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Xenopus helveticus, an Endangered Species?

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The British Connection

From the *Xenopus* history in the *"Developmental Biology in Britain"* issue of this journal (Gurdon and Hopwood, 2000), we learned that *Xenopus* is a child of the British Empire, its introduction into the laboratory and much of the early work on *Xenopus* development having been achieved in Britain. I do not intend to contest this claim or to redraw the early history of *Xenopus* that has been amply reviewed in that article. I simply try to add another episode to the *Xenopus* tale; namely the abduction and exploitation of this British child in a foreign country, on this occasion Switzerland.

Among the scientists conducting early *Xenopus* studies in Britain were two exiled Swiss researchers, Michail Fischberg and Max Birnstiel. Fischberg studied zoology in the institute of Ernst Hadorn in Zurich accomplishing his Ph.D. thesis on heteroploidy in *Triturus*. After successive moves to Basel and Edinburgh, he eventually became a lecturer at Oxford, where he stayed from 1951 through 1961 (Gloor and Gurdon, 1989; Gurdon and Hopwood, 2000). The generation of adult *Xenopus* from transplanted somatic cell nuclei (Gurdon *et al.,* 1958) and the discovery of the anucleolate *(O-nu)* mutant (Elsdale *et al.,* 1958) were the leading features of this lab that, last but not least, also produced a number of renowned British scientists.

Max Birnstiel, a Zurich-grown botanist interested in plant cell nuclei and nucleoli and student of Albert Frey-Wyssling, acquired novel techniques, in particular hybridisation of nucleic acids, during his post-doc stay in Pasadena, USA. At Edinburgh he met Hugh Wallace who had brought along a small colony of *O-nu* mutants from Fischberg's Oxford lab (Gurdon and Hopwood, 2000). They decided to study the nucleolar organiser. During this enterprise they could show that the *O-nu* mutant lacks ribosomal genes and could identify the nucleolar organiser as rDNA locus (Wallace and Birnstiel, 1966; Birnstiel *et al.,* 1966). What's more, by running CsCl gradients in an analytical Model E centrifuge, they isolated the first eukaryotic genes, the *Xenopus* genes coding for ribosomal RNA (Birnstiel, 1967; Birnstiel *et al.,* 1968).

The Swiss Origin

Although the two Swiss mercenaries eventually left Britain for home, each with a flock of English or Scottish post-docs, and their trunks full of whiskey and *Xenopus*, this was not the first implantation of *Xenopus* into a Swiss laboratory. Oddly enough, neither was it the laboratory of Ernst Hadorn in Zurich who introduced *Xenopus* to Swiss research. Hadorn initially worked on developmental aspects in *Triturus* but soon abandoned this topic and entirely focused on *Drosophila* (Weber, 1994).

As far as I know, the first Swiss *Xenopus* colony dwelled already in the early forties in the laboratory of Paul Gasche at the CIBA pharmaceutical company in Basel. Gasche's lab was involved in optimising pregnancy testing and to this end raised *Xenopus* in the

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laboratory (Gasche, 1943). It was from his lab that the first colony reached a Swiss university. The group of Fritz Lehmann in Bern decided to study tail regeneration in *Xenopus* tadpoles and, around 1950, fetched a few individuals from Gasche's colony. Rudolf Weber, a research associate in the lab, extended the initially planned studies on biochemical changes in the regenerating tadpole tail to the metamorphosing tail, allowing the role of cathepsins to be studied during growth as well as resorption. This lucky decision, taken to Lehmann's dismay, ineluctably led to investigations on hormone changes, hormone receptors and finally, hormone-mediated activation of target genes.

The arrival, in 1961, of Michail Fischberg and his English collaborators at Geneva considerably reinforced Swiss *Xenopus* developmental biology. The Station de Zoologie expérimentale, a research institute of the University of Geneva built with the help of the Rockefeller Foundation, became equipped with vast facilities for raising and maintaining the several species and subspecies of the *Xenopus* collection brought along from Oxford (listed in Balls, 1965). Initially, the main research carried out in Geneva was a continuation of work initiated at Oxford and was devoted to nuclear and germ cell transplantation. Ongoing studies on a putative lymphoid tumour eventually gave rise to the study of *Xenopus* immunology. On the other hand, Fischberg's traditional interest in polyploidy led to the study of DNA content and karyotypes of various *Xenopus* species and finally to the discovery of *Xenopus* speciation by allopolyploidy. This work greatly profited from the concourse of Hansrudolf Kobel from the nearby Genetics unit.

In 1971, *Xenopus* research at the Station de Zoologie expérimentale was reinforced by the arrival of Marco Crippa directing the new Molecular Embryology unit, working on molecular aspects of transcription.

Max Birnstiel, accompanied by his Scottish guard, moved to Zurich in the Fall of 1972 as director of the newly founded Molecular Biology unit II, second only by chronological numbering to Molecular Biology I run by Charles Weissmann. Introducing molecular biology to the University of Zurich was an initiative Ernst Hadorn took shortly before his retirement. The high-class barracks provisionally occupied at the veterinary clinic at Irchel (nowadays the main university campus) soon hummed with the sound of spinning centrifuges producing ever cleaner fractions of - sea urchin - histone genes. However, *Xenopus* remained the main research object of the Birnstiel lab. In addition to the genes coding for ribosomal 18S and 28S RNA, also those coding for 5S rRNA and tRNA were isolated and cloned in the mid seventies. Indeed, these sea urchin and frog genes were amongst the first eukaryotic genes to be cloned. To analyse the functioning of these various genes, the lab resolutely turned to the study of gene structure-function relationships. Injection of DNA into the *Xenopus* oocyte became a standard technique of this 'surrogate genetics' approach.

Disciples and Newcomers

None of the early *Xenopus* laboratory heads is active any longer in Switzerland. The first to leave, rather precipitously, was Crippa in 1984. In 1986, Birnstiel chose to move to Vienna where he founded the Institute of Molecular Pathology with cancer research interests. His ex-institute in Zurich was taken over by Walter Schaffner who only occasionally works with *Xenopus*. When Fischberg died in 1988 the pending projects were abandoned. His chair was attributed to the newly founded Department of Cell Biology and was occupied by Didier Picard, a former student in the 'no-toads' wing of the Birnstiel lab. Weber retired in 1988 and his successor, Daniel Schümperli, a former research associate in the Birnstiel group, just uses the *Xenopus* oocyte system for functional testing.

However, several of the post-docs and research associates of the early *Xenopus* labs remained faithful to *Xenopus* at least for a while after taking over their own groups abroad or in Switzerland. Several former members of the labs, if they had got in touch with *Xenopus* at all, sooner or later turned to different model systems. Among them we find some rather illustrious people and it would seem that reasonable work could be done with organisms other than *Xenopus*. On the other side, numerous new research groups transitorily or permanently joined the Swiss *Xenopus* clan.

