CONTRIBUTION OF NOVEL SOURCES OF GENETIC VARIATION TO SELECTION RESPONSE

R. Frankham
School of Biological Sciences, Macquarie University, Sydney, NSW 2109, Australia

SUMMARY

Genetic variation has recently been shown to be generated by transposon and retroviral insertions, retrotransposition and gene transfer between species, in addition to the well known mechanisms of base substitutions, duplications and deletions, and chromosomal rearrangements. Since it is possible to manipulate the movement of transposons and retroviruses, they may provide beneficial variation for use in plant and animal breeding.

INTRODUCTION

Until the late 1970s, selection response for quantitative characters was considered to result predominantly from frequency changes at single copy loci of allelic variants present in the base population. Subsequently, mutations have been shown to contribute significantly to long term selection response (see Yoo, 1980; Frankham, 1980, 1988a; Hill, 1982), and novel sources of genetic variation have been discovered and shown to have contributed to selection response as discussed below. Due to the paucity of direct information on the causes of selection response in animals and plants, I have extended the scope of selection response to include responses in microbes and cultured cells forced to adapt to novel substrates, responses to yield faster cell growth in the formation of tumours, and responses in natural populations over evolutionary time. This allows greater insights into the modes of generation of genetic variation.

SOURCES OF NEW GENETIC VARIATION

New genetic variation can arise from (1) base substitutions, (2) base additions or deletions, (3) gene conversion, (4) chromosomal rearrangements, (5) aneuploidy and polyploidy, (6) transposon mobilisation, (7) retrovirus mobilisation, (8) retrotransposition, (9) natural gene transfer between species, (10) artificial gene transfer between species, and (11) somaclonal variation.
Variation due to most or all of the above mechanisms may be generated in the nuclear genome or in the mitochondrial or chloroplast DNAs.

I will categorise 1 and 2 as conventional sources of variation, 3-5 as mildly novel (as they are rarely considered in quantitative genetics) and 6-11 as novel sources of genetic variation, with the main emphasis on 6-8. Chloroplast and mitochondrial DNA variation is considered briefly.

Selection response has been documented for most of the above potential sources of genetic variation, as discussed below.

Perhaps the most amazing array of mechanisms involved in generating variation in a single system is the generation of antibody diversity. This system involves extensive polymorphism, multigene families, alternative splicing and joining, gene conversion, somatic mutation and cell selection (see Watson *et*

al. 1987).

CONTRIBUTIONS TO SELECTION RESPONSE

(1) Base substitutions

Base substitutions have been shown to cause mutations responsible for adaptation of microbes to new substrates (see Carlile and Skehel, 1974) and for the acquisition of transforming properties by a carcinoma oncogene (Reddy *et al.* 1982). Both changes in coding regions and changes in promoter regions have been documented, though the latter are likely to be much more important in contributing to selection response for quantitative characters (see Wilson 1976).

(2) Base additions or duplications

Additions and subtractions of whole codons are evident in evolution from comparisons of amino acid sequences of polypeptides such as cytochrome C (Dayhoff, 1969). Changes of less than multiples of three bases are expected to contribute to selection response where this involves the inactivation of a gene product (such as appetite control), but I am not aware of any such example.

(3) Gene conversion

Gene conversion is a non-reciprocal recombinational process that appears to have been important in evolution. I know of no direct evidence for its contribution to selection response for a quantitative character but such contributions are to be expected.

(4) Chromosomal rearrangements

Chromosomal rearrangements are expected to cause mutation by deleting genes, duplicating genes, inactivating genes by breaking them, and modifying gene activity by placing them in the vicinity of new promoters, enhancers or suppressive sequences, or by generating anti-sense or promoter occlusion transcription (see Frankham, 1988b)

a. Deletions

Partial deletions of the rRNA multigene family generated by unequal exchanges have been shown to contribute to selection response for abdominal bristle number (see Coen and Dover, 1983; Gillings *et al.* 1987 Frankham, 1988a). Further, deletions have been shown to cause a number of human tumours (see Ponder 1988).

b. Duplications

Duplications are of profound importance in evolution as they allow new functions to evolve through duplication and divergence in function, whilst retaining the original function (see Ohno, 1970; Ohta, 1989). For example, the globin gene duplicated and diverged to give myoglobin and hemoglobins and thence to give α, β, γ, δ, and ε chains of hemoglobins.

Duplications have been shown to contribute to selection response in numerous cases, including increases in abdominal bristle number due to increases in rRNA gene copy number (from an abnormally low level) (Frankham et al. 1980; Gillings *et al* 1987), evolution of insecticide resistance (Devonshire and Sawicki, 1979; Hyrien and Buttin, 1986; Mouches *et al.* 1986), malignant transformation due to duplications of oncogenes (Taya *et al.* 1987), evolution of resistance to chemotherapeutic drugs in tumour cells (see Schimke, 1982), evolution of herbicide resistance in plants, and adaptation of microbes to new substrates (see Carlile and Skehel, 1974).

c. Inversions

Differences in the effects of inverted and normal sequence

chromosomes have been shown for reproductive fitness (see Dobzhansky, 1970) and sternopleural bristle number in *Drosophila* (Briscoe pers. comm.), though it is unclear whether these effects are due to linkage disequilibrium (that is known to exist - see Lewontin, 1974) or to position-effects on genes.

Inversions are associated with malignant transformations in mammalian cancers (Rabbitts *et al.* 1988) and with parathion resistance in the house fly (Wang and Plapp, 1980).

d. Translocations

Translocations (associated with changes in number of rRNA genes) caused selection response for abdominal bristle number in *Drosophila* (Coen and Dover 1983; Gillings *et al.* 1987). Insecticide resistance in *Myzus persicae* was associated with a translocation (Devonshire and Sawicki, 1979). Further, translocations that move oncogenes into the vicinity of strong promoters or enhancers are involved in causing a number of tumours (Bishop, 1987).

(5) Aneuploidy and polyploidy

Allopolyploidy has been of profound importance in plant evolution, 47% of angiosperms being polyploid (Grant, 1971). *Triticale* is a successful synthetic allopolyploid. By contrast, there are very few polyploids amongst higher animals.

Aneuploidy would rarely be expected to contribute to selection. It is associated with some cases of resistance to chemotherapeutic drugs in the form of unstable double minute chromosomes (Schimke, 1982).

(6) Transposon mobilisation

Transposons are genetic elements capable of autonomous transposition (often replicative) and excision. They were first found in maize in the late 1940s by Barbara McClintock (see McClintock, 1984), and have subsequently been discovered in bacteria, *Drosophila*, yeast, mice, man, etc., and are presumed to be ubiquitous.

Eukaryotic transposons have been classified into four classes as illustrated in Fig. 1 (see Finnegan, 1985, 1989). They show polymorphisms in location and are usually present in multiple copies in dispersed locations. In *Drosophila melanogaster* there are over 30 different families, each with about 30 copies per genome, comprising in all about 10% of the total genome (Rubin, 1983; Finnegan, 1989).

Transposon insertions cause about 50% of spontaneous mutations in *Drosophila* (Rubin, 1983; Echalier, 1989) and many insertional mutations have been described in maize, yeast and mouse. Transposons can cause mutations not only by inserting into and inactivating genes, but by altering the transcription of nearby genes (due mainly to transcriptional control sequences in the LTRs), by imprecise excision, by causing gross chromosomal rearrangements as a result of crossing over between different elements, by their transposases inducing chromosomal breaks, by creating a "synthetic" transposon as a result of two similar transposons inserting on either side of a gene, or by generating processed pseudogenes from mRNA (Echalier, 1989; Finnegan 1989).

Mackay (1984) recognised that transposons were likely to cause mutations for quantitative as well as qualitative characters. While there has been controversy about the experimental designs used in early experiments, her insight has proven to be correct. The evidence is briefly reviewed below.

Drosophila P elements transposons are mobilised in dysgenic crosses between males of stocks containing P elements and females

Figure 1 Mobile genetic elements. The structure of four different types of eukaryotic transposable elements (a-d, after Finnegan, 1989) and a typical retrovirus (e, after Temin, 1989). Elements a, b and e transpose via an RNA intermediate, while elements c and d transpose directly from DNA to DNA. Examples are given beneath elements a-d.

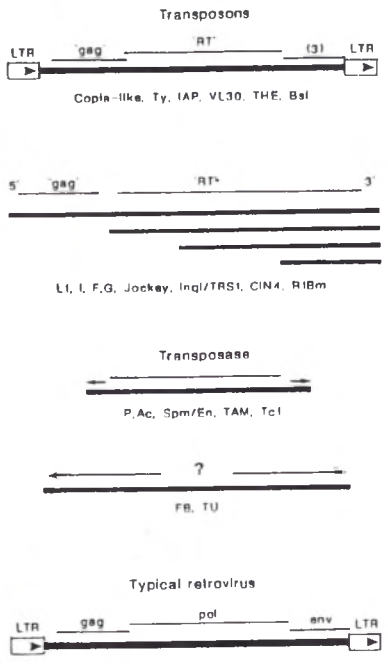
(a) Retrovirus-like elements (retrotransposons) have direct repeats (LTRs) at each end and up to three genes. The first of these has some similarity to the *gag* gene of a retrovirus, the second resembles a viral *pol* gene and encodes a potential reverse transcriptase (RT), while the third gene, when present, is in a similar position, but is unrelated to viral *env* genes.

(b) Elements with no terminal repeats (nonviral retrotransposons) usually have two genes, the first similar to a *gag* gene and the second encoding a potential reverse transcriptase. These elements are often deleted by varying amounts at the left hand (5') end, but have a fixed 3' end.

(c) Elements with short terminal inverted repeats. Some are known to contain a transposase gene required for their own transposition.

(d) Elements with long terminal repeats are heterogeneous in size. It is not known whether they contain a transposase gene.

(e) Retroviruses are RNA viruses with a DNA replicative intermediate that inserts into a host cells DNA as a provirus. A typical retrovirus consisting of Long Terminal Repeats (LTRs) at either end (essential for insertion into the host DNA) and genes coding for internal structural proteins (*gag*), viral enzymes including reverse transcriptase (*pol*) and viral envelope glycoproteins (*env*).



of stocks lacking them (see Engels, 1983). Mackay (1984, 1985) reported greater responses to selection in lines from dysgenic crosses (between non-isogenic stocks) than in lines from non-dysgenic crosses. However, this result was not repeatable (Morton and Hall, 1985; Shi, 1986; Torkamanzehi *et al.* 1988; Pignateli and Mackay, 1989). This experimental design suffers from three defects, namely that P elements are eventually mobilised in both crosses, that the X chromosome constitutions of the two crosses are not identical, and that responses due to transposon induced genetic variation must be distinguished from responses from base population polymorphisms and differences between the two stocks.

Unequivocal evidence for generation of genetic variation and selection response for abdominal bristle number due to P element mobilisation has been provided by Torkamanzehi (Moran and Torkamanzehi, 1990; Torkamanzehi, 1990; Torkamanzehi *et al.* in preparation) using an inbred M stock and a co-isogenic transformed P stock derivative to overcome design problems in previous experiments. Further, Frankham *et al.* (1990) have used the same experimental design to demonstrate generation of genetic variation and selection response for inebriation time.

Are transposons likely to produce variation useful to plant and animal breeders? Do transposon insertions have mainly deleterious effects? Effects on reproductive fitness characters are predominantly deleterious (see Mackay, 1989). However, selection response for inebriation time was greater in the high than the low direction (Frankham *et al.* 1990), even though inactivating mutations are likely to primarily reduce inebriation time. Detailed analyses of transposon induced mutations reveals that they result in both loss of function and excess function mutations (Echalier, 1989). Consequently, some transposon induced mutations should be of use in plant and animal breeding.

Further details on transposons are provided in the papers by Mackay and Moran in another session.

