagree over the genetic testing of apparently healthy children,⁹ and Smith suggested seeking "solutions that allow greater diversity of opinion and fewer claims of certainty."¹⁰ Potential benefits of neonatal detection of carrier status for infants and their families include informed future reproductive choice, education on the clinical implications of carrier status, and psychological and social empowerment resulting from "ownership" of genetic information.¹¹ These benefits need to be considered in relation to potential risks attributable to misdiagnosis, exposure of non-paternity, and the social and psychological sequelae of being identified as a carrier of an inherited condition.

Summary points

- Neonatal screening for sickle cell disorders detects between 17 and 100 carrier infants for each child detected as having sickle cell disorder
- Information on neonatal carrier status is an unavoidable outcome of the neonatal screening process
- Withholding information from parents is not justified
- Further research is needed to evaluate the benefits and risks of this information and the effectiveness of different policies for follow up
- This is relevant to future developments in molecular genetics, which may place health services under increasing pressure to test for a wide range of genetic conditions in early childhood

PARENTS' FUTURE REPRODUCTIVE CHOICE

Ascertainment of neonatal carriers has been described as opening a "genetic window" into the family, in that detection of previously unidentified carrier couples, through parental genetic testing, provides an opportunity for reproductive counselling in subsequent pregnancies.² Although genetic testing of parents of neonatally detected carriers may identify half of the couples at risk, some will already have been identified antenatally. Furthermore, future reproductive choice will be enhanced only if carrier couples are identified before the next pregnancy. Problems in contacting parents of presumptive carrier infants have been documented in the United States,^{12,13} but similar studies in this country are lacking.

CARRIER INFANT'S FUTURE REPRODUCTIVE CHOICE

Although neonatal ascertainment of carriers may present an opportunity to inform the child—nearer reproductive age—of his or her carrier status, such information may not be accurately relayed to the child then¹³ and access to counselling when the child is older

Potential benefits of neonatal detection of carrier status

- Informed future reproductive choice for parents
- Informed future reproductive choice for child
- Opportunity for educating families about the clinical implications of carrier status
- Social and psychological empowerment for families from ownership of genetic information

Fig 1—Sickled cell

is difficult to ensure.¹⁴ There are, in addition, logistic problems in achieving the long term follow up of such children as well as potential implications for confidentiality.

CLINICAL IMPLICATIONS OF CARRIER STATUS

Carriers of sickle cell disorders do not seem to have reduced life expectancy, but the risk of sudden unexplained death, although low, is higher than in non-carriers.¹⁵ Clinical problems among carriers seem to be rare, and the extent to which they are attributable to carrier status alone is uncertain.^{15 16} Hypoxia, acidosis, dehydration, and total vascular occlusion by tourniquet during anaesthesia may be hazardous to carriers and should be avoided.¹⁵

PRESUMPTIVE CARRIER STATUS INCORRECT

A screening test that reports an infant as a presumptive carrier may err in two directions. A report that the infant is a presumptive carrier when there is in fact a clinically important haemoglobin disorder may falsely reassure families and increase the risk of late diagnosis, while a report of presumptive carrier status when the infant is in fact neither affected nor a carrier may expose the child and the family to psychological stress and stigmatisation. Errors in either direction may raise doubts about paternity.

Although the test has been evaluated for the detection of affected infants,^{2 17 18} little information is available on the test's performance for carrier detection,^{12 17} and the optimum age for confirmation of a presumptive carrier result is unclear.^{19 20} Haemoglobin electrophoresis, isoelectric focusing, and, more recently, high performance liquid chromatography are currently used for neonatal screening in Britain^{4 6 21 22} but do not identify carriers of β thalassaemia. Neither RNA nor DNA analysis of dried blood spots^{23 24} is currently used for neonatal screening in Britain. A second tier screening test may be used to reduce the false positives associated with haemoglobin electrophoresis.^{6 21} Molecular confirmation of the genotype from the original sample may reduce the costs of collecting a second sample and minimise the delay in giving more definite information to families²⁵ but would not identify false positives and false negatives that are due to administrative or laboratory errors.¹⁸

EXPOSURE OF NON-PATERNITY

Genetic testing of the parents of neonatally detected carriers may show non-paternity—that is, the mother's partner is not the biological father of her child.