Though two of the early *Xenopus* labs initially investigated mechanisms of development, they both left the purely embryological field. Weber's group very soon addressed molecular aspects of gene regulation but kept doing so on developmentally relevant genes. Fischberg's group gradually focused on topics as diverse as immunology, speciation and evolution. The Birnstiel and Crippa labs concentrated from the beginning on molecular aspects of transcription, mainly of housekeeping genes of which several happened to be isolated from *Xenopus* but had little bearing on its development. Nothing much has changed over the years. Swiss *Xenopus* was to remain a heavily exploited 'au pair girl' employed if, and as long as it seemed suitable. At present, many groups exclusively maintain *Xenopus* to exploit the oocyte system for functional studies of expressed proteins, a topic so remote from 'genuine' *Xenopus* research as not to be mentioned at the 'International *Xenopus* Conference'.

However, it is often claimed that developmental biology embraces all disciplines of biological sciences. In the hope that this broad view is shared by the readers of *The International Journal of Developmental Biology*, I am going to review the full array of the 50 years of *Xenopus* research in Switzerland, or at least try to do so. The limited space does not allow this review to be extended to related work done outside our country, but this by no means reflects an underestimation of our foreign friends and competitors.

Xenopus Studies

Development

The question of whether nuclei of embryonic and adult cells remain capable of directing normal development, a heritage of Fischberg's Oxford time (Fischberg *et al.,* 1958; Gurdon *et al.,* 1958), remained the domain of John Gurdon's group at Oxford, but was not completely abandoned by the Geneva lab either. The intriguing question of whether malformations observed upon nuclear transfer and their 'clonal' occurrence in serial transplantation reflected systematic somatic mutations, or simply were a consequence of manipulation, or of incomplete replication of the donor nucleus, was the object of several studies (Fischberg and Blackler, 1963a,b). The production of viable frogs by transplanting nuclei from visibly differentiated cells (Gurdon and Uehlinger, 1966; Brun and Kobel, 1972; Kobel *et al.,* 1973; Wabl *et al.,* 1975) shifted the question to whether such cloned individuals were indeed fully fertile. This topic is still sometimes discussed by elderly biologists at the hotel bar.

Germ cell transplantation, initiated at Oxford, permitted the identification of the presence of germ cell precursors at the neurula stage, and demonstrated their capacity to differentiate according to the sex of the host (Blackler, 1962, 1965). For the nuclear transplantation studies, the *O-nu* mutant from Oxford (Elsdale *et al.,* 1958) and, later, the mutation for periodic albinism, a^p, isolated in Moscow (Hoperskaya, 1975) were used as markers. In addition, a highly reliable transplantation marker was devised, based on differential nuclear staining by banding techniques of *X. laevis* and *borealis* cells (Fig. 1; Thiébaud, 1983) and was used to follow neural crest development and cell migration (Sadaghiani and Thiébaud, 1987).

The interest in germ cells also incited studies on oocyte maturation culminating in the description of an autocatalytic maturation promoting factor (Drury and Schorderet-Slatkine, 1975) and extensive characterisation of hormone action and interfering drugs (Schorderet-Slatkine *et al.,* 1976, 1978, 1982). Sabine Schorderet-Slatkine eventually moved to the 'Maternité' and appropriately switched to mammalian oocyte maturation.

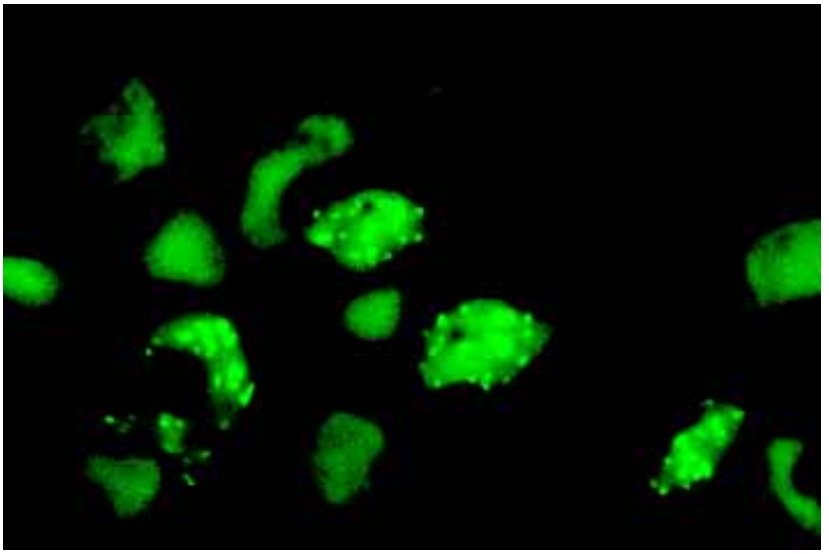

Fig. 1. Transplantation marker. *Squash of a stage 32* X. laevis *embryo having been injected at stage 9 into the blastocoele with* X. borealis *cells. Individual donor cells can easily be distinguished by their patchy staining pattern evoked by Q banding techniques. Courtesy of C.H. Thiébaud, Geneva.*

Rudolf Weber had introduced *Xenopus* into the lab in Bern in search of a suitable model system to monitor biochemical changes in the regenerating tadpole tail. However, the first publications to appear dealt with the ultrastructure of *Xenopus* liver and its mitochondria (Weber, 1952, 1954). Studies on enzyme activities in the regenerating tail, initially cathepsin (Jensen *et al.,* 1956; Weber, 1957), were completed by characterising changes in several other enzymes and also during metamorphosis. The lab then tried to induce metamorphic changes in isolated tails *in vitro* (Weber, 1962). This model system allowed for extensive studies of the mechanism of metamorphosis (Weber, 1967) and opened the way to study hormone action (Weber, 1970). The logical continuation was to assess changes in RNA synthesis occurring in various metamorphosing tissues. Unreliable gene activation by thyroxin nearly brought this project to a dead end until Gerhart Ryffel, a Ph.D. student in the lab, suggested trying oestrogen instead. This made it possible to analyse and functionally characterise the vitellogenin gene family regulated by this hormone (Ryffel *et al.,* 1977, 1980; Wahli *et al.,* 1980, 1981; Wahli and Ryffel, 1985).

The topic of hormone-regulated gene expression represented for years to come the main axis of research of Walter Wahli and his new laboratory at the University of Lausanne. Oestrogen-responsive elements were identified in the vitellogenin promoter (reviewed by Wahli, 1988) and their function extensively characterised by transcription assays *in vitro*, in the oocyte system, and after transfer into cultured cells (Martinez *et al.,* 1987; Corthésy *et al.,* 1988, 1990a,b; Green *et al.,* 1988; Theulaz *et al.,* 1988; Martinez and Wahli, 1989; Schild *et al.,* 1993). The discovery of a novel family of nuclear hormone receptors in liver cells, PPAR, the peroxisome proliferator activated receptors (Dreyer *et al.,* 1992), opened a new field of research tackling fatty acid metabolism in *Xenopus* and was later extended to mouse and man (Krey *et al.,* 1993; Devchand *et al.,* 1999).

Gerhard Ryffel left Bern for Karlsruhe, then Essen, where he continued to study the expression and regulation of liver-specific transcription factors, in particular HNF1 and its cofactors (Bartkowski *et al.,* 1993; Pogge von Strandmann and Ryffel, 1995; Holewa *et al.,* 1997; Ryffel and Lingott, 2000).

Taking advantage of improved methods to isolate RNA from liver (Schibler and Weber, 1974), the Weber group had also isolated the *Xenopus* albumin genes that are transcriptionally repressed by oestrogen (May *et al.,* 1982, 1983). Moreover, attracted by the observed haemoglobin transition at metamorphosis (Just *et al.,* 1980), the lab took up studies on the globin gene family of *Xenopus*. Larval and adult genes of this family were cloned (Hosbach *et al.,* 1983), and their structure and expression characterised (Sandmeier *et al.,* 1986). Discovery in Geneva of a third, embryonic haemoglobin variant (Kobel and Wolff, 1983) completed the documentation of the haemoglobin transitions between embryonic, larval, and adult *Xenopus* (Weber, 1996).

Establishing an embryonic cDNA library to monitor expression of transcribed repetitive sequence elements (Spohr *et al.,* 1981; Reith and Spohr, 1984; Kloc *et al.,* 1993), Georges Spohr from the former Crippa lab also isolated a sarcomeric actin gene (Stutz and Spohr, 1986). He recently resumed studies on muscle development during *Xenopus* embryogenesis by analysing the expression and function of the *Id* gene (Zhang *et al.,* 1995; Afouda *et al.,* 1999).

The group of André Brändli in Zurich is the most recent addition to the *Xenopus* labs in Switzerland and, what's more, is addressing questions relating to development. Brändli first got in touch with *Xenopus* as a student attending a practical embryology course given by Eddy De Robertis during his stay in Basel. After a post-doctoral stay in Marc Kirschners lab at the UC San Francisco and at Harvard Medical School, André Brändli transferred his research on *Xenopus* tyrosine kinases (Brändli and Kirschner, 1995) to his new lab at the ETH Zurich, focusing on the role of the receptor tyrosine kinase EphB4 and ephrin-B ligands in controlling angiogenic growth of embryonic veins in *Xenopus* (Helbling *et al.,* 2000). Pronephric kidney formation is controlled by *Pax* genes and the contribution by Pax-2 and Pax-8 and their isoforms is presently being sorted out (Brändli, 1999).

Fig. 2. *Xenopus* is an African child after all. *African women from Cameroon to Zaire know places where* Xenopus *may be found because they use it as a medicine* "to conceive, or to have strong babies". *Only in East Africa,* Xenopus *is occasionally consumed as regular food, sun-dried and well cooked to eliminate part of the toxins in its skin. The toad may be found in surprisingly small puddles, loves waters stinking of cyanide in ponds used for soaking Manioc tubercles, may stick its head through the foamy surface of a laundry pool, but also lives in decently clear ponds and river arms, as long as there is no current.*

While in Basel, De Robertis got even Walter Gehring to touch a *Xenopus*. Eddy de Robertis and his collegues cloned a *Xenopus laevis* gene containing a region homologous to the *Drosophila* homeobox (Carrasco *et al.,* 1984; Shepherd *et al.,* 1984) thus providing the first evidence that homeotic genes exist in vertebrates.

Xenopus also has a brain so some groups investigated cells of the central nervous system. Cell biological investigations documented the role of microtubules in neuronal cell shaping (Matus, 1990) and differential phosphorylation of microtubule-associated proteins in the central nervous system (Viereck and Matus, 1990). The peculiar occurrence of keratin and desmosomes in optic nerve astrocytes (Rungger-Brändle *et al.,* 1989) was later exploited as histochemical markers to follow the behaviour of astrocytes during regeneration of the optic nerve in *Xenopus* tadpoles (Rungger-Brändle *et al.,* 1995).

In spite of extensive oocyte microinjection activity, no systematic studies of the effect of ectopic overexpression of genes in the embryo were carried out in our country. As we will see later, if genes were injected into the zygote it was to analyse DNA replication or promoter - enhancer function in the embryo. Nevertheless, a first demonstration that a foreign gene injected into the zygote was correctly transcribed and the mRNA correctly spliced in the embryo was done in Zurich using the genomic rabbit *β-globin* gene (Rusconi and Schaffner, 1981). Injection of methylated promoter sequences and of genes coding for transcription factors into zygotes permitted to reveal the existence of a passive demethylation mechanism depending on both binding of transcription factor and DNA replication (Matsuo *et al.,* 1998). A technical improvement of antisense inhibition of gene expression consists in injecting into the zygote a vector read by RNA polymerase III that codes for antisense RNA. This tool was used to verify the role of the homeotic gene *Xhox1a* (Nichols *et al.,* 1995).

Cancer and Immunology

Xenopus immunology has been intensely investigated in Geneva and Basel. Among the Oxford collaborators of Fischberg was Michael Balls who continued his studies on spontaneous and transplanted *Xenopus* tumours in Geneva (Balls, 1962a,b, 1964, 1965; Rubens and Balls, 1964). No viral agent could be detected nor cell lines be established from this putative 'lymphosarcoma'. In fact, the tumour was, either from the beginning or during subsequent transfers, contaminated and superseded by mycoplasmic infection (Asfari, 1988; Asfari and Thiébaud, 1988). Be this as it may, four thymic tumours were found in three different *Xenopus* strains bred in Basel. From these tumours, T-cell lines could be established (Du Pasquier and Robert, 1992; Robert *et al.,* 1994).

Attempting to isolate the infectious agent of the Oxford-Geneva 'lymphoid tumour' Irandokht Hadji-Azimi in the Fischberg lab analysed serum proteins of affected animals (Hadji-Azimi, 1969, 1973) and subsequently reoriented her research toward lymphoid cells and immunoglobulins (Hadji Azimi, 1979; Hadji Azimi *et al.,* 1987, 1990).

Louis Du Pasquier at the Basel Institute of Immunology wondered why amphibian larvae, in spite of a very low number of lymphocytes, display specific immunological responses. The study was initially undertaken on *Rana catesbiana* but, in view of the impossibility to satisfactorily maintain this species, the lab switched to *Xenopus* in 1971 and started to establish genetically defined strains. Having discovered that *Xenopus* tadpoles produce a rather homogeneous population of low affinity antibodies, it was no longer necessary to postulate pluripotentiality of the lymphocytes (Du Pasquier and Wabl, 1977; Du Pasquier, 1982). Yet, single *Xenopus* lymphocytes may be temporarily double producers of two isotypes of immunoglobulin (Hadji-Azimi and Parinello, 1978).

