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Rostand's anomaly P in Palaearctic green frogs (*Pelophylax*) and similar anomalies in amphibians

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Abstract. The anomaly P is a polymorphic syndrome that affects many individuals in some populations of Palearctic green frogs (genus or subgenus *Pelophylax*). In its benign forms, it consists in simple polydactyly, either only in hind limbs or both in hind and fore limbs, whereas in its severe forms it includes brachymely, inguinal tumours, bony excrescences and even polymely. Tadpoles showing these extreme forms do not survive to metamorphosis. This anomaly is characterized by several constant features, including a postero-anterior gradient and a good, although not always perfect, bilateral symmetry. The anomaly is widely distributed in Europe and northern Africa. It affects several taxa of *Pelophylax* but is not known to occur in other amphibian groups. Despite extensive work on this anomaly, especially in the period 1949–1984, its cause remains unknown, although several potential factors can be discarded. It is not of genetic origin, not being transmitted to the offspring. It is caused by an unknown exogenous teratogenic factor, possibly a virus transmitted by fish, that acts very early in the development, as amputation of an abnormal hind limb bud in a young tadpole is followed by regeneration of a normal limb. It would appear appropriate to resume scientific work on this syndrome in order to solve the still unsolved questions, as the results might have unexpected implications in developmental biology and in conservation biology.

Keywords. Polydactyly, polymely, tumours; gradient, symmetry, lethality; regeneration; virus.

Zusammenfassung. Anomaly P stellt ein polymorphes Syndrom an Missbildungen dar, das in manchen Populationen paläarktischer Grünfrösche (Gattung oder Untergattung *Pelophylax*) an zahlreichen Individuen auftritt. In seiner milden Form besteht es aus einfacher Polydactyly, die entweder nur an den Hinterbeinen oder sowohl an den Hinter- als auch an den Vorderbeinen auftritt. Bei schwerwiegenden Formen kommen Brachymely, Tumore in der Leistenregion, Knochenwucherungen und selbst Polymely hinzu. Kaulquappen, die schwere Formen des Syndroms aufweisen, überleben die Metamorphose nicht. Anomaly P weißt mehrere konstante Merkmale auf. Hierzu gehören ein postero-anterior Gradient (d.h., die Schwere der Missbildungen nimmt von den Hinter- zu den Vorderbeinen ab) und eine gute, wenn auch nicht immer perfekte bilaterale Symmetrie. Anomaly P hat eine weite Verbreitung in Europa und Nordafrika. Sie befällt mehrere Taxa von *Pelophylax,* aber ist von anderen Amphibiengruppen bisher nicht nachgewiesen. Trotz umfangreicher Untersuchungen über diese Anomalie, die besonders in den Jahren 1949-1984 stattfanden, bleibt die Ursache ungeklärt. Verschiedene potentielle Faktoren können jedoch ausgeschlossen werden. Da Anomaly P nicht auf Nachkommen vererbt wird, kommen genetische Ursachen nicht in Frage. Sie wird vielmehr durch einen unbekannten exogenen, teratogen wirkenden Faktor hervorgerufen, bei dem es sich möglicherweise um ein von Fischen übertragenen Virus handelt. Dieser Faktor entfaltet seine Wirkung sehr früh in der Individualentwicklung: die Amputation missgebildeter Hinterbeinknospen in jungen Kaulquappen führt zur Regeneration normaler Hinterbeine. Die Wiederaufnahme wissenschaftlicher Forschung zu diesem Syndrom scheint angeraten, um die noch immer offenen Fragen klären zu können, denn die Antworten könnten entscheidende Kenntnisse für die Entwicklungsbiologie und den Naturschutz liefern.

Schlüsselwörter. Polydactylie, Polymelie, Tumore; Gradient, Symmetrie, Lethalität; Regeneration; Virus.