Potential risks of neonatal detection of carrier status

- Misdiagnosis if the presumptive screening result is incorrect
- Inadvertent exposure of non-paternity
- Social stigma for the individual and family
- Adverse psychological effects for the individual and family

Estimates of the prevalence of non-paternity in the United Kingdom vary from 1% to 30%.^{26 27} Fear of exposure of non-paternity may lead 1% of women to decline antenatal carrier testing.²⁷

STIGMA AND DISCRIMINATION

Stigmatisation is the effect of labelling a person or group as having "undesirable" characteristics²⁸ and may arise from releasing information about the genetic make up of an individual or group of individuals. In the United States carriers of sickle cell disorders have been refused health and life insurance, and difficulties in securing or retaining employment and in interactions with adoption agencies have been reported.²⁹ This discrimination not only is unfounded but is now illegal in the United States. Similar legislation is lacking in Britain; a parliamentary committee, however, has recently considered the implications of genetic testing, including those for insurance and employment prospects.³⁰

PSYCHOLOGICAL SEQUELAE

Information is limited about the psychological effects on the family of neonatal or childhood detection of carrier status for variant haemoglobins. Guilt and anxiety have been reported among parents of children diagnosed as carriers of sickle cell disorders, as well as difficulty in distinguishing between carrier and disease status.³¹ The attitude of a non-carrier parent towards a carrier child may have a negative impact on the child's self perception and esteem.³²

Anxiety^{33 34} and reduced optimism about future health³⁵ have been reported among carriers of sickle cell disorders and other recessive conditions. Although sickle cell disorders are rare, they have been diagnosed in non-black individuals,³⁶ and acceptance of carrier

Fig 2—Inheritance pattern for sickle cell anaemia and sickle cell trait

Fig 3—Dactylitis is a common presenting symptom in sickle cell anaemia

status may be more difficult for a condition usually associated with a different ethnic group.³⁷ The long term psychological consequences of this information for neonatally detected carriers of sickle cell disorders and their parents have not been assessed.

Policy options

Purchasers and providers should be reviewing local policies after a report in 1994 recommended universal antenatal and neonatal screening in areas where the antenatal population comprises more than 15% of ethnic groups at high risk of haemoglobin disorders.¹ However, although this report acknowledged that neonatal screening would identify infants who were carriers of sickle cell disease and whose families would need counselling and family studies,¹ it did not provide further guidance. Nationally 58% of haemoglobinopathy centres offer selective neonatal screening for infants born to known carrier mothers or whose mothers are from high risk ethnic groups.⁵ Logistic difficulties in targeting and in achieving high coverage for these groups have been reported for selective programmes²² but are not a feature of universal screening when it is linked to the existing metabolic (Guthrie) neonatal screening programme. Universal screening, however, detects more carrier infants than selective screening, including those whose fathers, but not mothers, are carriers and whose parents may thus not have been alerted to the possibility of a carrier infant through antenatal screening.

There is an onus on purchasers to ensure that district policies reflect the views of individuals and at risk communities, as well as those of professionals.^{38 39} The issue of neonatal carrier status is of particular interest to

black and other high risk ethnic groups, who have shown resolve and ability in demanding improved service provision for those affected by haemoglobin disorders.^{40 41} The views of such groups should be sought.

IS THERE AN OPTION TO WITHHOLD THIS INFORMATION FROM PARENTS?

Nationally, a fifth of haemoglobinopathy counselling centres do not routinely inform parents that their infant is a presumptive carrier.⁵ In the United States it has been argued that parents have the right of access to full disclosure of genetic information on their child,⁴² and withholding such information is against legislative guidelines in many states.² No equivalent legislation exists in Britain. Motulsky, who chaired the American Committee on Assessing Genetic Risks, considered that this information should be given to parents.⁴³

IS THERE AN OPTION TO REPORT PRESUMPTIVE CARRIER RESULTS AS NEGATIVE?