Production of isogenetic clones through gynogenesis, fertilising diploid eggs spawned by interspecies hybrids with irradiated sperm (Kobel and Du Pasquier, 1975), proved extremely useful for immunological studies. Advantage was also taken of the polyploid nature of several *Xenopus* species to study the fate of duplicated, immunologically relevant genes (Kobel and Du Pasquier, 1986).

The still ongoing immunological studies of the Du Pasquier group deal with antibody repertoire, somatic mutation, and maturation of the immune response (Du Pasquier, 1982; Wilson *et al.,* 1992).

Moreover, they characterised MHC complexes at the molecular and functional level (Du Pasquier *et al.,* 1975; Flajnik and Du Pasquier, 1988), a novel type of non-MHC-linked class I genes (Flajnik *et al.,* 1993) as well as CTX, a new type of signalling molecule involved in thymic selection (Chrétien *et al.,* 1996) and prototype of a protein family now found to be highly conserved throughout the vertebrates (Du Pasquier *et al.,* 1999). Throughout this work, ontogenetic and evolutive aspects of the *Xenopus* immune system were evaluated (Du Pasquier and Wabl, 1977; Du Pasquier *et al.,* 1989, 2000; Schwager *et al.,* 1991).

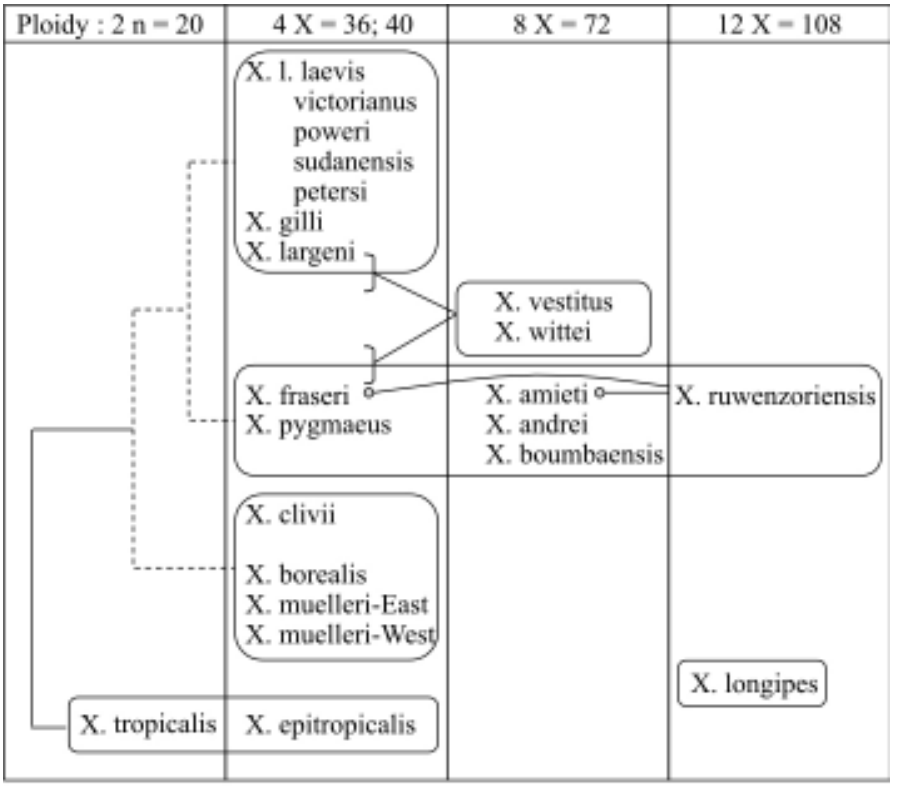

Fig. 3. The genus *Xenopus*. *Relationship of* Xenopus *species according to morphology, ploidy, and analysis of mitochondrial rDNA sequences. From Kobel* et al.*, 1998. With permission from Herpetological Journal.*

Xenopus *Genetics and Speciation*

Perhaps because Fischberg had studied polyploidy during his thesis project, or perhaps because several species and subspecies of *Xenopus* had been collected already at Oxford and been moved to Geneva, the Fischberg group always had a latent interest in aspects of speciation. Likewise, different species were hybridised (Blackler and Fischberg, 1968), and interspecific nuclear transplants (Gurdon, 1961) or transfer of germ cells between species (Blackler, 1962) were carried out in Oxford as well as in the early Geneva lab. Tonie Blackler pursued such studies also after having left Geneva for Ithaca, namely by transferring germ cells through the body of another species (Blackler and Gecking, 1972a,b).

As to *Xenopus* genetics, the phenotypes of spontaneous mutations appearing in the stocks were characterised to a certain degree (Droin, 1991). Three approaches to establish a genetic map of *Xenopus* were developed. Crossing of *X. laevis* subspecies allowed linkage groups to be followed (Graf, 1989). Alternatively, aneuploid *X. laevis* eggs were produced by fertilising, with *laevis* sperm, the aneuploid small eggs of triploid interspecies *laevis/gilli* hybrids. The resulting hypotriploid or hyperdiploid individuals, from which the non-pairing *gilli* chromosomes are randomly eliminated, again allow linkage groups or distinct loci to be assigned to a given chromosome (Kobel and Du Pasquier, 1979, Graf and Kobel, 1991). Finally, even single copy genes may be mapped by *in situ* hybridisation to metaphase *Xenopus* chromosomes (Courtet *et al.,* 2001).

Analysing *Xenopus* speciation included monitoring DNA content, karyotypes, chromosome banding and enzyme isoforms of various species (Thiébaud and Fischberg, 1977; Tymowska, 1991). To link the useful with the pleasant, numerous collecting trips to the "white spots" of the African *Xenopus* map, i.e., nearly the entire sub-Saharan continent, were organised (Fig. 2). Finally, all known and several new species and subspecies of *Xenopus* were assembled in the aquaria of Geneva and Basel.

The striking chromosome counts (20, 40 - 36, 72, 108) clearly reflect the pseudopolyploid nature of most *Xenopus* species. To this came suggestive observations in the wild, for instance the coexistence of two 36-chromosome species and one 72-chromosome species in one and the same little pond. Moreover, hybrid *Xenopus* females lay large, diploid eggs necessarily giving rise to polyploid hybrids. Numerous crosses in the lab, and verification in the wild confirmed the allopolyploid origin of the *Xenopus* species (Fig. 3; Kobel and Du Pasquier, 1986, Kobel, 1996; Kobel *et al.,* 1998).

Of the material collected over many years, all species (Kobel *et al.,* 1996), the *O-nu* mutant (Elsdale *et al.,* 1958) and the mutation for periodic albinism, a^p, (Hoperskaya, 1975) are maintained at the Geneva stock centre. The a^p albino strain that, probably due to extensive inbreeding, had developed a spectacular oedematous and else shaky constitution was out- and back-crossed. It now forms a vigorous and fertile population. Most often, the stock centre furnishes *O-nu* and a^p mutants, or the only diploid species, *X. tropicalis*, that offers certain advantages for genetic studies. For some time, common *X. laevis* was in demand. Indeed, during the international ban on South Africa the centre extensively 'laundered' *Xenopus* by transiting them to many foreign labs. All clonable hybrids, several partially inbred *X. laevis* strains, albino strains, and several species are kept in Basel.