Résumé. L'anomalie P est un syndrome polymorphe qui affecte de nombreux individus dans certaines populations de grenouilles vertes Paléarctiques (genre ou sous-genre *Pelophylax*). Ses formes bénignes consistent en une simple polydactylie, qui touche seulement les membres postérieurs ou également les membres antérieurs. Ses formes sévères incluent d'autres anomalies, comme la brachymélie, des tumeurs inguinales, des excroissances osseuses ou même la polymélie. Les têtards qui manifestent ces symptômes extrêmes ne survivent pas à la métamorphose. Cette anomalie se caractérise par plusieurs particularités constantes, notamment l'existence d'un gradient postéro-antérieur et une bonne, quoique souvent imparfaite, symétrie bilatérale. L'anomalie est largement répandue en Europe et en Afrique du Nord. Elle touche plusieurs taxons de *Pelophylax* mais n'est pas connue pour affecter les Amphibiens d'autres groupes. En dépit d'importants travaux sur cette anomalie, particulièrement dans la période 1949–1984, sa cause reste

inconnue, bien que plusieurs facteurs potentiels aient pu être mis hors de cause. Elle n'est pas d'origine génétique, n'étant pas transmise à la descendance. Elle est causée par un facteur tératogène exogène inconnu, peut-être un virus transmis par des poissons, qui agit très tôt dans le développement, puisque l'amputation d'un bourgeon de patte postérieure anormale chez un jeune têtard est suivie de la régénération d'une patte normale. Il serait souhaitable que des travaux soient de nouveau effectués pour élucider les questions que pose encore ce syndrome, car les réponses à ces questions pourraient avoir des implications inattendues en biologie du développement et en biologie de la conservation.

Mots-clés. Polydactylie, polymélie, tumeurs; gradient, symétrie, léthalité; régénération; virus.

1 Introduction

One of the longest studied cases of mass anomalies in amphibians is the syndrome of European green frogs now known as *anomaly P*. Although the first report of this syndrome was by Bonnet & Rey (1937), this isolated observation did not attract attention until the anomaly had been rediscovered and studied by Jean Rostand.

Within the frame of his survey of anomalies in natural populations of French amphibians, Jean Rostand found several examples of polydactylous common toads, *Bufo bufo* (Linnaeus, 1758), with six toes on each foot. In some cases, crossing one of them with a normal toad resulted in normal offspring, whereas crosses between two polydactylous specimens produced polydactylous toadlets. Therefore, this anomaly was interpreted as caused by a recessive mutation (Rostand 1947a,b, 1950a, 1951b). In other cases, a dominant mutation seemed to be involved, as polydactylous toads were obtained from crossing a single abnormal toad with a normal one (Rostand 1949a, 1951b).

2 The anomaly P syndrome

In the hope of finding also mutations responsible for polydactyly in the genus *Rana*, Rostand examined thousands of specimens of this genus and was thus led to the discovery, at Trévignon in Finistère (Brittany), of a population of green frogs (then referred to *Rana esculenta* Linnaeus, 1758) including many adult polydactylous specimens (Rostand 1949b). This polydactyly was very polymorphic and showed a postero-anterior gradient (Rostand 1949b, 1950d, 1951b): in all abnormal specimens, the hind limbs were touched by polydactyly (from 6 to 9 toes), whereas the fore limbs were touched only in some cases, when polydactyly on hind limbs was strong (more than 6 toes). Other morphological peculiarities of this syndrome included a good, although not always perfect, bilateral symmetry (Fig. 1): i.e., the number of additional digits was always roughly the same on both sides, with sometimes one more toe or finger on one side, but never an excess of several digits on one side (e.g., 6-7, 7-7 or 7-8 toes, but never 6-8). The first additional toe was usually longer than the "first" normal toe, which gives the feet of these frogs a very special aspect (Fig. 2D, E), quite different from that of usual polydactyly, e.g. in *B. bufo* (Fig. 2B). This polydactyly turned out to be only the weakest form of a very polymorphic syndrome, which could take much more severe forms in tadpoles, including stronger polydactyly (up to 15 toes), polymely (presence of small supernumerary hind limbs; Fig. 3), brachymely (shortened limbs) and various types of bony excrescences and tumours especially in the inguinal region (Rostand 1952a, 1955a, 1958a). Rostand (1952a) gave this syndrome the name of "*anomaly P*".