By viewing the neonatal haemoglobin screening result as either positive (the infant is likely to be affected by a clinically important haemoglobin disorder) or negative (likely to be unaffected), a presumptive carrier could be reported as having a negative result. In some respects such a policy is analogous to the "couple" approach proposed for antenatal screening for cystic fibrosis. However, it may be misleading and result in subsequent misdiagnosis or delayed diagnosis; it may not be acceptable to parents⁸ or be considered ethical; and it would need to be considered in the context of adequately informed consent to testing, which is a requirement of all genetic screening programmes.⁴⁴

DELIVERING INFORMATION

The method used to inform parents of a presumptive carrier result will be influenced by the need for and importance placed on confirmatory diagnostic testing. Nationally, current practices for giving information on infant carrier status to parents vary among centres⁵ and have not been formally evaluated. Families are given presumptive carrier results together with further written or oral information, or both, in appropriate languages, as well as a contact telephone number or an appointment for counselling and further genetic studies—by post, telephone, or in person.

The impact on parents of learning that their child is a carrier will be influenced by their prior knowledge about the disease and what carrier status means, and although some may acquire this knowledge through family and community sources, there are additional opportunities to educate and inform families at various points in the screening process. Antenatal counselling of women identified preconceptionally or antenatally as carriers could include information on the probability and implications of having a carrier infant. Oral or written information, or both, on the likely outcomes of neonatal screening for haemoglobin disorders could also be given by the midwife at the time of the heel prick sample. Midwives and medical staff, however, have been reported to have a low level of knowledge about these disorders.²² It is also unclear how this information, even if accurately relayed, is interpreted and retained by mothers.⁴⁵

FOLLOW UP FOR THOSE WITH PRESUMPTIVE CARRIER SCREENING RESULTS

It may be difficult to justify giving information on infant carrier status to parents without also giving counselling.^{31 34} An approach that requires parents to make any necessary appointments may allow those who believe they will benefit from counselling to make an appointment.¹³ Experience from North America sug-

Fig 4—Neonatal detection of carrier status can provide informed future reproductive choice for parents and child (published with family's permission)

Responding to presumptive carrier result

- Identify means of delivering test results to parents of presumptive carrier infants
- Define the follow up to be offered to families of presumptive carrier infants
- Identify the staff responsible for counselling families of presumptive carrier infants
- Identify the training needs of the staff involved

gests that between a third and a half of all parents respond,^{13 20} but issuing a prearranged appointment may prove costly if uptake is low.²⁰ Comparable data are lacking for Britain, where almost all families are registered with a general practitioner, who in some districts may initially communicate positive neonatal screening results for congenital hypothyroidism and phenylketonuria.

WHO SHOULD BE COUNSELLING?

Counselling embraces two distinct activities: education of parents and decision making in relation to genetic testing.² Reliance on haemoglobinopathy counsellors, who are in short supply in the United Kingdom,⁴⁰ to provide both components of counselling may not be cost effective. An alternative option is to train primary healthcare staff or other health professionals to deliver the educational component, with specialist counsellors being employed to provide support for families making decisions about the genetic testing.^{2 44} Both general practitioners and health visitors, however, have important gaps in their knowledge of haemoglobin disorders.^{48 49} The training needs of members of the primary care team participating in delivering antenatal and neonatal screening have to be addressed,⁵⁰ and it has been recommended that genetic counsellors should come from similar ethnic backgrounds to those whom they are counselling.^{46 51}

Conclusion

Neonatal detection of carriers is an inadvertent consequence of neonatal screening for haemoglobin disorders. While withholding information from parents is not justified, further research is needed to evaluate both the consequences of this for infants and parents and the cost effectiveness of different models of delivering test results and follow up within the screening programme. This is relevant to future developments in molecular genetics, which may place health services under increasing pressure to test for a wide range of genetic conditions in early life, many of which have no immediate implications for health.⁹

We thank Sally Hargreaves for supporting LL's secondment and Mike Gill, Bernadette Modell, Jocelyn Skeete, Anne Yardumian, and colleagues at the Institute of Child Health for their helpful comments. The illustrations of a sickled cell and of dactylitis are published with permission from Pharmacia and Upjohn from *Sickle Cell, a Scope publication*, and the line drawing is based on a slide produced by the Medical Illustration Department of the Institute of Child Health and the Hospitals for Sick Children.

Funding: LL was seconded to the Institute of Child Health by the North Thames Regional Health Authority; CD is supported by the Wellcome Trust; ENA was supported by a grant from the Department of Health.

Conflict of interest: None.