The Geneva stock centre will cease to function within a few years. The Basel Institute of Immunology has been closed down and its *Xenopus* colony is presently being disbanded. Institutions willing to take over and grant the existence of consistent parts of these collections are kindly invited to manifest themselves.

The Oocyte

The *Xenopus* oocyte is most often named in conjunction with the word 'system' and this precious tool will be dealt with in a separate chapter. However, the oocyte as a cell is a splendid object for biological and molecular investigations.

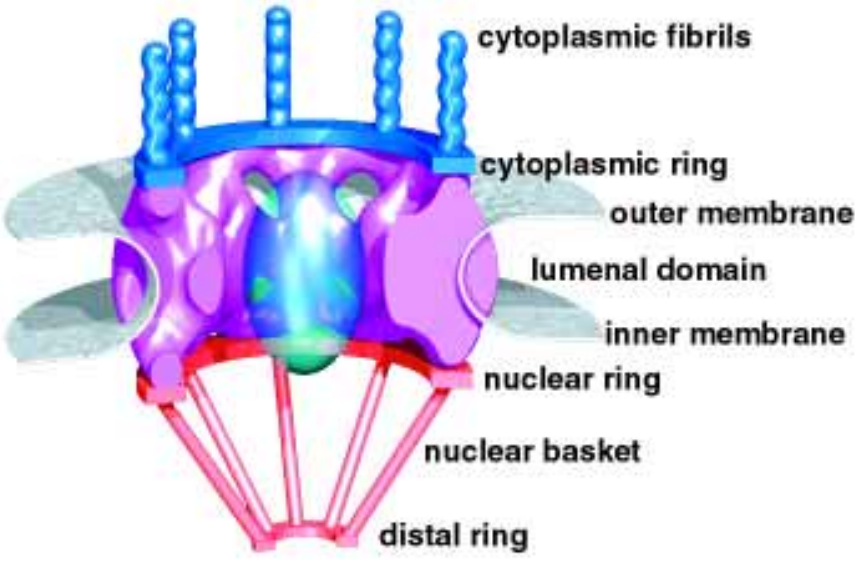

Fig. 4. The nuclear pore complex. *Recent model based on the work by Aebi and collaborators (for references, see text). Courtesy of Ueli Aebi, Basel.*

The Nucleolus

The nucleolus received intensive and long-lasting attention by several Swiss labs. As mentioned, the ribosomal genes of *Xenopus* were isolated in Edinburgh (Wallace and Birnstiel, 1966; Birnstiel, 1967). The structural analysis of the ribosomal cistrons (Birnstiel *et al.,* 1968, Loening *et al.,* 1969, Speirs and Birnstiel, 1974) still represented a main object of study in the early Zurich lab. In collaboration with Weber's lab in Bern, a final map of the ribosomal precursor was established (Schibler *et al.,* 1976).

Amplification of the ribosomal cistrons in *Xenopus* oocytes was extensively analysed (Perkowska *et al.,* 1968; Bird and Birnstiel, 1971; Bird *et al.,* 1973). A Swiss post-doc, Jean-David Rochaix, at that time in the lab of Joe Gall at Yale, showed that rDNA is amplified by rolling circles (Rochaix *et al.,* 1974).

Analysing the primary transcript of the ribosomal genes, the Crippa group in Geneva documented the occurrence of spacer transcripts that form individual small RNAs or may remain linked to the rRNA precursor (Rungger and Crippa, 1977; Rungger *et al.,* 1979a). Spacer transcripts could also be visualised by chromatin spreading (Rungger *et al.,* 1978) in collaboration with the group of Werner Franke at Heidelberg, Germany, who had described "prelude regions" earlier on (Franke *et al.,* 1976). The Birnstiel lab sequenced the ribosomal cistrons (Boseley *et al.,* 1979) and assessed the function of putative promoter elements and promoter-like sites within the spacer by functional testing in the *Xenopus* oocyte system (see below).

Chromatin

In the context of the ongoing discussion of nucleosomal superstructures, zigzag and superhelical arrangement (Thoma *et al.,* 1979), the group of Theo Koller in Zurich systematically carried out investigations on chromatin structure depending on the conditions applied during spreading. Such investigations were done also on active nucleolar chromatin of *Xenopus* (Labhart and Koller, 1982). Paul Labhart later joined the lab of Ron Reeder at Seattle, USA and continued to work on rDNA transcription (Labhart and Reeder, 1987). Another member of the chromatin group, Jose Sogo used, besides many other systems, also *Xenopus* cells, embryos and oocytes to study replication and replication fork barriers (Lucchini and Sogo, 1992; Lucas *et al.,* 2000). Formation of pre-replication centres in *Xenopus* egg extracts was described in Geneva (Adachi and Laemmli, 1994).

Metaphase Chromosome

The *Xenopus* oocyte was also exploited for studies on metaphase chromosome structure. Injection into the oocyte of antibodies directed against actin blocked the condensation of chromosomes during subsequent meiosis induced by the addition of progesterone (Rungger *et al.,* 1979b). By depleting histones from HeLa cell metaphase chromosomes, Uli Laemmli who arrived from Princeton to Geneva, had described the existence of the contractile chromosome scaffold with the DNA attached in loops along this skeleton (Paulson and Laemmli, 1977; Marsden and Laemmli, 1979). To analyse chromosome structure in more detail, he reconstituted chromosomes from DNA and protein fractions prepared from litres of *Xenopus* oocytes. Depleting certain components of these extracts by antibodies allowed identifying topoisomerase II as the main scaffold component granting condensation (Adachi *et al.,* 1991). In the course of this work, also a Ref-binding protein, B23, was isolated.

Nuclear Trafficking and the Nuclear Pore

Testing the function of the Ref/B23 complex hooked a post-doc in Laemmli's lab, Elisa Izaurralde, on nuclear import-export, a topic she thoroughly pursued by microinjection studies in the oocyte system through her personal shuttling between Geneva and Heidelberg (see e.g., Jarmolowski *et al.,* 1994; Schmitt *et al.,* 1999).