The anomaly touched a very high proportion of the larvae in the population, but most of them would die during metamorphosis or shortly afterwards, mostly from internal haemorrhages due to mechanical problems of the malformed specimens. This explains why the rate of anomalies is much higher in tadpoles than in adults (Rostand 1971, Dubois 1979, 1984).

Fig. 1: Severe expression of anomaly P in *Pelophylax esculentus*, with the forelimbs being affected by polydactyly in addition to the hindlegs. Characteristic for anomaly P is also the symmetric expression of the anomaly. Source: Rostand (1958a: Fig. 37).

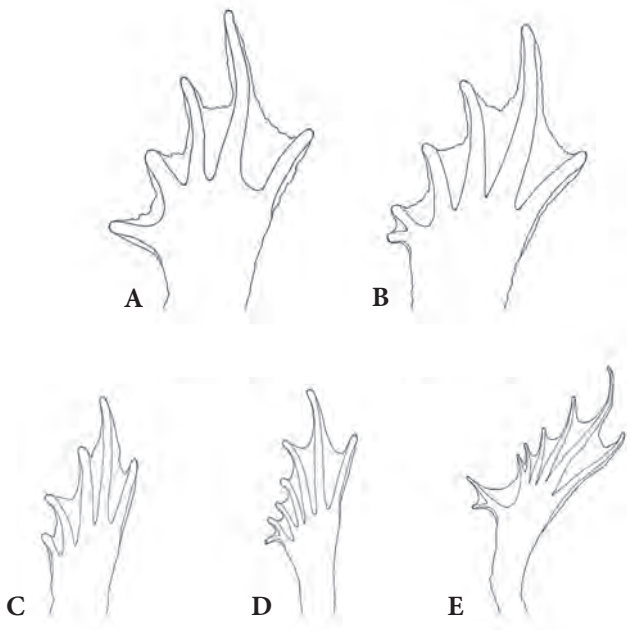

Fig. 2: Polydactyly in hind limbs of *Bufo bufo* and *Pelophylax esculentus*. (A) Normal specimen of *B. bufo* (5 toes) (Rostand 1955a: Fig. 14). (B) Polydactylous specimen of *B. bufo* (6 toes), polydactyly caused by a dominant mutation (Rostand 1955a: Fig. 15). (C) Normal specimen of *P. esculentus* (5 toes) (Rostand 1955a: Fig. 25). (D) Polydactylous specimen of *P. esculentus* (7 toes) (Rostand 1955a: Fig. 27). (E) Polydactylous specimen of *P. esculentus* (8 toes) (Rostand 1955a: Fig. 28). The two latter specimens are from Trévignon (Bretagne, France) and show different severities of polydactyly belonging in the anomaly P syndrome.

Fig. 3: Severe expression of anomaly P in *Pelophylax esculentus*; specimen cleared with potassium and stained with alizarine red; the hindlegs show small supernumerary limbs (polymely), gross malformation of the bones (taumely) and a large number of supernumerary toes (polydactyly). Source: Rostand (1958a: Fig. 38).

At the scale of a whole population, the anomaly shows a strong variability in time, being very frequent some years and very rare or absent in other years, with a possible return after several years of absence. In Trévignon, from 1949 to 1967, the frequency of the anomaly P varied from 0 to 80 % in tadpoles and from 2.6 to 14.5 % in adults; in another population from central France, Champdieu (Loire), from 1950 to 1976 the frequency varied from 0 to 6.3 %, whereas in a third one, Lingé (Indre), from 1961 to 1970 the frequency in tadpoles varied from 14 to 70 % (Dubois 1979, 1984, 2014). The frequency of the most severe forms, lethal at metamorphosis, is also variable from year to year (e.g., from 26.9 to 47.1 % in Trévignon from 1952 to 1958), but is not higher when the frequency of abnormal specimens is higher (Rostand 1959). The frequency of the anomaly is also different, within the same year, at different dates and seems to grow when the temperature in the ponds gets higher (Rostand & Darré 1969, Rostand 1971).

First discovered in a Brittany pond, the anomaly P was found or suspected to occur in many other populations of green frogs of the Palearctic region (for details, see Dubois 1984). The complete syndrome in adults and larvae was observed in several regions of France (see map in Dubois 1984), in the Netherlands and Morocco. Mass polydactyly, or polydactyly which on morphological grounds closely resembles that of the anomaly P, was reported from various other regions of France and from Austria, Belarus, Germany, Switzerland and Turkey (European part). Finally, isolated cases of polydactyly, possibly also belonging to the anomaly P, were reported from France, Germany, Greece, the Netherlands, Poland and Russia.

3 The search for the cause

Contrary to his expectation, when Rostand crossed specimens affected by the anomaly P, he obtained only normal offspring, even if both parents were polydactylous, some of them severely (Rostand 1950d). Despite these negative results, he first remained convinced that a genetic factor, possibly polygenic or transmitted by cytoplasm, was involved (Rostand 1951a,b). However, when the stronger polymorphism of anomalies in tadpoles was discovered, Rostand (1952a) started considering the possibility of its infectious determinism.

In a crucial series of experiments, Rostand (1952b) showed that amputation, in young tadpoles, of the distal part of a hind limb touched by the anomaly P, was followed by regeneration of a normal limb, which demonstrated that the teratogenic factor, whatever it may have been, had stopped being active at the time of regenera-

tion. Such a result, associated with those of the crossings, strongly suggested that the anomaly was caused by an exogenous teratogenic factor having a precocious and temporary action on the limbs of tadpoles. As many such factors could be suspected, Rostand carried out varied experiments in the hope of reproducing artificially, in the laboratory, polydactyly and the other anomalies observed in the anomaly P syndrome. However, he did not succeed in reproducing such anomalies by the action of various chemicals (Rostand 1950b,c), by raising eggs and larvae in brackish water or in water from the ponds where the anomaly was present (Rostand 1952c, 1958a), by the action of various physical aggressions, including thermal shocks, long exposure to high or low temperature or to sun, dehydration, etc. (Rostand 1950d, 1959) or even in provoking overripeness of egg before fertilization (Rostand 1951c).

Through ultraviolet irradiation of just hatched larvae of common brown frogs (*Rana temporaria* Linnaeus, 1758), Rostand (1955b, 1958b) obtained a few cases of polydactyly, polymely and even brachymely, but these anomalies were morphologically very different from those observed in the anomaly P syndrome. In 1957, many abnormal green frogs were found in a canal of Amsterdam where nuclear waste had been thrown, which elicited various papers in popular newspapers incriminating radioactivity as the cause of these anomalies (Rostand 1971). However, the anomalies observed were similar to those of Trévignon and were soon referred to the anomaly P (Hillenius 1959). Artificial radioactivity linked either to civil or military human activities can be dismissed as the possible cause of the anomaly P, as isolated cases of the latter have been reported since the beginning of the 19th century (Virey 1819) and mass occurrence of polydactyly clearly referable to the anomaly P have been known since before the Second World War (Bonnet & Rey 1937). Rostand (1957, 1959) also gave arguments to reject the hypothesis of an action of natural radioactivity. So other causes had to be sought for this syndrome.

All these observations led Rostand to think that the anomaly P was not due to a chemical or physical agent and to favour the hypothesis, suggested to him by Caullery in 1949 (Rostand 1952a), of an infectious agent, which could be a teratogenic virus. Furthermore, as eggs of green frogs collected in the Trévignon ponds gave birth, in the laboratory, only to normal larvae (Rostand 1959), it was possible to suppose that this factor was not active during embryogenesis, but between hatching and the appearance of the hind limb buds.