1 Standing Medical Advisory Committee. *Sickle cell, thalassaemia and other haemoglobinopathies*. London: HMSO, 1994.

2 Sickle Cell Disease Guideline Panel. *Sickle cell disease: screening, diagnosis, management, and counselling in newborns and infants*. Rockville: Agency for Health Care Policy and Research, 1993.

- Stephens A. Management of sickle cell anaemia and thalassaemia. In: *Sickle cell anaemia and thalassaemia*. London: City and Hackney Community Health Council, 1987:11-9.
- Davies SC, Henthorn JS, Graham VV. Neonatal screening for haemoglobinopathies in north west London, UK. In: Farriaux J-P, Dhondt J-L, eds. *New horizons in neonatal screening: proceedings of the 9th international screening symposium and the 2nd meeting of the international society for neonatal screening, Lille, France, 13-17 September 1993*. London: Excerpta Medica, 1994:195-8.
- Eboh W, Van den Akker O. Service provision for sickle cell disease. *British Journal of Midwifery* 1995;3:189-95.
- Horn ME, Dick MC, Frost B, Davis LR, Bellingham AJ, Stroud CE, et al. Neonatal screening for sickle cell diseases in Camberwell: results and recommendations of a two year pilot study. *BMJ* 1986;292:737-40.
- Cooling H. Neonatal screening for sickle cell disease in Camberwell. *BMJ* 1986;292:958.
- Dalby S. Genetic Interest Group response to the UK Clinical Genetics Society report "The genetic testing of children." *J Med Genet* 1995;32:490-2.
- Clarke A. The genetic testing of children: report of a working party of the Clinical Genetics Society (UK). *J Med Genet* 1994;31:785-97.
- Smith T. Genes and ethics. *BMJ* 1995;311:574.
- Marteau T, Michie S. A positive screening test for an untreatable condition provides psychological relief from uncertainty. *BMJ* 1995;311:58-9.
- Githens JH, Lane PA, McCurdy RS, Houston ML, McKinna JD, Cole DM. Newborn screening for hemoglobinopathies in Colorado. The first 10 years. *American Journal of Diseases of Children* 1990;144:466-70.
- Grossman LK, Holtzman NA, Charney E, Schwartz AD. Neonatal screening and genetic counseling for sickle cell trait. *American Journal of Diseases of Children* 1985;139:241-4.
- Rowley PT. Parental receptivity to neonatal sickle trait identification. *Pediatrics* 1989;83:891-3.
- Sears DA. Sickle cell trait. In: Embury SH, Hebbel RP, Mohandas N, Steinberg MH, eds. *Sickle cell disease: basic principles and clinical practice*. New York: Raven Press, 1994:381-94.
- Serjeant GR. The sickle cell trait. In: Serjeant GR, ed. *Sickle cell disease*. Oxford: Oxford University Press, 1992:415-25.
- Lorey F, Cunningham G, Shafer F, Lubin B, Vichinsky E. Universal screening for haemoglobinopathies using high-performance liquid chromatography: clinical results of 2.2 million screens. *European Journal of Human Genetics* 1994;2:262-71.
- Papadea C, Eckman JR, Kuehnert RS, Platt AF. Comparison of liquid and dried blood for neonatal hemoglobinopathy screening: laboratory and programmatic issues. *Pediatrics* 1994;93:427-32.
- British Society for Haematology. Guidelines for haemoglobinopathy screening. *Clin Lab Haematol* 1988;10:87-94.
- Hurst D. Newborn screening for sickle cell anaemia and other hemoglobinopathies: northern California's experience. *Pediatrics* 1989;83:868-71.
- Griffiths PD, Mann JR, Darbyshire PJ, Green A. Evaluation of eight and a half years of neonatal screening for haemoglobinopathies in Birmingham. *BMJ* 1988;296:1583-5.
