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Henrik Kacser (1918–1995): an Annotated Bibliography

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Introduction

Henrik Kacser's bibliography disproves some myths of modern science, in particular the belief that to become the recognized leader of one's field one must publish a great many papers that appear regularly over one's career and constitute a coherent whole. Some also believe that to make a significant contribution one must publish one's major ideas early in life, with everything that follows just consolidation. However, it is difficult to relate much in Henrik Kacser's work published before 1957 with the ideas for which he is best known; moreover, as illustrated in Fig. 1, his career was astonishingly late to develop, and even at its end his total number of publications was less than some scientists produce in a year. Anyone assessing Henrik Kacser in 1970 by the sort of criteria that have become commonplace would find it hard to avoid concluding that his research career was over, and that the best use of his talents would be to administer car parking at Edinburgh University. Perhaps, indeed, this was exactly the assessment that was made.

Yet 1970 was mid-way between the first suggestions of what we now call metabolic control analysis (Kacser & Burns, 1967) and its triumphant unveiling in the classic paper *The control of flux* (Kacser & Burns, 1973). Far from being over, his work was just beginning; far from declining, his output accelerated after the mid-1980s.

There is another surprise in the early work of Henrik Kacser for those of us who thought of him, as to some degree he did himself, as a classical geneticist turned biochemist: his early papers include work in practical chemistry, the kinetics of enzyme reactions, and very little genetics. His expertise in genetics became evident only in the third phase of his career, when he set out to find experimental models to demonstrate the correctness of his views on metabolic control.

In general, his publications fall fairly naturally into four phases: (1) building a foundation in physical chemistry; (2) development of metabolic control analysis; (3) consolidation; (4) expansion. The borderline between the third and fourth phases is perhaps arbitrary, but can be justified as the moment when the main points of metabolic control analysis were widely accepted and it was time to fill in the details and show how it could be applied.

1. Early Work in Chemistry: from the Inorganic World to Proteins (1949–1957)

The initial phase of Henrik Kacser's career reflects his undergraduate training in chemistry and post-graduate research in physical chemistry. A good understanding of physical chemistry, especially thermodynamics and kinetics, laid the foundation for clear thinking about biological control later on, but there is little suggestion of the interest in metabolic control that came to dominate the later part of his career, despite a steady trend from pure chemistry at the beginning to the chemistry of living systems at the end. Nonetheless, the closing words of his discussion of gene structure (Kacser, 1956) foreshadow ideas familiar to the modern reader: "The evidence that the plant viruses contain ribose nucleic acid only (where one definitely does not find base pairs) should serve as a reminder that genetic mechanisms should not be looked for in the properties of particular substances but in the way the whole system is organized." In this paper, and the earlier one on aconitase kinetics (Kacser, 1952), Kacser's readiness to draw attention to flaws in arguments advanced by such figures as Crick, Delbrück and Lynen should perhaps have warned contemporary readers that they were not dealing with a scientist who would always be willing to remain on the sidelines.

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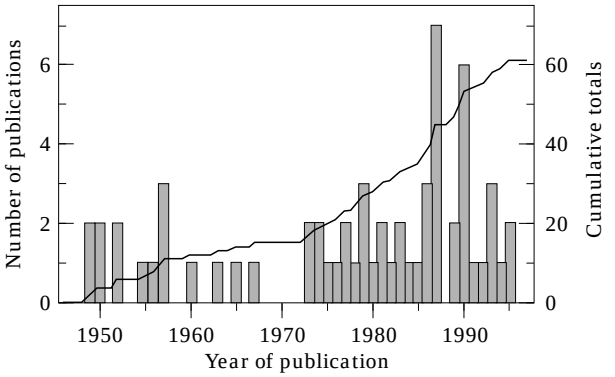

FIG. 1. Published work, 1949–1995. The continuous line shows the cumulative totals.

