100 YEARS AGO

The remarkable subsidences which have often occurred in and around the town of Northwich, in Cheshire, form the subject of a paper by Mr. T. Ward, recently issued by the Institution of Mining Engineers. The subsidences are chiefly due to mining in the Upper Bed of rock-salt, and the too rapid removal of brine by means of modern pumps. In a natural condition the water in or on the salt-beds becomes saturated with salt and then ceases to dissolve it, but now the brine is continually pumped up in immense quantities, and the fresh water which flows to take its place dissolves the salt pillars which have supported the roof and overlying strata, with the result that there is a depression towards each pumping centre. In almost every case the mines in the Upper Bed of rock-salt are destroyed by water rapidly eroding the salt pillars in this way. Another cause of subsidence is the pumping of brine from off the rock-head, that is, the surface of the Upper Bed of rock-salt… By degrees the town is becoming one of framework buildings, and will, for England, be unique in this respect. The accompanying illustration, which we are enabled to give from Mr. Ward's paper, shows a subsiding house in a street at Northwich.

From *Nature* 28 March 1901.

50 YEARS AGO

John Constable's Clouds. **This is more of a philosophical than a meteorological treatise. The author is mainly concerned to demonstrate the influence upon John Constable and, incidentally, also upon Goethe, of Luke Howard's system of cloud classification. There have been other great cloud painters such as Turner and Ruisdael; but Constable's work rests on a knowledge of Howard's system and it is this which makes the dynamical quality of his cloud studies, so suggestive of rapid change, highly interesting to meteorologists. This is surely a striking example of the aid which science can render art…**

From *Nature* 31 March 1951.

an early representation of the masked grey grapheme? After all, it would not be surprising that something that was not seen would not influence later processing (colour naming in this case). To tackle this question, Mattingley *et al.* used the same graphemes, visual mask and temporal parameters in another study. Now, though, the coloured patch was replaced by either the same or a different grapheme but in a different case. For example, a lower-case masked grey 'a' was followed by an upper-case unmasked grey 'A'. The task was to name the upper-case letter, which the participants saw clearly.

Although neither synaesthetic participants nor controls consciously saw the masked grey grapheme, all were affected by it. That is, they were quicker at naming the letter 'A' when it was preceded by an 'a' rather than a 'b'. The implication is that although the participants were not consciously aware of the identity of the masked graphemes, their brains were. Nonetheless, the masked graphemes did not evoke synaesthesia. The synaesthetic experience occurred only when the evoking stimulus was consciously perceived, not when it was represented below the level of awareness.

What does all this have to do with the problem of 'binding' visual features of an object into a whole? Neurobiological evidence has shown that separate features of visual information are projected to different cortical regions of the human brain. Colour and shape are separated relatively early during the processing of visual stimuli[8], and the brain can encode these features without awareness. The new work[3] supports this idea of modularity in the human cortex.

It is possible that a flaw in this modular organization accounts for colour-graphemic synaesthesia[9]. Mattingley *et al.*'s results agree with this possibility; it seems that the cortical regions for processing shape and colour are abnormally linked, but only during awareness. The authors' findings are consistent with evidence that 'attention' signals — associated with awareness and generated outside these cortical regions — are required to produce normal binding[4]. For colour-graphemic synaesthetes, 'normal' means seeing a selected grapheme in a particular colour; some degree of awareness is needed to bind colour and grapheme together into one visual object. 'Normal' for other people means seeing the grapheme as the colour it actually is and, again, awareness is likely to be fundamental in binding together colour and shape. ■

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1. Treisman, A. *Phil. Trans. R. Soc. