SYMPOSIUM ON
‘METABOLISM AND LACTATION’

Questions of validity in mammary physiology: methodology and ethics

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An analysis of the type presented is highly unusual, but most timely in view of the rapid changes occurring in this and other branches of applied biology. Mammary physiology is here interpreted broadly to include cognate sciences, fundamental and applied aspects, and both medical and dairying contexts, though references to the latter predominate. To aid discussion, ‘validity’ is considered under four headings, i.e., empirical, experimental, epistemological and ethical: the categories are not absolute and each is, in a sense, contained in its succeeding category, like a set of Russian dolls. Several examples quoted are decidedly ‘historical’; but the principles they illustrate have equal validity today.

Empirical validity

This refers to perception and recording of sense data by the experimenter; transmission in publications; and interpretation as facts by other scientists. Conceptually, the process involved is simply data transfer. Although apparently unproblematical, in practice, many developments in physiology can be traced to identification of errors perpetrated at this level.

For example, Graham et al. (1938) made deductions about the blood precursors of milk protein in goats which cannot be sustained by examination of their recorded data, as was pointed out in an exemplary review by Barry (1961). A more amusing case is the recording of information on milk composition for guinea-pigs, through mistranslation of the German word ‘Meerschwein’ (porpoise) (see Jenness & Sloan, 1970). A particularly apposite example is that cited by Widdowson (1984), i.e., the incorrect description of the treatment of rats in feeding experiments reported in the classic paper by Gowland Hopkins (1912), which led to the discovery of vitamins.

Generally speaking, opportunities for error at the empirical level range from fraud (see Broad & Wade, 1983) to selective quotation of findings (citing the ‘best’ as ‘typical’). Many scientists would defend the exclusion of obviously aberrant values caused by operational error, but since this is usually a post hoc decision it is susceptible to unintentional abuse.

Experimental validity

Experiments in mammary physiology may be classified as: (1) in vivo non-surgical, (2) in vivo surgical, (3) in vitro. Category (1) includes: variations in milking frequency, intraductal infusion, teat cannulation, gland volume measurement by water displacement-
ment. Surgical procedures (category 2) include: mammary blood flow estimation, arterio-venous difference determination, intravascular infusion, gland autotransplantation and biopsy, and mastectomy. Among in vitro methods used (category 3) are: isolated gland perfusion, organ, explant and cell culture, light and electron microscopy, also combined with histochemical and autoradiographic techniques. Other techniques sometimes used with those previously mentioned are: isotopic tracers, endocrinectomy and hormone replacement therapy, nutritional and climatic modification. These techniques (and the list is incomplete) are discussed in one or more of the following reviews: Linzell (1974), Fleet & Mepham (1983), Pitelka & Hamamoto (1983), Bissell & Hall (1987).

It is evident that an exceptionally wide range of methods is applicable to the study of mammary function. The most distinctive are those used in dairy animals, which are made possible by the convenient size and position of the mammary glands and the availability of large quantities of milk in response to abnormal milking stimuli. For example, the arterio-venous difference technique coupled with blood flow assay permits estimation of substrate uptake in relation to output of synthetic products in milk, under stress-free conditions in vivo: in few other procedures can so much valuable information be obtained with so little physiological intervention. A critical evaluation of several of these techniques is provided by Fleet & Mepham (1983).

However, a major predicate of most experiments is that they involve perturbation of normal conditions. Because there are limitations to adopting this approach in vivo, not least because of the complexity of responses, in vitro systems are widely used. The crux of the problem of experimentation is that the simpler, more controllable and more quantifiable the system, the further it is likely to be from physiological normality. Bissell & Hall (1987) have indicated how results of experiments with primary cell cultures are highly dependent on the culture conditions, i.e. whether the substratum is plastic, attached collagen or released collagen. Depending on such conditions protein secreted may correspond more or less closely to those in milk. Remarkably, in some cases the cells secrete proteins not present in milk, implying removal of a repressor or the presence of an inducer under culture conditions.