Microinjection into Xenopus oocytes had already been used by Eddy De Robertis in Basel to study nuclear import of the newly cloned Xenopus nucleoplasmin (Bürglin and De Robertis, 1987; Bürglin *et al.,* 1987). Iain Mattaj, yet another Scotsman and postdoctoral fellow at the Friedrich Miescher Institute at Basel, collaborated with Eddy's lab and got acquainted with oocyte injection (Mattaj *et al.,* 1983; Mattaj and De Robertis, 1985). He continued using this system after his moving to the EMBL at Heidelberg and produced impressive results on RNA processing and nuclear import export (Görlich and Mattaj, 1996, Izaurralde *et al.,* 1995). A recent achievement is the characterization of importin-exportin cycles and their regulation by RanGTP (Hetzer and Mattaj, 2000; Gruss *et al.,* 2001). The oocyte approach was also used by Erich Nigg during his Ph.D. studies in Zurich and in his later labs at Lausanne and Geneva to study nuclear trafficking (Borer *et al.,* 1989; Schmidt-Zachmann *et al.,* 1993). Functional tests in the *Xenopus* oocyte or egg extracts were still applied when Nigg's lab eventually got involved in studying components regulating the cell cycle (Blangy *et al.,* 1995; Dévault *et al.,* 1995; Descombes and Nigg, 1998).

The control gate of nuclear traffic, the nuclear pore complex, has been characterised in great detail by Ueli Aebi and coworkers

at the Basel Biocenter. Aebi met *Xenopus* for the first time at Johns Hopkins University, Baltimore USA, where he worked as an assistant professor. From Barbara Sollner-Web he learned to hand-isolate nuclei from stage 3-6 oocytes. The isolated nuclear envelopes crammed with nuclear pore complexes represented an ideal starting material for the painstaking study of the components that make up this elaborate structure (Aebi *et al.,* 1986; Reichelt *et al.,* 1990, Jarnik and Aebi, 1991; Panté and Aebi, 1993, 1996; Yokoyama *et al.,* 1995; Görlich *et al.,* 1996). Whereas several molecular components of the pore complex were identified in yeast (see e.g. Schlaich *et al.,* 1997), high resolution 3-D reconstruction of native pore complexes was again done on *Xenopus* germinal vesicle envelopes (see e.g. Fahrenkrog *et al.,* 2001). A recent model of the nuclear pore complex derived from such investigations is represented in Fig. 4.

The *Xenopus* Oocyte System

The discovery that messenger RNA injected into the oocyte cytoplasm is efficiently translated (Gurdon *et al.,* 1971) and DNA injected into the nucleus is faithfully transcribed and subsequently translated (Mertz and Gurdon, 1977) made the *Xenopus* oocyte an invaluable assay system. The 'Gurdon test tube' has been used for all sorts of applications all over the world and particularly so in Switzerland. Part of the early characterisation and several new applications of this system were elaborated in our country. A short overview of the various technical possibilities described in hundreds of local publications based on this system may give some useful information for present users.

Protein Expression

Initially, translation in the oocyte system was mostly studied from a mechanistic point of view. Likewise, it was shown in Geneva that the oocyte carries out correct proteolytic cleavage of precursor proteins (Mach *et al.,* 1973) and regulation of β-globin translation could be achieved by injection of haemin (Giglioni *et al.,* 1973). The group of Eric Kubli in Zurich demonstrated that the *Xenopus* oocyte uses all three stop codons (Bienz *et al.,* 1981). Yet, competition experiments with different tRNA isoacceptors in the oocyte system revealed an *'in vivo'* amino-acid codon preference (Meier *et al.,* 1985).

A useful early application of the oocyte system was to inject an mRNA or cDNA with the aim to verify that they code for the expected protein. This identification was particularly helpful at a time when no sequencing data were available. Since that time, protein expression is primarily used to test the function of the protein produced. In our country, this is preferentially done with constituents of membrane pumps and channels and components of transport systems.

The group of Daniel Bertrand in Geneva adopted the oocyte system to functionally characterise neuronal nicotinic acetylcholine receptors. The channel subunits were produced from cDNA expression vectors under the control of an SV40 promoter. This yielded a much higher channel activity than that obtained with the best *in vitro* synthesised mRNA (Ballivet *et al.,* 1988, Bertrand *et al.,* 1991). The Bertrand lab used the oocyte system to thoroughly characterise the functioning of chick and human neuronal channels from desensitisation, potentiation, responsiveness to various agonists and antagonists (Revah *et al.,* 1991; Valera *et al.,* 1992; Eisele *et al.,* 1993) till mutant nicotinic receptors in patients suffering from autosomal dominant nocturnal frontal lobe epilepsy (Picard *et al.,* 1999). Just to make you suffer; Daniel Bertrand developed a - non commercialised - robot carrying out nuclear injection into oocytes as well as whole-cell clamping including addition of agonists and measurement of electrophysiological parameters.

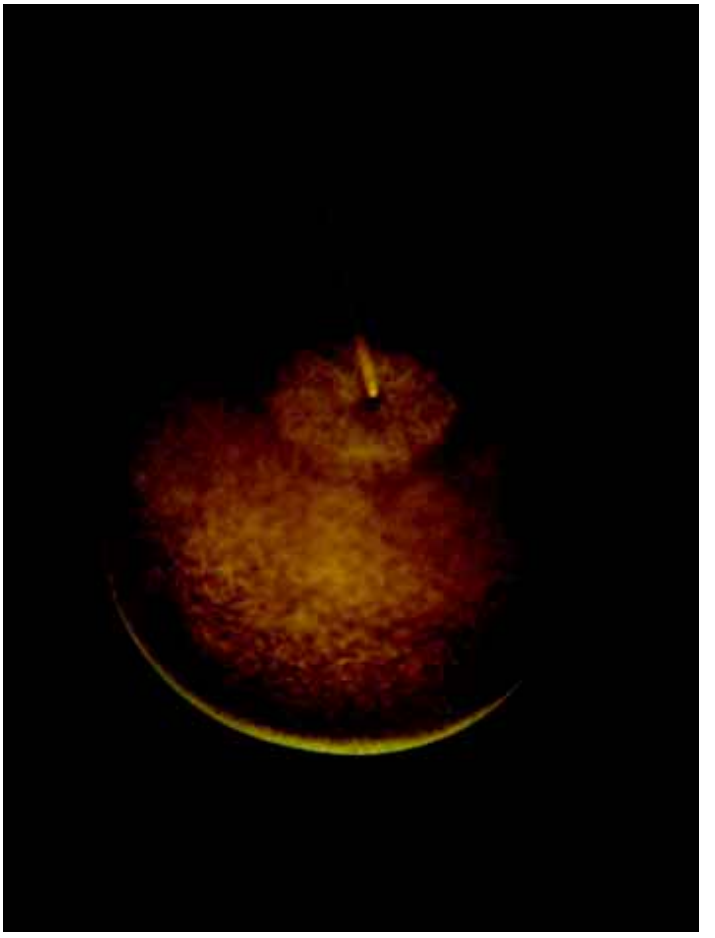

Fig. 5. How to inject the nucleus. *The position of the germinal vesicle becomes visible in centrifuged oocytes (Kressmann and Birnstiel, 1980), greatly facilitating nuclear injection.*

The group of Bernard Rossier in Lausanne set out to reconstitute the heterodimeric Na,K-ATPase pump they had isolated from *Xenopus* A6 cell lines and were able to assess the physiological role of its β-subunit (Geering *et al.,* 1989). This experiment could only work because the *Xenopus* oocyte expresses only one of the two subunits of Na,K-ATPase, which prompted a study of its role during early *Xenopus* development (Han *et al.,* 1991; Burgener-Kairuz *et al.,* 1994). The characterisation of the Na,K-ATPase pump remains the topic of Kathi Geering's lab today (see e.g., Beggah *et al.,* 1999; Crambert *et al.,* 2000). The nearby lab of Jean-Daniel Horisberger collaborated in several Na,K-ATPase studies (Hasler *et al.,*1998; Beguin *et al.,* 1998) and developed new approaches to the study of the structure-function relationship of a P-type ATPase (Horisberger and Wang, 1997). With the group of Olivier Staub, they also investigated the role of mem-

brane protein ubiquitination in ENaC function (Abriel *et al.,* 1999) and that of the cardiac voltage-gated Na channel (Abriel *et al.,* 2000).

