Secher calls our analogy between antibodies and enzymes "not very appropriate" because "enzymes are homogenous and so multispecificity in substrate binding could not enhance their specificity . . .". Perhaps we were unclear in our paper. We were not trying to draw a functional analogy but were trying to indicate that all protein–ligand interactions rely on the same play of short range forces and geometry. Hence, if enzymes are multispecific, it should not be surprising to find that antibodies are also multispecific.

We should like to comment also on Secher's suggestion that the best antibodies (with binding constants of $10^9$–$10^7$ l mol$^{-1}$) may be highly specific (that is, not multispecific). From our point of view, this is not a logical conclusion. Whether a binding constant for a ligand is $10^9$ l mol$^{-1}$ or $10^6$ l mol$^{-1}$, the character of the binding site of the antibody is no different. It still should be able to accommodate other ligands and interact with them. Presumably the binding constant of a cross reaction could be even higher than that of the reaction with the immunogen.

We should like to thank Secher for reminding us of the early suggestions of Talmage[5]. We are embarrassed by our failure to cite his paper.

D. J. Cameron
B. F. Erlanger

*Department of Microbiology, Columbia University, New York, New York 10032*

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SECHER REPLIES – Enzymes (and antibodies) can bind ligands (antigens) other than the 'primary ligand'. Ligands with very similar chemical structure may bind almost as tightly as the main ligand and one might expect to find a series of compounds of decreasing association constant and decreasing chemical similarity to the primary ligand. The concept of multispecificity (as used by Inman for example) is different. It implies that two or more antigens of unrelated structure can bind specifically to a single antibody molecule. This could take place at distinct sites, overlapping sites, or the same site, but presumably will use different contacts between the antibody and the antigen.

The former phenomenon is well known for both enzymes and antibodies. However there are only a few claims of examples of multispecificity (in both systems), and even these are controversial.

With reference to the specific points that Cameron and Erlanger raise above. Binding of antigen is only one aspect of the biological significance of a cross-reaction. The ability to trigger lymphocytes into division and antibody production must also be considered, and also the extent to which such cross-reactions are representative of the total antibody population or are rare exceptions.

I agree that if "enzymes are multispecific then it should not be surprising to find that antibodies are also multispecific". To what extent these generalities have been demonstrated is still not clear (see above for definition of multispecificity).

The final sentence of my original article was intended to be taken as pure speculation and not as a logical conclusion.

Cross-reactions with binding (association) constant higher than that of the immunogen do indeed exist and have been named 'heteroclitic'[1].

(An error in my original article has been corrected[2]).

David S. Secher

*MRC Laboratory of Molecular Biology, Cambridge, UK*

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## Marsupial trophoblast and mammalian evolution

We present here a view of marsupial–eutherian origins and evolutionary trends, which constitutes an alternative to the view of Lillegraven[1,2] recently discussed by Cox in a *Nature News and Views* article[3].

The trophoblast constitutes the outer foetal boundary of the eutherian chorioallantoic placenta where it functions as the major foetal component of the placental barrier as well as a site of endocrine activity. The trophoblast is also a foetal component of the eutherian yolk sac placenta. In most marsupials, maternal–foetal transfers occur solely through a yolk sac placenta where trophoblast associates with both vascular and avascular regions. An important exception occurs in the marsupial bandicoots where both yolk sac and chorioallanotoic placentae develop; trophoblast differs in form regionally within the boundaries of each type of placenta[4–6].

The trophoblastic layer persists until term in the chorioallantoic placenta of all mammals except bandicoots, in which the layer disappears shortly before term[4–6]. Lillegraven, however, states (page 713, ref. 2) that "trophoblast is strictly found only in placental mammals," thus misquoting his authorities, Davies and Hesseldahl, who say that trophoblast is a peculiar mammalian structure. Lillegraven (page 720, ref. 2) states further that "The 'invention' of trophoblastic tissues by primaeval eutherians was probably the single most important evolutionary event in the history of the infraclass". This has led to the mistaken conclusion that it is the evolution of trophoblast which enables only Eutheria to obviate immunological crisis during pregnancy[2,3].

Lillegraven says (page 101, ref. 1) that " . . . true implantation by erosion of the maternal epithelium never occurs in marsupials". It has long been known that in the bandicoot chorioallantoic placenta trophoblast disappears as a layer late in gestation[4–6], probably through fusion with the uterine luminal epithelium[6]. Comparable fusion may also occur during early implantation of certain Eutheria[6]. Similar, less extensive invasion of uterine epithelium by trophoblastic cells occurs at the yolk sac placenta in several marsupials (such as in *Dasyurus viverrinus* and *Sminthopsis crassicaudata*), the uterine epithelial layer becoming modified at the placental site by interaction of foetal and maternal tissues during implantation.

Thus, evidence concerning trophoblast and uterine erosion tends to unite rather than separate evolutionary aspects of eutherian and marsupial placentation. Although it is not known whether marsupial trophoblast contains immunological or endocrine properties comparable with those proposed for eutherian trophoblast[7], attention is being focused on this important problem[8]. Because trophoblast is certainly not a eutherian innovation, the argument for the "competitive inferiority" of marsupials is considerably weakened, as Kirsch[9], on other grounds, has also concluded.

J. Mary Taylor

*Department of Zoology, The University of British Columbia, Vancouver, British Columbia, V6T 1W5, Canada*

Helen A. Padykula

*Laboratory of Electron Microscopy, Wellesley College, Wellesley, Massachusetts 02181*

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