1. KACSER, H. & UBBELOHDE, A. R. (1949). A thermostatically controlled micro-polarimeter-tube. *J. Soc. Chem. Ind.* **68,** 135–138.
2. KACSER, H. & UBBELOHDE, A. R. (1949). Thermodynamic conditions for the retention of solvents by crystals: the system brucine/benzene. *Nature* **164,** 445–446.
3. KACSER, H. & UBBELOHDE, A. R. (1950). Thermodynamic factors in stereospecific processes. *J. Chem. Soc.* 2152–2158.
4. KACSER, H. (1950). The purification of brucine. *J. Chem. Soc.* 2908.
5. KACSER, H. (1952). The specificity and kinetics of aconitase. *Biochim. Biophys. Acta* **9,** 406–415.
6. KACSER, H. (1952). The probability factor in bimolecular reactions. I. Uncomplicated ion-dipole systems. *J. Phys. Chem.* **56,** 1101–1106.
7. KACSER, H. (1955). The cortical changes on fertilization of the sea-urchin egg. *J. Exp. Biol.* **32,** 451–467.
8. KACSER, H. (1956). Molecular organization of genetic material. *Science* **124,** 151–154.
9. BEALE, G. H. & KACSER, H. (1957). Studies on the antigens of *Paramecium aurelia* with the aid of fluorescent antibodies. *J. Gen. Microbiol.* **17,** 68–74.
10. KACSER, H. (1957). The heat inactivation and serum neutralization sites of bacteriophage T2. *Proc. Roy. Phys. Soc. Edinburgh* **26,** 1–6.

2. The Birth of Metabolic Control Analysis (1957–1973)

Henrik Kacser's first exposition of the idea that understanding systems required a systemic treatment (Kacser, 1957) came in a 60-page invited appendix to a book. So it must have been evident to his colleagues from his conversation and spoken criticisms of the ideas that were then current that he was interested in systems, even if the bibliography before 1957 contains little suggestion of this. The first steps towards metabolic control analysis came in 1967 (Kacser & Burns, 1967), unless we read more into note 16 (''a discussion of ... the problems connected with meiosis, mutations, and differentiation is in preparation'') of Kacser (1956) than he probably intended; but it had to wait 6 years (of apparent silence!) before the appearance of what has come to be universally regarded as the classic paper (Kacser & Burns, 1973) that opened up the whole field. This paper has recently been updated and re-published (Kacser *et al*., 1995).

The other papers of this section have received little attention in recent years, but two in particular (Kacser, 1957, 1960) were influential in establishing the important idea that biological organization could be understood in terms of chemical kinetics. Peacocke (1983) discussed this in his book, in a passage that is reproduced elsewhere in the present volume (Peacocke, 1996). Kacser (1960) himself described one of these papers ''very briefly, and therefore very inaccurately,'' as ''the interpretation of biology in terms of chemistry'', a description that may well apply to the whole of his work.

11. KACSER, H. (1957). Some physico-chemical aspects of biological organisation. Appendix to *The Strategy of the Genes* by C. H. Waddington, pp. 191–249. London: George Allen and Unwin.
12. KACSER, H. (1960). Kinetic models of development and heredity. *Symp. Soc. Exp. Biol.* **14,** 13–27.
13. KACSER, H. (1963). The kinetic structure of organisms, in *Biological organization at the cellular and supercellular level* (Harris, R. J. C., ed.), pp. 25–41, Academic Press, New York and London.
14. BURNS, J. A., CURTIS, C. F. & KACSER, H. (1965). A method for the production of a desired buffer gradient and its use of the chromatographic separation of argininosuccinate. *J. Chromatog.* **20,** 310–318.
15. KACSER, H. & BURNS, J. A. (1967). Causality, complexity and computers, in *Quantitative biology of metabolism* (Locker, A., ed.), pp. 11–23. Berlin: Springer Verlag.
16. KACSER, H., BULFIELD, G. & WALLACE, M. E. (1973). Histidinaemic mutant in the mouse. *Nature* **244,** 77–79.
17. KACSER, H. & BURNS, J. A. (1973). The control of flux. *Symp. Soc. Exp. Biol.* **27,** 65–104.