(7) Retrovirus mobilisation

Retroviruses are RNA viruses with a DNA replicative intermediate that is capable of inserting into many sites in the host cell's chromosomes (see Temin, 1989). They are frequently involved in causing tumours.

In the present context, retroviruses are similar to transposons, especially retrotransposons (see Fig. 1e). Both are mobile genetic elements capable of causing insertional and other mutations. Retroviral insertion mutations have been described in mouse (see Harbers *et al.* 1984; Rinchik *et al.* 1985; Stoye *et al.* 1988) and chickens (Bacon *et al.* in Crittenden and Salter, 1988). For example, the dilute coat colour mutation in mouse is due to the insertion of an ectropic murine leukemia virus (see Rinchik *et al.* 1985).

While selection response for a quantitative character due to retroviral insertion mutations has not breen documented, the dominant sex-linked slow feathering allele in chickens is probably due to a retrovirus insertion (Bacon *et al.* 1988). This allele is is used in feather sexing crosses, but is associated with increased susceptibility to lymphoid leukosis (see Bacon *et al.* 1988).

(8) Retrotransposition

Processed pseudogenes are presumed to result from reverse transcription of mRNA into DNA and insertion of this DNA into a chromosome. A substantial number of processed pseudogenes have been discovered (see Rogers, 1985). They are usually non-

functional since they have no promoters. However, they may occasionally insert next to a promoter such that they are expressed. A calmodulin gene in chickens and a phosphoglycerate kinase gene in humans may have evolved in this fashion (see Finnegan, 1989). Retrotransposition would be expected to lead to insertional mutations, though I know of no examples.

(9) Natural gene transfer between species

While natural gene transfer across species boundaries in eukaryotes seems rare, several known and putative cases exist. Insertions of retroviruses have been discussed above. In a related vein, crown gall tumours in plants are due to *T-DNA* insertions from *Ti* plasmids carried by the soil bacterium *Agrobacterium tumefaciens* (see Zambryski, 1988). Both cat retroviruses and *Drosophila* P element transposons appear to have moved across species boundaries (Benveniste *et al.* 1975; Finnegan, 1989) and there is speculation that other genes may have hitched a ride.

(10) Artificial gene transfer between species

Artificial transfers of genes from one species to another have been done in many plants, animals and microbes. Such gene transfers are expected to profoundly affect plant and animal breeding. Transgenic plants containing exogenous genes are under field test and are expected to be marketed in the next few years. Transgenics are considered in detail in the session devoted to that topic.

(11) Somaclonal variation

An elevated mutation rate is frequently found in plants subject to tissue culturing (see Larkin and Scowcroft, 1981; Evans, 1989), though the mechanism is unclear. Many useful variants for both single gene and quantitative traits have been identified and some have resulted in varieties that have been released commercially. While somaclonal variation has not been documented in animals, checks should be made for variation among genetically identical animals produced by *in vitro* culturing as part of embryo splitting and nuclear transplantation procedures.

Mitochondrial and chloroplast DNA variation

Mitochondria and chloroplasts both contain DNA that codes for some of the proteins they require for their functions of energy production and photosynthesis, respectively. They also code for their own rRNAs and tRNAs.

Extensive polymorphisms have been revealed in mitochondrial DNAs by restriction enzyme analyses (see Avise, 1986). Mitochondrial DNA lesions cause slow growing mutations in yeast and *Neurospora* (see Strickberger, 1985), and a broad spectrum of human neuromuscular diseases has recently been associated with mitochondrial DNA lesions and reduced mitochondrial energy production (see Wallace, 1989). These show maternal inheritance as predicted. Maternally inherited variation has recently been suggested to affect growth, reproduction and lactation traits in livestock (Bell *et al.* 1985; Huizinga *et al.* 1986; Toelle *et al.* 1986; Tess *et al.* 1987; Schultz and Freeman, 1988) and in one case this has been associated with mitochondrial DNA variation (Brown *et al.* 1989).

Chloroplast DNA exhibit polymorphisms and chloroplast DNA encoded mutations are known (see Strickberger, 1985). Such variation is expected to contribute to selection response, though I not aware of any documented cases.