Although each method has its limitations it is possible that in mammary physiology a judicious combination of the wide range of approaches available may facilitate validation. Certainly, history warns against the dangers of undue reliance on a single method, as is indicated by Liebig's theory of casein secretion based on its alleged correspondence with the plant protein, legumin (see Mepham, 1986).

Epistemological validity

Epistemology is the theory of knowledge, so the concern here is with the theoretical interpretation of empirical observations. The aim is to outline prominent philosophical interpretations and relate them to mammary physiology.

Kuhn (1962) envisages science as developing in two stages, normal science and science in crisis. Normal science, the day-to-day occupation of most scientists, consists of 'articulation' and extension of 'paradigms', the conceptual frameworks which define the problems, legitimize the methods and prescribe the standards of acceptability of 'solutions'. The genetic basis of heredity is a prime example of a paradigm. Normal science is cumulative, stable and 'successful', but Kuhn's (1962) historical analyses show that eventually the build-up of internal inconsistencies precipitates a 'scientific revolution', in which the validity of the paradigm is challenged and overthrown. Thereafter, empirical observations are re-interpreted in terms of a new theory, which is also able to accommodate the previously incompatible observations which led to the crisis.
Kuhn's (1962) theory throws light on many events in the history of mammary physiology. For example, in the nineteenth century, milk secretion was explained according to the paradigm of vital forces, through the attribution to mammary tissue of such properties as 'latent sensibility' and 'imperceptible contractibility' (see Mepham, 1986).

A crucial element in Kuhn's (1962) analysis is that the paradigm determines expectations, i.e., scientists' observations are theory-dependent in that they see what they expect to see. A perfect example is the claim of Heidenhain (1883), a distinguished microscopist, that mammary cells possess two nuclei, one of which is lost from the cell during secretion and suffers a process of disintegration or 'chromatolysis'. This, from modern perspectives, extraordinary claim, becomes understandable in the light of Lubavin's (1871) earlier description of casein as a 'nucleoalbumin', a product of the combination of nuclear material and albumin. For the theory to be tenable lysis of cell nuclei was necessary, and Heidenhain (1883) duly 'saw' this (see Mepham, 1986). Presumably, the empirical observations would now be dismissed as sectioning artefacts.

Inconsistent observations challenging established paradigms are examples of what Popper (1972) calls 'refutations' or 'falsifications': his prescription for scientific method involves 'bold conjectures and ingenious and severe attempts to refute them'. Theories gain in strength if they resist attempted refutations, as successful species survive in the struggle for existence. A naive Popperian approach would lead to abandonment of a theory if apparently refuted in a single instance, but this rule hardly seems valid, philosophically or practically. Lakatos (1978) proposed an alternative analysis, in which scientists are claimed to operate within 'research programmes', characterized by a 'hard-core' of background information and a 'positive heuristic', i.e., a programme for defining and solving problems.

That Popper's (1972) refutational principle has been claimed as a crucial insight by eminent biologists such as Eccles (see Popper & Eccles, 1983) and Medawar (1967) suggests the importance of considering it in the present context. One example must suffice. The most widely held theory of secretion of the aqueous phase of milk (Linzell & Peaker, 1971) states that K⁺ and Na⁺ diffusion into milk is constrained by an apical membrane potential difference induced by lactose secretion. Accordingly, the K:Na ratios in intracellular fluid (ICF) and milk are identical; and lactose, through its osmotic action, determines water flow so that milk and blood plasma are isosmotic. Apparently falsifying observations are those of Berga & Neville (1985), indicating that K:Na in milk and ICF of mouse mammary tissue are not identical; results of Peaker & Goode (1978) indicating that elephant seal milk is hyperosmotic to blood plasma; and findings from several species indicating the virtual absence of lactose in milk (Davies et al. 1983).

Clearly, a naive Popperian criterion has not applied; but Linzell & Peaker's (1971) theory continues to provide a 'positive heuristic' for a research programme (Lakatos, 1978): time will tell whether it is a 'progressive' or 'degenerating' one.