After various laboratory experiments that did not bring additional support for the virus hypothesis (Rostand 1952c, 1959, 1960, 1971), a series of experiments realized in the field brought new interesting insights. Whereas tadpoles raised from eggs hatching in large cages directly submerged in a pond where the anomaly P was present did not show any anomaly (Rostand et al. 1967), tadpoles raised in such cages but with fishes, i.e., tenches [*Tinca tinca* (Linnaeus, 1758)] and eels [*Anguilla anguilla* (Linnaeus, 1758)], collected in this pond showed severe anomalies belonging to the anomaly P syndrome (Rostand & Darré 1967). The sensitive period for the induction of anomalies in such conditions turned out to be limited to the first days of free larval life (Rostand & Darré 1968). Finally, Rostand & Darré (1969) reported having obtained abnormal specimens in the laboratory by feeding just hatched tadpoles with intestinal contents of fish from the pond: in such conditions some specimens showed even some anomalies more severe than those observed until then in the field. Thus the factor responsible for the anomaly P seems to be present in the digestive tract of fish living in some ponds. This does not mean that this factor exists only there: it could as well be present in some plants or aquatic invertebrates on which the fish feed. This factor has not yet been isolated but the hypothesis that it could be a teratogenic virus agrees with the data published so far.

This factor appears not to be evenly distributed in the habitat, as the frequency of the anomaly varies among different parts of ponds (Rostand et al. 1967, Rostand & Darré 1968, 1969, Rostand 1971). The zones in which the anomaly P appears with high frequencies change from year to year and, after ecological changes that are not understood, it may even disappear completely, sometimes temporarily, sometimes definitively (Rostand 1971).

The variability, and hence the unpredictability, of the appearance, frequency and severity of the anomaly P in a given pond and at a given spot is a serious handicap for the study of its causes. On several occasions, rather heavy experimental protocols, involving the comparison of control tadpoles with tadpoles fed with fish intestinal contents, either intact or submitted to ebullition, freezing, filtration or chromatographic fragmentation, did not give any results, but this was not surprising in view of the fact that, in the same year, the anomaly P proved to have been absent from the ponds (Dubois 1979, 1984). In the world of contemporary research, where obtaining rapidly publishable results is a constraint for obtaining funding for research, this difficulty is a major one for pursuing the study of this question. This probably explains in part why this question remains unresolved today, as after the patient research, for several decades, by Jean Rostand, an individual "amateur" without funding or support of any kind, the study of this anomaly has never been seriously undertaken by any institutional laboratory over the whole of Europe.

As of today, a teratogenic virus appears the best hypothesis to account for the various observations summarized above, but it is still not demonstrated. If it proved true, and if this virus could be isolated, it would provide research with a very powerful teratogenic factor, which could throw some lights on problems of cell proliferation and differentiation, with possible impacts on research on cancers and other pathologies that imply uncontrolled cell multiplication.

4 Ecological significance of anomaly P

Whatever its causes, the anomaly P is an important phenomenon for the populations of green frogs where it occurs, as it affects the survival of frogs (Rostand 1962, Rostand & Darré 1968). Before metamorphosis, the survival of strongly affected larvae does not seem to be affected and artificial or spontaneous prolongation of the larval condition allows keeping these specimens alive for very long periods, up to one year and a half (Rostand 1959). However, even in protected conditions in captivity, specimens exhibiting the severe forms of the anomaly (with brachymely and various supernumerary bony formations) all die within the first weeks after metamorphosis, merely because of internal injuries caused by the bony excrescences in the hind limbs (Rostand 1955c). Thus, for purely mechanical reasons, the anomaly in its severe forms is totally lethal at metamorphosis or just after and only the frogs showing the benign form of the anomaly (simple polydactyly) do survive. Since the frequency of the severe forms often reaches 40 or 50 % of the abnormal specimens, which in turn may represent up to 80 % of the tadpoles of a population, in some cases about 40 % of the tadpoles of a given pond may die at metamorphosis. Such a mortality rate, especially if repeated for several years, might have a significant impact on the dynamics of these natural populations. However, until now no study has been devoted to this question.

