Amphibian regeneration and cellular heterochrony

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Abstract. It is posited that the initiating event of amphibian regeneration of a limb, is 'retrodifferentiation' of what are to become the developing cells of the blastema. These cells reiterate a larval or premetamorphic ontogenic repertoire, induced by elevated levels of prolactin with adequate innervation. Subsequent redifferentiation of the blastema cells occurs, controlled by thyroxine and innervation.

This temporal displacement of cellular morphologic characters in regeneration should be looked upon as a function of the ability to reiterate larval characters and subsequently metamorphose. If correct, this would explain why amphibians which metamorphose only once, lose the ability to postmetamorphically regenerate. An exception to this, *Xenopus laevis*, an anuran which can epimorphically regenerate, to some extent, will be discussed.

1. Introduction

The pioneering work of Schotté (1926) established that hypophysectomized adult newts were unable to regenerate amputated limbs. He also showed that hypophysectomy did not effect regeneration in larval newts. Schotté's career, to a large extent, was spent in the search for a 'regeneration hormone' (Liversage, personal communication). It is curious that after researching the influence of the pituitary in amphibian regeneration, Schotté failed to show interest in prolactin. A possible explanation is that prolactin's role in urodele metamorphosis was not shown conclusively until 1973 (Gona et al.); very near the end of Schotté's career. Even so, as early as 1958, Niwelinski showed that prolactin restored regeneration in adult hypophysectomized newts. Waterman (1965) achieved similar results, and it has recently been confirmed by a number of investigators (Tassava, 1979; Maier, 1981; Stewart, 1981). What has been lacking, to date, is a theory as to the role of endogenous prolactin in amphibian regeneration.

2. Cellular heterochrony and second metamorphosis in urodeles

The term 'heterochrony' was introduced by Haeckel, but as Gould (1977) points out, by transmutation, de Beer's redefinition of the word has been adopted to illustrate parallels between the phylogeny and the ontogeny of organisms. The term 'cellular heterochrony' has been coined (Pearson, 1981)

*Uriel's term, 'retrodifferentiation' (1979) will be used throughout, instead of 'dedifferentiation' which appears most commonly in the literature on regeneration.
to illustrate, by analogy, similarities in the modes of speciation between the heterochronic evolution of organisms, and the changes witnessed in individual cells which revert to juvenile phenotypes.

**Prolactin and thyroxine**

In the larval and metamorphosing stages in the life cycle of amphibians, thyroxine and prolactin act in a competitive synergism. Prolactin acts to juvenilize tissues, while thyroxine induces metamorphosis, stimulating adult traits in anurans and urodeles. In urodeles which undergo a 'second' metamorphosis, prolactin stimulates regrowth of the tail fin, the return of smoother mucoid skin, and causes the behavioural return of the 'water drive' (Gona et al., 1973). Prolactin, then, is responsible for the initial cellular heterochronic, or larval morphologic changes in features. Increasing levels of thyroxine complete the process, heralding the onset of second metamorphosis with subsequent stimulation and reappearance of adult structures.

3. Regeneration, cancer and cellular heterochrony

Uriel (1979a) has reported that the cells of regenerating rat liver 'retrodifferentiate', taking on 'juvenile' patterns of antigenic and genetic behaviour. This retrodifferentiation is followed by a process of 'redifferentiation' to normal tissue type. Interestingly enough, he notes that neoplastic liver cells undergo retrodifferentiation, but fail to redifferentiate and continue in a pattern of juvenile-like transition.

*Anaplasia*

'Anaplasia', the term created by von Hansemann (1892), is now recognized to be a widespread, if not universal lineament in a tumour's evolution to malignancy.

A number of studies have attempted to relate cancer to thyroid gland hypofunction, by showing a higher incidence in hypothyroidism and a lower incidence in euthyroid and hyperthyroid states. This evidence prompted an early investigator to comment that... the less tendency to cancer formation' (Loeser, 1954). It has long been suspected that prolactin plays an important role in the etiology of one form of cancer (mammary tumourigenesis) (Welsch et al. 1977). The author has hypothesized that the hormones which render amphibians pre-metamorphic (return of juvenile characteristics by prolactin) — and metamorphic (loss of these juvenile characteristics due to thyroxine), are also responsible for triggering timing changes (cellular heterochrony) in cells and tissues of other metazoans (Pearson, 1982). This hypothesis would explain both regeneration (retrodifferentiation → redifferentiation) and malignancy (retrodifferentiation) and possibly even the reversal of malignancy (retro-