- Adjaye N, Bain BJ, Steer P. Prediction and diagnosis of sickling disorders in neonates. *Arch Dis Child* 1989;64:39-43.
- McCabe ER, Huang S, Seltzer WK, Law ML. DNA microextraction from dried blood spots on filter paper blotters: potential applications to newborn screening. *Hum Genet* 1987;75:213-6.
- Zhang Y, McCabe ER. RNA analysis from newborn screening dried blood specimens. *Hum Genet* 1992;89:311-4.
- Jinks DC, Minter M, Tarver DA, Vanderford M, Hejtmancik JF, McCabe ER. Molecular genetic diagnosis of sickle cell disease using dried blood specimens on blotters used for newborn screening. *Hum Genet* 1989;81:363-6.
- Macintyre S, Sooman A. Non-paternity and prenatal genetic screening. *Lancet* 1991;338:869-71.
- Brock DJH, Shrimpton AE. Non-paternity and prenatal genetic screening [letter]. *Lancet* 1991;338:1151.
- Markel H. The stigma of disease: implications of genetic screening. *Am J Med* 1992;93:209-15.
- Billings PR, Kohn MA, Cuevas de M, Beckwith J, Alper JS, Natowicz MR. Discrimination as a consequence of genetic testing. *Am J Hum Genet* 1992;50:476-82.
- Science and Technology Committee. *Human genetics: the science and its consequences*. London: HMSO, 1995.
- Hampton ML, Anderson J, Lavizzo BS, Bergman AB. Sickle cell "nondisease"—a potentially serious public health problem. *American Journal of Diseases of Children* 1974;128:58-61.
- Woodridge EQ, Murray RF. The health orientation scale: a measure of feeling about sickle cell trait. *Soc Biol* 1989;35:123-36.
- Zeesman S, Clow CL, Cartier L, Scriber CR. A private view of heterozygosity: eight year follow-up on carriers of Tay-Sachs gene detected by high school screening. *Am J Med Genet* 1984;18:769-78.
- Antley MA, Antley RM, Hartlage LC. Effects of genetic counselling on parental self concepts. *J Psychol* 1973;83:335-8.
- Marteau TM, van-Duijn M, Ellis I. Effects of genetic screening on perceptions of health: a pilot study. *J Med Genet* 1992;29:24-6.
- Ballas SK, Park D, Warner RJ. Neonatal screening for sickle cell disease in a metropolitan university hospital: efficacy and problems. *Journal of Medical Screening* 1994;1:229-32.
- Marteau T, Anionwu EN. Evaluating carrier testing: objectives and outcomes. In: Marteau T, Richard MPM, eds. *The troubled helix: social and psychological implications of the new genetics*. Cambridge: Cambridge University Press, 1996:123-39.
- NHS Management Executive. *Sickle cell anaemia*. Leeds: NHSME, 1994.
- Balarajan R, Raleigh V. *Ethnicity and health: a guide for the NHS*. London: Department of Health, 1993.
- Anionwu EN. Sickle cell and thalassaemia: community experiences and official response. In: Ahmad WTU, ed. *"Race" and health in contemporary Britain*. Buckingham: Open University Press, 1993:76-95.
- Sickle Cell Society. *Sickle cell disease: the need for improved services*. London: SCS, 1981.
- Pelias MZ. Duty to disclose in medical genetics: a legal perspective. *Am J Med Genet* 1991;39:347-54.
- Committee on Assessing Genetic Risks. *Assessing genetic risks: implications for health and social policy*. Washington: National Academy Press, 1994.
- Nuffield Council on Bioethics Working Party on Genetic Screening. *Genetic screening: ethical issues*. London: Nuffield Council on Bioethics, 1993.
- Statham H. Mothers' consent to screening newborn babies for disease. *BMJ* 1993;306:858-9.