Using oocyte expression Bernard Rossier had indeed isolated an epithelial sodium channel (ENaC) involved in arterial hypertension and respiratory distress and that could not be purified by biochemical methods (Canessa *et al.,* 1993, 1994). A regulatory protein, a serine protease that modulates ENaC activity at the plasma membrane, was also cloned by a novel complementation assay in the *Xenopus* oocyte system (Vallet *et al.,* 1997). François Verrey from Rossier's lab moved to Zurich and continued working in the *Xenopus* oocyte system, characterising aldosterone-regulated gene products isolated from the A6 line, one of them being K-Ras2. Coexpression, with ENaC, of K-Ras2 revealed its regulatory action (Mastroberardino *et al.,* 1998a). Another aldosterone-regulated product represents a novel type of amino acid transporter which has to be associated with a glycoprotein to be functionally installed at the cell surface (Mastroberardino *et al.,* 1998b, Pfeiffer *et al.,* 1999a,b).

Erwin Sigel in Bern characterised plasma membrane proteins (Sigel, 1990, 2001), in particular the effects of combining different subunits of γ–aminobutyric acid type A (GABAA) receptors (Sigel *et al.,* 1990) and monitored altered functions of point-mutated receptors (Buhr and Sigel, 1997).

A Swiss post-doc, Matthias Hediger successfully used the newly developed oocyte expression cloning technique for transport systems in the lab of Ernie Wright in Los Angeles USA (Hediger *et al.,* 1987). He gave some hints to Andi Werner, a Ph.D. student in the lab of Heinrich Murer in Zurich. There, the technique was applied to clone a single transport system for cystine, dibasic and neutral amino acids (Bertran *et al.,* 1992), human and rat renal cortex Na/Pi (Magagnin *et al.,* 1993) and rat renal Na/SO_4 cotransporters (Markovich *et al.,* 1993). Electrophysiological measurements (Forster *et al.,* 1998) and topological studies on protein mutants (Lambert *et al.,* 1999) were carried out on the Na/Pi cotransporter.

Hepatic transport systems were analysed by the group of Peter Meier in Zurich. Expression cloning allowed the components of the sulphobromophtalein uptake system (Jacquemin *et al.,* 1991) and the Na+/bile acid cotransport system (Hagenbuch *et al.,* 1991) to be isolated and characterised. Moreover, the rat liver organic anion (Jacquemin *et al.,* 1994) and canalicular sulphate transporters (Bissig *et al.,* 1994) and an isoform of the multidrug-resistance associated protein (Madon *et al.,* 1997) were identified.

Originally working on acetylcholine (ACh) release in *Torpedo* electric organ, Yves Dunant and his group in Geneva reconstituted correct calcium-dependent release of this neurotransmitter in *Xenopus* oocytes (Cavalli *et al.,* 1991). This activity could be blocked by the addition of anti-mediatophore antisense probes (Cavalli *et al.,* 1993). The study was extended by expressing ACh in transfected cells, inducing its release by mediatophore transfection, and registering ACh release by whole cell patch clamping on cocultured myocytes from *Xenopus* embryos (Falk-Variant *et al.,* 1996; Bloc *et al.,* 1999).

Promoter Analysis

An elaborate application of the oocyte system consists of analysing the function of putative promoter elements by introducing structural alterations in genes and spacers and subsequently analysing their effects on gene expression. This approach was termed 'surrogate genetics' (Birnstiel and Chipchase, 1977; Kressmann and Birnstiel, 1980) and the first such experiment was done over two decades ago (Kressmann *et al.,* 1978). A technical refinement consisting of centrifuging the oocytes to visualise the position of the nucleus (Fig. 5) greatly facilitated nuclear injection. With this tool in hand, the Zurich lab hit gold.

Polymerase III Genes

A special form of polymerase from oocytes of *Xenopus* was described in Geneva (Wilhelm *et al.,* 1974) and turned out to be RNA polymerase III (Long and Crippa, 1976). The *Xenopus* tRNA genes read by this polymerase were initially characterised in Edinburgh (Clarkson *et al.,* 1973a,b), and were then isolated and cloned in Zurich (Clarkson and Kurer, 1976; Clarkson *et al.,* 1978). Functional testing of elaborate mutant constructs revealed that these genes are controlled by an intragenic promoter composed of two short sequence blocks (Telford *et al.,* 1979; Kressmann, *et al.,* 1979; Hofstetter *et al.,* 1981; Galli *et al.,* 1981). Interestingly, the nucleosome pattern of transfer DNA was found to change during cell differentiation in *Xenopus* from a non-phased (active) to a phased configuration (mainly repressed state) (Bryan *et al.,* 1981). The promoter of the 5SrRNA gene was characterised in the lab of Don Brown at Carnegie, Washington USA, using transcription assays in germinal vesicle extracts. In this context it may be mentioned that the Crippa lab devised a method to mass-isolate germinal vesicles and nucleoli (Scalenghe *et al.,* 1978) but for once mass production did not conquer the market.

After his move to Geneva, Stuart Clarkson continued his work on *Xenopus* tRNA transcription (Hipskind and Clarkson, 1983), termination (Mazabraud *et al.,* 1987) and developmental regulation (Stutz *et al.,* 1989) as well as the (lack of) function of the La protein in these processes (Scherly *et al.,* 1993; Lin-Marq and Clarkson, 1998). One day, immunoprecipitating the La protein, they stumbled over the frog homologue of the *Xeroderma pigmentosum* group G factor and switched to human DNA repair disorders. And there went one more 'Swiss' *Xenopus* veteran.