5 Species affected

Most of the observations on the anomaly P summarized above are older than the discovery that Palaearctic green frogs consist of several "normal species" and of several *kleptons*, i.e., particular species derived from hybridization between two "normal species" but with a particular meiosis that allows the maintenance of "first generation hybrids" over many generations (Tunner 1974, Dubois 1977, 1991, 2011, Dubois & Günther 1982, Graf & Polls Pelaz 1989). Therefore, it is currently unknown which of these species and kleptons are touched by the anomaly, but the distribution of the latter, briefly surveyed above, is large enough to be sure that it concerns at least several taxa, if not all European green frogs, currently placed in the subgenus *Pelophylax* Fitzinger, 1843 of the genus *Rana* Linnaeus, 1758 (Dubois 1992) or even by some authors (Fei et al. 1990, Frost et al. 2006) in a full genus *Pelophylax*. Currently, 20 species and 3 kleptons are recognized by taxonomists in this group, among which 9 species and 3 kleptons occur in Europe and northern Africa (Dubois & Ohler 1995, Dubois 1998, Ohler 2007). From the distributional data on the anomaly P (see above), at least the species *Pelophylax lessonae* Camerano, 1882, *Pelophylax ridibundus* Pallas, 1771, *Pelophylax perezi* Seoane, 1885 and *Pelophylax saharicus* Boulenger, 1913, and the kleptons *Pelophylax* kl. *esculentus* Linnaeus, 1758 and *Pelophylax* kl. *grafi* Crochet, Dubois, Ohler & Tunner, 1995 appear to be affected by the anomaly. Possibly other taxa might also be involved in some cases.

No report of anomalies clearly belonging to the anomaly P in other groups of frogs traditionally referred to the genus *Rana* but now placed in several subgenera or genera (Dubois 1992, Frost et al. 2006) has been published so far. In particular, this syndrome is unknown in Palaearctic brown frogs (genus or subgenus *Rana* s. str.) and in North American green frogs, now placed in the subgenus *Aquarana* Dubois, 1992 (Dubois 1992) or in the genus *Lithobates* Fitzinger, 1843 (Frost et al. 2006). In any case, the data available now are enough to state that the anomaly P is not species-specific and can touch several taxa in the *Pelophylax* group (Dubois 2014). Almost everything remains to be done to answer the following questions: (1) Are some of the taxa of *Pelophylax* more sensitive than others to the anomaly P and are some of them immune from it? (2) More specifically, in the mixed populations involving two or more distinct taxa of *Pelophylax*, does the anomaly P touch them indiscriminately or not? (3) Does the sensitivity to the anomaly P causative factor depend in any way on the special kind of meiosis that occurs in kleptons?

These questions make sense especially as no hard data exist to document the fact that amphibian species of groups other than the genus or subgenus *Pelophylax* can be touched by the anomaly P, even in the habitats where this anomaly is present in green frogs. In a few species – particularly *Lissotriton helveticus* (Razoumowsky, 1789), *Triturus cristatus* (Laurenti, 1768) and *Rana temporaria* – various limb anomalies have been found in ponds where the anomaly P occurs, or obtained by rearing larvae in contact with fish from such ponds, but it is not at all established whether these anomalies were indeed caused by the anomaly P factor (Dubois 1974, 1979, 1984).

Various other kinds of anomalies have been described so far in natural populations of many amphibian species. They are reviewed in another paper of this volume (Henle et al. 2017). The causes of only a small proportion of them have been scientifically established so far, but none of them seems to result from the anomaly P factor, whatever it is, or from similar causes. In a few cases the causes were shown or supposed to be non-genetic (either through crosses or through regeneration experiments) but remain mysterious (Dubois 1979, 1984) and, in this respect only, remind the anomaly P. Few of them have been studied as thoroughly as the anomaly P and re-examination of these few cases might prove rewarding.

6 Conclusion

Much still remains to be known about the anomaly P: its cause, its geographic distribution, exactly which taxa are affected and why, what is the impact of this syndrome on frog populations, etc. Although this problem attracted the attention, especially of an amateur naturalist, Jean Rostand, mostly in the years 1950-1970, no

studies are apparently under way nowadays, in any laboratory or European country, to elucidate these questions. This is surprising and even shocking, especially in view of the strong interest raised in recent years by amphibian anomalies in conservation biology (Henle et al. 2017). Given the fact that this syndrome involves facts of cellular abnormal multiplication and tissue differentiation and growth, its understanding might throw interesting or important lights on some developmental biology problems. More attention should certainly be paid to this unsolved problem by the international scientific community.

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