- 46 Working Party on Prenatal Diagnosis and Genetic Screening. *Prenatal diagnosis and genetic screening: community and service implications*. London: Royal College of Physicians of London, 1989.
- 47 Anionwu EN. Sickle cell and thalassaemia: some priorities for nursing research. *J Adv Nurs* 1996;23:853-6.
- 48 Shickle D, May A. Knowledge and perceptions of haemoglobinopathy carrier screening among general practitioners in Cardiff. *J Med Genet* 1989;26:109-12.

- 49 Choiseul M, Allen A, May A. Training and needs of health visitors in the haemoglobinopathies. *Health Visitor* 1988;61:205-6.
- 50 King's Fund forum consensus statement: screening for fetal and genetic abnormality. *BMJ* 1987;295:1551-3. (Conference report.)
- 51 Anionwu EN. Ethnic origin of sickle and thalassaemia counsellors: does it matter? In: Kelleher D, Hillier S, eds. *Researching cultural differences in health*. Routledge, 1996:160-89.

(Accepted 16 May 1996)

How can impact factors be improved?

Eugene Garfield

Impact factors are widely used to rank and evaluate journals. They are also often used inappropriately as surrogates in evaluation exercises. The inventor of the *Science Citation Index* warns against the indiscriminate use of these data. Fourteen year cumulative impact data for 10 leading medical journals provide a quantitative indicator of their long term influence. In the final analysis, impact simply reflects the ability of journals and editors to attract the best papers available.

Counting references to rank the use of scientific journals was reported as early as 1927 by Gross and Gross.¹ In 1955 I suggested that reference counting could measure "impact,"² but the term "impact factor" was not used until the publication of the 1961 *Science Citation Index (SCI)* in 1963. This led to a byproduct, *Journal Citation Reports (JCR)*, and a burgeoning literature using bibliometric measures. From 1975 to 1989, *JCR* appeared as supplementary volumes in the annual *SCI*. From 1990-4, they have appeared in microfiche, and in 1995 a CD ROM edition was launched.

Calculation of current impact factors

The most used data in the *JCR* are impact factors—ratios obtained from dividing citations received in one year by papers published in the two previous years. Thus, the 1995 impact factor counts the citations in 1995 journal issues to "items" published in 1993 and 1994. I say "items" advisedly. There are a dozen major categories of editorial matter. *JCR*'s impact calculations are based on original research and review articles, as well as notes. Letters of the type published in the *BMJ* and the *Lancet* are not included in the publication count. The vast majority of research journals do not have such extensive correspondence sections. The effects of these differences in calculating journal impact can be considerable.^{3,4}

Absolute citation counts

The ubiquitous and sometimes misplaced use of journal impact factors for evaluation has caused considerable controversy. They are probably the most widely used of all citation based measures. They were invented to permit

Large journals that publish many papers may not have as high an impact as smaller review journals

reasonable comparison between large and small journals. Absolute citation counts preferentially give highest rank to the largest or the oldest journals. For example, in 1994, articles published in the *BMJ* regardless of age were cited 37 600 times. Of these, 5800 citations—about 15%—were to items published in 1992 and 1993.

Table 1 shows absolute citation counts for nine English language clinical journals as well as the *Journal of Biological Chemistry*, which is included to emphasise the difference between absolute and relative citation of large journals. Table 2 lists these same journals ranked by 1994 impact. It is important to note that of the thousands of journals published and cited in *SCI* only 337 achieved a current impact higher than 3.0. The *SCI* processes over 3300 source journals and cites thousands more, but it does not include as sources hundreds of low impact applied and clinical journals. This has been a source of frustration to editors from the Third World. They often ask how they can improve impact so as to warrant inclusion.

Impact of review journals

It should be apparent from reviewing the two tables that the ranking relationship between quality and citation is not absolute. The *Journal of Biological Chemistry* is one of the most cited journals in the history of science but it is also among the largest. Publishing over 4000 research manuscripts a year (as do other high volume journals like *Physical Review*) inevitably leads to considerable variation in quality and impact of individual articles. As a consequence, while these journals publish many papers which become "citation classics," their current impact may not be as high as some smaller journals, especially certain review journals. Indeed, one of the highest impact journals is *Annual Review of Biochemistry*—with a current impact of 42.2. But as the data for *Annual Review of Medicine*

Institute for Scientific Information, 3600 Market Street, Suite 450, Philadelphia, PA 19104, USA
Eugene Garfield, chairman emeritus
email: garfield@aurora.cis.upenn.edu
BMJ 1996;313:411-3

Table 1—Absolute citation counts, 1994 and 1989

Title	Rank in 1994	Times cited (thousands) in 1994 (from all years)	Rank in 1989	Times cited (thousands) in 1989 (from all years)
<i>Journal of Biological Chemistry</i>	1	265.3	1	183.4
<i>New England Journal of Medicine</i>	10	98.9	9	72.4
<i>Lancet</i>	11	85.5	12	68.0
<i>JAMA</i>	41	41.0	40	29.4
<i>BMJ</i>	45	37.7	34	32.6
<i>Annals of Internal Medicine</i>	51	31.7	48	26.5
<i>American Journal of Medicine</i>	75	22.1	60	21.7
<i>Archives of Internal Medicine</i>	138	13.7	130	10.4
<i>Medicine</i>	502	4.3	421	3.9
<i>Annual Review of Medicine</i>	1118	1.6	999	1.4