Epistemological questions extend far beyond the immediate concerns of the laboratory, because science is largely conditioned by the precepts of the social milieu in which it is practised. Thus, external forces, such as governments and commercial organizations, effectively mould the shape of the discipline by selective patronage. Virtually all research in mammary physiology is 'applied', being pursued either in connection with dairying or medicine (i.e., related to breast feeding and breast cancer), but despite this, studies at the fundamental level (strategic research) often have significance to the much wider fields of reproductive biology and nutrition.

In dairy research animals are seen as production units, and a major objective has been to increase output of milk per unit, without proportionately increasing inputs, thereby
increasing financial profits. In such terms, the average increase in annual milk yield per
cow in the United States of America, from 2500 kg in 1950 to 5500 kg in 1980 (Clarke &
Davis, 1983), provides unequivocal validation of the procedures adopted. Dairy research
is a classic example of what Krohn & Schafer (1982) call ‘finalized science’, in which a
specific aspect of nature is constructed purposefully in terms of a specific goal. Latterly,
the goals have changed and public support for dairy research, in common with most
agricultural research, has markedly declined. I have argued elsewhere (Mepham, 1987a)
that dairy research still has a crucial role in promoting economic and nutritional
development in both developed and less developed countries.

According to Merton (1967), academic science is characterized by the attributes of
communalism, universalism, disinterestedness and organized scepticism: research results
are published freely, informed criticism is encouraged, and scientists have no vested
interests in the outcome of their research. In large measure such qualities were broadly
applicable to government research institutes before implementation of the Rothschild
proposals in the 1970s. Although many would claim that Merton’s (1967) analysis is
idealistic, to the extent that such qualities do not apply, the implicit aim of science, of
gaining reliable understanding of the natural world, is likely to be frustrated.

A major change in external direction of dairy research in recent years stems from
increasing investment by commercial companies, particularly those based in biotech-
nology; and this raises important questions about the likely impact on the Mertonian
norms described. Consider a fictitious bioengineered product, hSH22, produced by a
handful of transnational companies. Imagine that it shows promise, when administered
to cows subcutaneously, of decreasing the saturated fat content of milk without affecting
flavour: clearly a highly attractive proposition for people fearful of the alleged
association between saturated fat intake and heart disease. To win public acceptability,
government and university laboratories are enlisted in testing the product for efficacy
and safety, an opportunity gratefully seized by financially ailing public institutions. Not
surprisingly, research results must remain confidential and, because the companies’
major concern is profit, there will be a tendency to promote aspects of the research effort
serving that end and to ignore others. The impact on the scientist is likely to be profound:
no longer is he able to exchange findings and hypotheses freely, and the informed
criticism which should be a feature of scientific practice is likely to be either absent or
biased. Should he happen to hit upon some adverse effect of the product, e.g., on animal
welfare, his revelation of the fact would have to be taken in the knowledge that the
project might be abandoned and, with it, his job. The significance of the name, hSH22,
should now be clear: it denotes both secrecy and the scientist’s dilemma (by allusion to
Joseph Heller’s novel ‘Catch 22’).

Threats to epistemological validity are also posed by the greatly reduced investment in
dairy research, which diminishes the chances of replication and testing of theories
between laboratories. The nature of the research projects, often employing large,
commercially valuable animals, exacerbates this problem. By contrast, research
primarily related to mammary carcinogenesis seems not to suffer to such an extent, both
by virtue of the numbers of researchers in the field and for methodological reasons.

Ethical validity

The necessity for exploring ethical matters stems from the fact that the implications of
intuitive beliefs about ‘rightful actions’ need constant reappraisal as social and physical
environments change. Ethical issues are considered under three headings: (1) animal
welfare; (2) human welfare, at both individual and societal levels; (3) ‘cultural’
implications.
1. Animal experimentation. This is a prominent concern for many physiologists. The usual justification is utilitarian, i.e., the belief that benefits for people and other animals outweigh a degree of animal suffering. Contrasting views are expressed by Clark (1984), Frey (1983), Fox (1986) and Paton (1984). The issues are too complex to address here, but clearly, wherever the line is drawn, the objective should be to reduce animal suffering and maximize potential gains from experiments. Many experiments on lactation may be exempt from most criticism because they would be invalidated by the factor of concern, stress.