INDUCING MUTATIONS WITH TRANSPOSONS AND RETROVIRUSES

Can transposons and retroviruses be mobilised to deliberately generate beneficial new genetic variation, especially in highly improved, commercially valuable strains? What agents cause them to mobilise? Can they be stabilised? A range of means has been used to mobilise these elements as follows:

Crosses

P elements in *Drosophila* may be mobilised in dysgenic crosses as discussed in (6) above. The mobilisation is so extreme that not only are new mutations and chromosome breakages produced, but sterility frequently results (see Engels, 1983). The P element mobilisation is temperature sensitive and restricted to the germ line. IR and *hobo* elements in *Drosophila* may also be mobilised in dysgenic crosses. Jenkins and Copeland (1985) used crosses between a line of mice lacking ectropic murine leukemia proviruses and a line containing three ectropic viruses, to generate new germline insertions of retroviruses.

Microinjection

Artificially modified P elements lacking a functional transposase gene have been constructed and used as transformation vectors. These may be inserted into genotypes lacking them by microinjection into early embryos, along with an exogenous source of transposase (see Spradling, 1986; Robertson *et al.* 1988). Inserts are stably inherited in the absence of transposase. However, they can be induced to re-mobilise by supplying exogenous transposase. Microinjection has been used to produce retroviral insertion mutations in mice (Gridley *et al.* 1987).

Infection

Infection with retroviruses has been used to produce insertion mutations in mice (Gridley *et al.* 1987). In a like manner, infection with *Agrobacterium tumefaciens* containing *Ti* plasmids has been used to produce insertion mutations in a plant (Feldman *et al.* 1989).

Tissue culturing

Several retrotransposons in *Drosophila* are known to amplify in cell lines and to show bursts of transposition, especially during the early culture phase (see Echalier, 1989). Activation of transposons has been detected in maize plants regenerated following tissue culturing (Peschke *et al.* 1987).

Heat shocking

Junakovic *et al.* (1986) reported that heat shocks induce transposition of *copia*-like elements in *Drosophila*.

Chemical treatment

Hormones have been shown to regulate the transcription of one *Drosophila* retrotransposon and a few mammalian retroviruses, and may affect their transposition (see Echalier, 1989).

Jaensich *et al.* (1985) reported activation of silent retroviral genomes as a result of 5-azacytidine treatment, an agent that is known to modify gene methylation.

In conclusion, a rapidly increasing range of methods have been described for manipulating transposons and retroviruses to produce mutations. Consequently, it should be possible to utilise these to produce beneficial mutations for use in plant and animal breeding. The more difficult practical problem will be to efficiently screen out the valuable mutations from the deleterious ones.

ACKNOWLEDGEMENTS

I am grateful to for Stuart Barker, Grant Daggard, John James, Hatch Stokes, Millar Whalley, Alan Wilton and especially Chris Moran for supplying references and for comments on the manuscript, and to Trudy Mackay and Chris Moran for supplying copies of manuscripts in press.

REFERENCES

AVISE, J.C. 1986. Phil.Trans.R.Soc.Lond.B 312: 325-342.

BACON, L.D., SMITH, E., CRITTENDEN, L.B. and HAVENSTEIN, G.B. 1988. Poult.Sci. 67: 191-197.

BELL, B.R., MCDANIEL, B.T. and ROBISON, O.W. 1985. J.Dairy Sci. 68: 2038-2051.

BENVENISTE, R.E., SHERR, C.A. and TODARO, G.J. 1975. Science 190: 886-888.

BISHOP, J.M. 1987. Science 235: 305-311.

BROWN, D.R., KOEHLER, C.M., LINDBERG, G.L., FREEMAN, A.E., MAYFIELD, J.E., MYERS, A.M., SCHULTZ, M.M. and BEITZ, D.C. 1989. J.Anim.Sci. 67: 1926-1932.

CARLILE, M.J. and SKEHEL, J.J. (eds.) 1974. Evolution in the Microbial World. Cambridge University Press, Cambridge.