3. Consolidation (1974–1983)

The control of flux (Kacser & Burns, 1973) is a model of coherent argument and clear exposition, and is now generally regarded as the starting point, though as it happens experimental evidence that some enzymes have extremely low flux control coefficients had been published some 10 years earlier (Kacser, 1963). The appearance of an independent study leading to similar conclusions (Heinrich & Rapoport, 1974) should have convinced the sceptics of the general correctness of the ideas in the 1973 paper. It is remarkable, therefore, how much of the subsequent decade passed before it became widely known and accepted (see Fig. 2), and how much effort needed to be put into providing experimental evidence (e.g. Barthelmess *et al*., 1974; Flint *et al*., 1980), and recasting the same material in a ''popular'' form (Kacser & Burns, 1979). In 1980 the main ideas had scarcely begun to penetrate the general biochemical

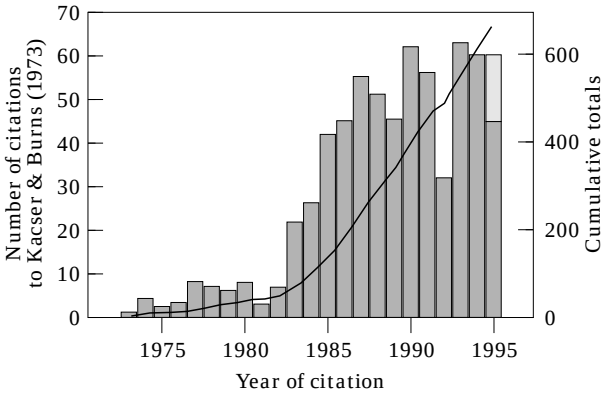

FIG. 2. Citations to Kacser & Burns (1973). The data are derived from the *Science Citation Index*, the value for 1995 being obtained by scaling up the value for January–September 1995. The continuous line shows the cumulative totals.

consciousness, and the field was still largely confined to its originators.

Within this group of papers mention must be made of the analysis of dominance and recessivity (Kacser & Burns, 1981), which resolved a puzzle that had existed for more than a century. This paper is discussed by Porteous (1996) elsewhere in the present volume.

18. BULFIELD, G. & KACSER, H. (1974). Histidinaemia in man and mouse. *Arch. Dis. Childh.* **49,** 545–552.
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20. BULFIELD, G. & KACSER, H. (1975). Histamine and histidine levels in the brain of the histidinaemic mutant mouse. *J. Neurochem.* **24,** 403–405.
21. KACSER, H. (1976). The proper solutions of Kacser's developmental model. *J. theor. Biol.* **63,** 239–241.
22. BURNS, J. A. & KACSER, H. (1977). Allosteric repression: an analysis. *J. theor. Biol.* **68,** 199–213.
23. KACSER, H., MYA, K. M., DUNKER, M., WRIGHT, A. F., BULFIELD, G., MCLAREN, A. & LYON, M. F. (1977). Maternal histidine metabolism and its effect on foetal development in the mouse. *Nature* **265,** 262–266.
24. BULFIELD, G., MOORE, E. A. & KACSER, H. (1978). Genetic variation in activity of the enzymes of glycolysis and gluconeogenesis between inbred strains of mice. *Genetics* **89,** 551–561.
25. KACSER, H., BULFIELD, G. & WRIGHT, A. F. (1979). The biochemistry and genetics of histidinaemia in the mouse, in *Models for the study of inborn errors of metabolism* (Hommes, F. A., ed.), pp. 33–43. Amsterdam: Elsevier.
26. KACSER, H., MYA, K. M. & BULFIELD, G. (1979). Endogenous teratogenesis in maternal histidinaemia, in *Models for the study of inborn errors of metabolism* (Hommes, F. A., ed.), pp. 43–53. Amsterdam: Elsevier.
27. KACSER, H. & BURNS, J. A. (1979). Molecular democracy: who shares the controls? *Bioc. Soc. Trans.* **7,** 1149–1161.
28. FLINT, H. J., PORTEOUS, D. J. & KACSER, H. (1980). Control of flux in the arginine pathway of *Neurospora crassa*. The flux from citrulline to arginine. *Biochem. J.* **190,** 1–15.
29. KACSER, H. & BURNS, J. A. (1981). The molecular basis of dominance. *Genetics* **97,** 639–666.
30. WRIGHT, A. F., BULFIELD, G., ARFIN, S. H. & KACSER, H. (1982). Comparison of the properties of histidine ammonia-lyase in normal and histidinaemic mutant mice. *Biochem. Genet.* **20,** 245–263.
31. FLINT, H. J., TATESON, R. W., BARTHELMESS, I. B., PORTEOUS, D. J., DONACHIE, W. D. & KACSER, H. (1981). Control of flux in the arginine pathway of *Neurospora crassa*. Modulations of enzyme activity and concentration. *Biochem. J.* **200,** 231–246.
32. KACSER, H. (1983). The control of enzyme systems *in vivo*. Elasticity analysis of the steady state. *Biochem. Soc. Trans.* **11,** 35–40.
33. MIDDLETON, R. J. & KACSER, H. (1983). Enzyme variation, metabolic flux and fitness: alcohol dehydrogenase in *D. melanogaster*. *Genetics* **105,** 633–650.