New issues potentially affecting animal welfare are those due to novel biotechnological procedures. For example, endocrine treatment of dairy animals to enhance yields might pose health problems not evident in the short term or under ideal conditions on experimental farms. The consequences of misuse, intentional or unintentional, as much as other considerations, compels ethical evaluation of such technologies. Rollin (1986) has discussed ethical matters relating to transgenic animals: concern must be focused on the dangers of implementing radical changes too rapidly.

2. Human welfare. Since science is ‘permeated with valuational presuppositions’ (Rollin, 1986), it is not difficult to identify its intended beneficiaries. Privately financed research is pursued to increase private profits and this will not necessarily have much to do with social need. Even with publicly financed research there is a marked tendency for the ‘hi-tech’ ethos of science to generate technological advances only exploitable by already highly sophisticated practitioners. Frequently it is claimed that such research increases efficiency, a concept most usually interpreted in monetary terms. But ‘efficiency’ can be defined in many ways (Spedding et al. 1981), and short-term financial gain is not necessarily the best. It is certainly not obvious that the technological innovations predicted to reduce by 51% the number of US dairy farms by the year 2000 (Mix, 1987) are an unalloyed blessing.

The view that research should be aimed at increasing public good rather than private gain attains unequivocal ethical validity in relation to the 500 million people in less-developed countries (LDCs) suffering severe malnutrition (World Commission on Environment and Development, 1987) as well as many more suffering slightly lesser privation. The situation is sure to deteriorate because most population growth will be in LDCs (for example, Blaxter, 1987). Advances in dairy research could make a valuable contribution to promoting nutritional and economic development in LDCs (Smith, 1985). The potential role of British research in this context has been identified by the Agricultural and Food Research Council (1985) when referring to ‘the contribution it could make to the developing world’ and emphasizing that ‘agricultural research is a valuable and relatively inexpensive form of aid’.

3. Cultural implications. This category refers to public acceptability of biotechnological innovations, several of which involve mammary physiology. ‘In the final analysis public money pays for science and ever-increasingly demands accountability. A failure . . . to clearly define moral issues growing out of (scientific) activity, and to deal with them, puts its very existence in peril’ (Rollin, 1986). The ethical approach is, thus, often the prudential approach.

There seems, in fact, no legitimate alternative to convincing the general public of the value of biotechnological innovations before their introduction, and this requires open debate on costs and benefits. As Cantley (1987) has pointed out ‘if there is “ignorant democracy”, control without understanding, there is danger not only to science and technology but to society itself’. Public education was the motive for the Royal Society’s recent campaign, launched with publication of The Public Understanding of Science (Royal Society, 1985). Scientists have a crucial role to play in this educative process, but
they will certainly not be credible in that capacity if their pronouncements are shrouded in vested interests. The wider concerns which the author believes should be an ingredient of the education of all applied biologists are discussed elsewhere (Mepham, 1987b).

**Coda**

Mammary physiology is relevant to a wide range of human concerns. Thus, breastfeeding is vital for survival and development of the vast majority of infants and, in global terms, is the most usual means of birth control; whereas breast-cancer is a common cause of female morbidity and mortality in many Western countries. Animal milk, consumed raw or in the form of various dairy products, is a significant dietary component for millions of people, and hence of major economic importance; while, more generally, through its role in animal growth, lactation subserves valuable aims, e.g., involving animal use in meat production, for draught power and in conservation programmes.

There must, however, be concern that the basis of the discipline which, despite its breadth, has remarkable coherence, is threatened by under-investment and by encroachment of commercial activity into studies at a fundamental level. Biotechnological advances hold promise for significant nutritional and economic development on a global scale. An ethical and prudential approach would ensure that they were appropriately employed to benefit those most in need.

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