COEN, E.S. and DOVER, G.A. 1983. Cell 33: 849-855.

CRITTENDEN, L.B. and SALTER, D.W. 1988. In: Proceeding of the Second International Conference on Quantitative Genetics (eds. Weir, B.S., Eisen, E.J., Goodman, M.M. and Namkoong, G.) Sinauer Associates, Inc., Sunderland, Mas. pp. 207-214.

DAYHOFF, M.O. 1969. Scient.Amer. 221(1): 85-95.

DEVONSHIRE, A.L. and SAWICKI, R..M. 1979. Nature 280: 140-141.

DOBZHANSKY, T. 1970. Genetics of the Evolutionary Process. Columbia University Press, New York.

ECHALIER, G. 1989. Adv.Virus Res. 36: 33-105.

ENGELS, W.R. 1983. Ann.Rev.Genet. 17: 315-344

EVANS, D.A. 1989. TIG 5: 46-50.

FELDMAN, K.A., MARKS, M.D., CHRISTIANSON, M.L. and QUATRANO, R.S. 1989. Science 243: 1351-1354.

FINNEGAN, D.J. 1985. Int.Rev.Cytol. 93: 281-325.

FINNEGAN, D.J. 1989. TIG 5: 103-107.

FRANKHAM, R. 1980. *In* Selection Experiments in Laboratory and Domestic Animals. *Edited* by A. Robertson. Commonwealth Agricultural Bureaux, Slough. pp. 56-68.

FRANKHAM, R. 1988a. In: Proceeding of the Second International Conference on Quantitative Genetics (eds. Weir, B.S., Eisen, E.J., Goodman, M.M. and Namkoong, G.) Sinauer Associates, Inc., Sunderland, Mas. pp. 236-242.

FRANKHAM, R. 1988b. J.Theor.Biol. 135: 85-107.

FRANKHAM, R., BRISCOE D.A., and NURTHEN, R.K. 1980. Genetics 95: 727-742.

FRANKHAM, R., TORKAMANZEHI, A. and MORAN, C. 1990. Theor.Appl.Genet. (submitted).

GILLINGS, M.R., FRANKHAM, R., SPEIRS, J., and WHALLEY, M. 1987. Genetics 116: 241-251.

GRANT, V. 1971. Plant Speciation, Columbia Univ. Press, New York.

GRIDLEY, T., SORIANO, P. and JAENISCH, R. 1987. TIG 3: 162-166.

HARBERS, K., KUEHN, M., DELIUS, H., and JAENISCH, R. 1984. Proc.Nat.Acad.Sci.USA 81: 1504-1508.

HILL, W.G. 1982. Genet.Res. 40: 255-278.

