phosphorylated after forskolin treatment. EP3C has only one Ser and does not conform to the PKA consensus sequence. Thus the work by Namba *et al.*³ may provide insights into the mechanisms of negative, as well as positive, regulation of G-protein-coupled receptors.

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Water in life

SIR — Segel and Tyson in Correspondence¹ tried to defend Maddox's assertion² that molecular biology lacks a quantitative dimension. Maddox then went on to discuss³ an example of an attempt to redress the balance in describing a quantification of the hydration of glucose⁴.

In describing the interaction of glucose and water, the assumption in classical biochemistry has been that metabolically active glucose is free within the pathways of the cell and that water is just 'ordinary' free water⁵⁻⁷. When a calculable theory is available, quantitative considerations fall easily into place, that of classical biochemistry being the law of mass action.

Maddox's suggestion in the first of his two articles mentioned above² was to resurrect the law of mass action, but the past 20 years have shown that this may apply only following cataclysmic cell disruption to yield aqueous solutions *in vitro*⁸, and is generally inappropriate to the interior of the cell *in vivo*. It is because no adequate or simple alternative has been found that molecular biology languishes in its role as a descriptive discipline.

Maddox's second article on this topic³ finished with the words "real water". The problem of describing the physical state of water is extremely complex⁷, and as yet no calculable theory exists with which to begin to consider water's interactions with other molecules. Albert Szent-Györgyi himself said⁹ that "life is water dancing to the tune of the solids".

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Death and c-fos

SIR — Smeyne *et al.*¹ suggest that continuous expression of *c-fos* precedes programmed cell death (apoptosis) *in vivo*. They do not show, however, that *fos-lacZ* is expressed in the specific cells that go on to die *in vivo* and the developmental examples they choose do not exclude other explanations for *c-fos* expression.

First, their tooth example (Fig. 1d of ref. 1) discusses and illustrates the so-called enamel knot. But the structure expressing the *lacZ* marker they show is not the enamel knot but the dental papilla mesenchyme. The enamel knot is a transitory structure present at the late cap stage of development within the enamel organ². The *fos-lacZ* labelled cells of the dental papilla mesenchyme do not normally undergo programmed cell death, but differentiate into the cells that will form dentine (odontoblasts) and the adult dental pulp.

Their second example is the midline epithelium of the secondary palate¹. Medial edge epithelial cells of the palate, however, do not die, but rather migrate³; indeed, the reference quoted by Smeyne *et al.*¹ makes this very point⁴. Further, the *c-fos* expression patterns in the palate are not consistent with *c-fos* expression preceding programmed cell death. For many years, it has been known that the biochemical changes which precede medial edge epithelial cell differentiation (death?) occur about 24 hours before the event (see ref. 5 for review). However, Smeyne *et al.*¹ illustrate *c-fos* expression only where the medial edge epithelia touch and fuse to form a midline epithelial seam (their Fig. 1e). Where the medial edge epithelia are not in contact (Fig. 1f) there is no *c-fos* expression. However, these events are separated by only a few hours. If *c-fos* is a harbinger of death, one would expect to see the expression about 24 hours previously.

Interestingly, these patterns of *fos-lacZ* expression in the developing tooth and palate¹ resemble those of various cytokines, particularly transforming growth factor- β family members^{6,7}. In the palate, transient expression of transforming growth factor β 3 in the medial edge epithelia⁶ matches closely that reported by Smeyne *et al.* for *fos-lacZ*. Prolonged *c-fos* expression in development may therefore correlate better with cytokine signalling at sites of cellular interactions

than with imminent programmed cell death.

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MORGAN AND CURRAN REPLY — Ferguson suggests that we do not show that cells expressing *fos-lacZ* go on to die *in vivo*. But Fig. 2 of our paper shows *fos-lacZ* staining in the cytoplasm and remnants of hippocampal neurons following treatment with the neurotoxin kainic acid. We cited several examples of the association between *fos-lacZ* expression and cell death *in vivo*, but not that the *fos-lacZ*-positive cells went on to die in all cases. We had to remove an additional figure demonstrating further examples of the association because of *Nature's* space constraints. We did not wish to imply that *fos-lacZ* expression occurs exclusively in dying cells; indeed, we have previously documented *c-fos* expression in proliferating and differentiating cell populations.

Ferguson further suggests that the developmental examples we chose are problematic. Unfortunately, for reasons of space we had to delete data on *fos-lacZ* expression in the periderm, interdigital web cells and hypertrophic chondrocytes; all circumstances in which developmentally programmed cell death is documented. Expression of *fos-lacZ* in the medial edge epithelium of the palate is indeed a complex phenomenon, and our discussion of this point was also curtailed for the sake of brevity. It is certainly of great interest to determine the fate of *fos-lacZ*-positive cells in this structure.

Regarding *fos-lacZ* expression in the developing tooth, we have published a correction¹ about our misidentification of the enamel knot. We thank A. Lumsden and I. Thesleff for bringing this to our attention, and apologise again for any confusion this may have caused.

The association of *fos-lacZ* expression with TGF β family members was also omitted from our paper for space reasons, and is mentioned in ref. 8. Ferguson may wish to consider the possibility we are now investigating, that cytokines such as TGF β may actually contribute to cell death.

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Scientific Correspondence

Scientific Correspondence is intended to provide a forum in which readers may raise points of a scientific character. They need not arise out of anything published in *Nature*. In any case, priority will be given to letters of fewer than 500 words and five references.

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