Polymerase I Genes

Sequencing of the ribosomal cistrons had indicated that the putative promoter is duplicated within the spacer region that otherwise is composed of numerous short repeats (Boseley *et al.,* 1979; Moss and Birnstiel, 1979). Injecting *X. laevis* genes into *X. borealis* oocytes and the use of specific probes permitted to measure transcripts from the injected genes without the endogenous background. The outcome of such functional tests allowed defining the basic promoter placed next to the gene start. Duplicated promoters near the BamH1 sites within the spacer give rise to spacer transcription (Moss, 1982). Tom Moss continued to characterise the function of the ribosomal spacer after his return to Great Britain, notably showing that the repetitive spacer elements function as transcriptional enhancers (Moss, 1983) and characterising the ribosomal transcription factor UBF (Bachvarov and Moss, 1991).

Polymerase II genes

Sea urchin histone gene clusters were in turn highly purified, cloned and sequenced in Zurich (Birnstiel, *et al.,* 1974; Clarkson *et al.,* 1976; Schaffner *et al.,* 1978), and cloning of *Xenopus* histone genes soon followed (Moormann *et al.,* 1980). The sea urchin data revealed the TATA box and some nearby conserved sequences, as well as a terminal palindrome (Büsslinger *et al.,* 1979). To sort out their functioning, promoter mutants were produced by restriction-deletion and by inversion of DNA segments. Functional tests in the

oocyte allowed determining the role of the TATA box as 'selector' of transcription initiation and the role of an 'initiator' sequence (Grosschedl and Birnstiel, 1980) necessary for maximal, accurate transcription initiation (Hentschel *et al.,* 1980). Such functional studies also documented the stimulatory role of upstream modulator sequences that could be inverted with no deleterious effect, the first observation of a eukaryotic enhancer (Grosschedl and Birnstiel, 1980). The study of enhancer elements became the research topic of Walter Schaffner who, with the help of the surrogate genetic approach, isolated the enhancers of SV40 and of the immunoglobulin gene using transfection into cell lines.

Max Birnstiel concentrated on histone mRNA processing using the trick to isolate nuclei from 'boiled eggs' (Georgiev *et al.,* 1984). The nucleus may then easily be separated from the cytoplasm and the distribution of RNA intermediates be followed. To obtain correct 3' processing the *Xenopus* oocyte had to be complemented with a 60 nucleotide long RNA (Stunnenberg and Birnstiel, 1982; Birchmeier *et al.,* 1984). Such observations led to the discovery of a sea urchin U7 RNP, an snRNP catalysing histone mRNA 3'-processing (Strub *et al.,* 1984). One of the research associates, Daniel Schümperli, working on U7 snRNP later exported this topic to Bern, where he became the successor of Rudolf Weber. *Xenopus*, murine, and human snurps constitute the central theme of research of his group, still involving functional testing in the oocyte system (Stefanovic *et al.,* 1995a,b). De Robertis' lab at Basel, isolated Xenopus U snRNA genes (Zeller *et al.,* 1984; Mattaj *et al.,* 1985). Iain Mattaj focused his interests on U snRNP interactions and nuclear import (Mattaj and De Robertis, 1985) and, as mentioned, pursued this topic at the EMBL (Izaurralde *et al.,* 1995; Palacios *et al.,* 1997).

The intensive analysis of the promoters of hormone-induced genes, in particular oestrogen-responsive elements by the groups of Rudolf Weber and Walter Wahli has already been reviewed above. Other genes whose regulation was studied in the oocyte system were *Drosophila* and human heat shock genes (Voellmy and Rungger, 1982; Voellmy *et al.,* 1985). Moreover, Marianne Bienz who had joined Gurdon's lab in Cambridge analysed the regulation of *Xenopus* heat shock genes (Bienz, 1986; Bienz and Pelham, 1986). Still other polymerase II promoters were analysed by functional testing in the oocyte system but space limitations preclude their review here.

Transactivation Assay

Some of the above studies involved complementation of the oocyte with foreign components from other cell types. Correct 3' processing of histone mRNA was dependent on the addition of snRNPs (Stunnenberg and Birnstiel, 1982) and, transcription of the vitellogenin promoter on that of nuclear proteins from liver nuclei (Knowland *et al.,* 1984; Corthésy *et al.,* 1991). Such experiments anticipated later complementation experiments, providing cisactive factors to modulate transcription of tissue specific genes in the oocyte. The Rungger lab in Geneva developed a transactivation approach allowing to functionally test cis- and transactive elements in the oocyte system (Rungger *et al.,* 1990). With this tool, a repression-derepression mechanism was characterised that regulates the interleukin-2 promoter (Mouzaki and Rungger, 1994) as well as the HIV-1 LTR (Mouzaki *et al.,* 2000) in genuine T helper cells. Transactive factors may also be produced in the oocyte by injecting their mRNA or cDNA, as was done in analysing the activation mechanism of heat shock factor HSF-1 (Zuo *et al.,* 1995) and in testing the repressing activity of *Xenopus* Id3 on myoD function (Zhang *et al.,* 1995).

As mentioned, most DNA injections into the zygote were done with the aim to follow DNA replication or promoter functioning. Likewise, the expression pattern of the c-myc gene was monitored in embryos (Modak *et al.,* 1993). Coinjecting a target gene with cDNA vectors coding for transcription factors or recombinant proteins also allowed to assess transactivation mechanisms in the embryo. In this way, cellular and viral activators of transcription were found to function differently in oocytes and embryos (Xu *et al.,* 1994).

The Endangered Species

Since its introduction to Swiss universities some fifty years ago, *Xenopus* has become an indispensable model system for many laboratories. In spite of the fact that some of the large *Xenopus* swamps of Switzerland have ceased to exist or are drying out, the highly adaptive toad remains firmly established in many small ponds. Certainly, *Xenopus helveticus* lives dangerously but for the moment there is no urgency to place it on the red list.

Summary

This review traces the history of *Xenopus* research in Switzerland, its worldwide beginnings and British chapters having been summarised previously (Gurdon and Hopwood, 2000). As in other countries, *Xenopus* was initially used in the pharmaceutical industry at Basel for pregnancy testing. Developmental biologists became interested in this peculiar amphibian because it may be induced to ovulate all year round. Swiss *Xenopus* research is reviewed over 50 years, from the introduction of *Xenopus* by Rudolf Weber to the University of Bern, the return from Great Britain of two Swiss expatriates, Michail Fischberg and MaxBirnstiel through the numerous pupils of the founder labs to the independently arisen *Xenopus* research units in the country. Besides developmental biology, Swiss *Xenopus* research engaged in immunology, genetics and cell biology, the latter focusing mainly on the oocyte. It set highlights in molecular biology by isolating some of the first eukaryotic genes and analysing their transcriptional regulation and post-transcriptional modifications through 'surrogate genetic' approaches in the oocyte system. An important line of research applied this system to study nuclear trafficking. Presently, functional testing mainly serves to characterise the function of proteins produced from expression vectors injected into the oocyte. A main accent of developmental studies was, from the early beginnings and still today, set on molecular characterisation of gene function in the embryo.

KEYWORDS: *Xenopus development, molecular biology, oocyte system, surrogate genetics, historical article.*

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