4. Expansion (1984–1995)

By the mid-1980s the central ideas of metabolic control analysis were becoming far more widely accepted, and more groups started to enter the field each year. It was time to expand it, by developing new and more powerful experimental methods for studying real systems, to remove some of the limitations that were present in the first analyses, to improve our understanding of metabolic regulation and molecular evolution, and to show how metabolic control analysis could be applied to problems of medicine and biotechnology. Henrick Kacser played a major role in most of these aspects, and as his accelerating rate of publication in the last years of his life shows, his interest not only remained active but even increased. It is altogether characteristic of him that his last paper to appear during his lifetime should be about the future development of his subject (Kacser, 1995), but equally characteristic that it was not his last paper: not only did he have another in proof (Cascante *et al*., 1995) at the time of his death, but he was almost ready to submit a stimulating and original paper on a subject he had not dealt with previously, a subject, moreover, that could hardly be more topical for 1996. This paper (Kacser & Small, 1996) appears elsewhere in this issue.

34. FLINT, H. J., DIBLE, S. & KACSER, H. (1985). Derepression of enzyme synthesis in response to arginine limitation in *Neurospora crassa*. *J. Gen. Microbiol.* **131,** 2891–2900.
35. BEEBY, R. & KACSER, H. (1984). Evolution of catalytic proteins. *J. Mol. Evol.* **20,** 38–51.
36. TORRES, N. V., MATEO, F., MELÉNDEZ-HEVIA, E. & KACSER, H. (1986). Kinetics of metabolic pathways. A system *in vitro* to study the general control of flux. *Biochem. J.* **234,** 169–174.
37. STUART, F., PORTEOUS, D. J., FLINT, H. J. & KACSER, H. (1986). Control of the arginine flux in the arginine pathway of *Neurospora crassa*: effects of co-ordinate changes of enzyme concentration. *J. Gen. Microbiol.* **132,** 1159–1166.
38. HOFMEYR, J.-H. S., KACSER, H. & VAN DER MERWE, K. (1986). Metabolic control analysis of moiety-conserved cycles. *Eur. J. Biochem.* **155,** 631–641.
39. KACSER, H. & PORTEOUS, J. W. (1987). Control of metabolism: what do we have to measure? *Trends Biochem. Sci.* **12,** 5–14.