HUIZINGA, H.A., KORVER, S., MCDANIEL, B.T. and POLITIEK, R.D. 1986. Livest.Prod.Sci. 15: 11-26.
HYRIEN, D. and BUTTIN, G. 1986. TIG 2: 275-276.
JAENISCH, R., SCHNIEKE, A. and HARBERS, K. 1985. Proc.Nat.Acad. Sci.USA 82: 1451-1455.
JENKINS, N.A. and COPELAND, N.G. 1985. Cell 43: 811-819.
JUNAKOVIC, N., DI FRANCO, C., BARSANTI, P. and PALUMBO, G. 1986. J.Mol.Evol. 24: 89-93.
LARKIN, P.J. and SCOWCROFT, W.R. 1981. Theor.Appl.Genet. 60: 197-214.
LEWONTIN, R.C. 1974. The Genetic Basis of Evolutionary Change. Columbia University Press, New York.
MACKAY, T.F.C. 1984. Genet.Res. 44: 231-237.
MACKAY, T.F.C. 1985. Genetics 111: 351-374.
MACKAY, T.F.C. 1989. In: Evolution and Animal Breeding (Hill, W.G. and Mackay, T.R.F. eds.) C.A.B. International, Wallingford. pp. 113-119.
MCCLINTOCK, B. 1984. Science 226: 792-801.
MORAN, C. and TORKAMANZEHI, A. 1990. In: Ecological and Evolutionary Genetics of *Drosophila* (Barker, J.S.F., Starmer, W.T. and MacIntyre, R.J. eds.) Plenum Press, New York. pp. 99-117.
MORTON, R.A. and HALL, S.C. 1985. Dros.Inf.Serv 61: 126-128.
MOUCHES, C., PASTEUR, N., BERGE, J.B., HYRIEN, O., RAYMOND, M., DE SAINT VINCENT, R.B., DE SILVESTRI, M. and GEORGHIOU, G.P. 1986. Science 233: 778-780.
OHNO, S. 1970. Evolution by Gene Duplication. Springer-Verlag, Berlin.
OHTA, T. 1989. Genome 31: 304-310.
PESCHKE, V.M., PHILLIPS, R.L. and GENGENBACH, B.G. 1987. Science 238: 804-807.
PIGNATELLI, P.M. and MACKAY, T.F.C. 1989. Genet.Res. (in press).
PONDER, B. 1988. Nature 335: 400-402.
RABBITTS, T.H., BOEHM, T. and MENGLE-GAW, L. 1988. TIG 4: 300-304.
REDDY, E.P., REYNOLD, R.K., SANTOS, E. and BARBACID, M. 1982. Nature 300: 149-152.
RINCHIK, E.M., RUSSELL, L.B., COPELAND, N.G. and JENKINS, N.A. 1985. TIG 6: 170-176.
ROBERTSON, H.M., PRESTON, C.R., PHILLIS, R.W., JOHNSON-SCHLITZ, D.M., BENZ, W.K. and ENGELS, W.R. 1988. Genetics 118: 461-470.
ROGERS, J.H. 1985. Int.Rev.Cytol. 93: 187-279.
RUBIN, G.M. 1983. In: Mobile Genetic Elements (Shapiro, J.A. ed.), Academic Press, New York. pp. 329-361.
SCHIMKE, R.T. 1982. Gene Amplification. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.
SCHULTZ, M.M. and FREEMAN, A.E. 1988. J.Dairy Sci. 71(Suppl. 1): 144.
SHI, Y. 1986. M.Rur.Sci. thesis, Univ. New England.
SPRADLING, A.C. 1986. In: *Drosophila* a practical approach (Roberts, D.B. ed.), IRL Press, Oxford. pp. 175-197.
STOYE, J.P., FENNER, S., GREENOAK, G.E., MORAN, C. and COFFIN, J.M. 1988. Cell 54: 383-391.
STRICKBERGER, M.W. 1985. Genetics (3rd edition), MacMillan, New York.
TAYA, Y., TERADA, M. and SUGIMURA, T. 1987. Adv.Viral.Oncol. 7: 376-388.
TEMIN, H.M. 1989. Genome 31: 17-22.

TESS, M.W., REODECHA, C. and ROBISON, O.W. 1987. J.Anim.Sci. 65: 675-684.
TOELLE, V.D., MCDANIEL, B.T. and ROBISON, O.W. 1986. J.Anim.Sci. 63(Suppl 1): 203.
TORKAMANZEHI, A., MORAN, C. and NICHOLAS, F.W. 1988. Genet.Res. 51: 231-238.
TORKAMANZEHI, A. 1990. Ph.D. thesis, Univ. Sydney.
WALLACE, D.C. 1989. TIG 5: 9-13.
WANG, T.C. and PLAPP, F.W. 1980. J.Econ.Ent. 73: 200-203.
WATSON, J.D., HOPKINS, N.H., ROBERTS, J.W., ARGETSINGER STEITZ, J. and WEINER, A.M. 1987. Molecular Biology of the Gene (4th edition). Benjamin/Cummings, Menlo Park.
WILSON, A.C. 1976. In: Molecular Evolution (ed. Ayala, F.J.). Sinauer, Sunderland. pp. 225-234.
YOO, B.H. 1980. Genet.Res. 35: 19-31.
ZAMBRYSKI, P. 1988. Ann.Rev.Genet. 22: 1-30.