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42. Keightley, P. D. & Kacser, H. (1987). Dominance, pleiotropy and metabolic structure. *Genetics* **117,** 319–329.
43. Burns, J. A. & Kacser, H. (1987). Genetic effects on susceptibility to histidine-induced teratogenesis in the mouse. *Genet. Res. Camb.* **50,** 147–153.
44. Kacser, H. (1987). On parts and wholes in metabolism, in *The organization of cell metabolism* (Welch, G. R. & Clegg, J. S., eds.), pp. 327–337. New York: Plenum.
45. Kacser, H. (1987). Dominance not inevitable but very likely. *J. theor. Biol.* **125,** 505–506.
46. Acerenza, L., Sauro, H. M. & Kacser, H. (1989). Control analysis of time-dependent metabolic systems. *J. theor. Biol.* **137,** 423–444.
47. Kacser, H. (1989). Quantitative variation and the control analysis of enzyme systems, in *Evolution and animal breeding* (Hill, W. G. & Mackay, T. F. C., eds), pp. 219–226. C.A.B. International.
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49. Sauro, H. M. & Kacser, H. (1990). Enzyme-enzyme interactions and control analysis. 2. The case of non-independence: heterologous associations. *Eur. J. Biochem.* **187,** 493–500.
50. Meléndez-Hevia, E., Torres, N. V., Sicilia, J. & Kacser, H. (1990). Control analysis of transition times in metabolic systems. *Biochem. J.* **265,** 195–202.
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56. Kacser, H. & Acerenza, L. (1993). A universal method for achieving increases in metabolite production. *Eur. J. Biochem.* **216,** 361–367.
57. Small, J. R. & Kacser, H. (1993). Responses of metabolic systems to large changes in enzyme activities and effectors. 1. The linear treatment of unbranched chains. *Eur. J. Biochem.* **213,** 613–624.
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63. Kacser, H. & Small, J. R. (1996). How many phenotypes from one genotype? The case of prion diseases. *J. theor. Biol.* **000,** 000–000.

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APPENDIX

Some Quotations from Kacser's Earlier Papers

When one is discussing the synthesis of new genetic material, it is not helpful to explain it in terms of the hypothetical property of a substance or body called a "self-duplicating ability". No property of this type is known for any molecule except the trivial one of autocatalysis, where already preexisting material is released. The relevant phenomenon is autosynthesis which is the property of a *system* . . . (Kacser, 1956).

The belief that a living organism is "nothing more" than a collection of substances, albeit a very complex collection of very complex substances, is as widespread as it is difficult to substantiate . . .

The problem is therefore the investigation of *systems*, i.e. components related or organised in a specific way. The properties of a system are in fact "more" than (or different from) the sum of the properties of its components, a fact often overlooked in zealous attempts to demonstrate "additivity" of certain phenomonena. It is with these "systemic properties" that we shall be mainly concerned . . .

One may wonder how Mendel could have laid the foundations of genetics. Fortunately for him and later investigators most of the effects will be eliminated by buffering and, of the remaining, many will not be apparent by inspection. In general, many mutations must occur which have no apparent effects . . . (Kacser, 1957b).

An analogue is clearly an analogue of something. Billiard balls on a table may be an analogue of gas molecules in a vessel, or they may be a source of

relaxation for tired University Professors, or they may be the beginning of the ruin of a promising student. It therefore appears that it is the use to which objects are put that marks them out as analogues . . .

If our questions are then directed towards the present, we see the genes not as dictators of every action within their realm but rather like civil servants who work within a framework of tradition. Some of the reasons for doing things are buried in the past. But as good servants they faithfully carry on, fitting themselves into the conditions as they find them. (Kacser, 1960).

An organism is not simply a mixture but a system of interacting molecules. It is therefore to these interactions that we must look for an elucidation of biological behaviour . . .

The widespread phenomena of dominance, pleiotropy and epistasis in genetics and of regulation and differentiation in embryology have shown the inadequacy of such a view. There is, however, as yet no comprehensive scheme which links the evidence for the unitary genetic determination of protein structure with the bewildering array of epigenetic and metabolic consequences . . . Some of the conclusions of the treatment which follows may therefore appear intuitively strange—but so much the worse for intuition . . .

The existence of specific feed-back mechanisms such as inhibition, induction and repression in bacteria and which also may exist in other organisms, is of course additional to the phenomena here described . . .

In a system with many interactions many properties arise which cannot be assigned to any one isolable entity . . .

Which particular enzymes are in positions of importance may vary from organism to organism, but it is impossible for *all* of them to be . . . (Kacser, 1963).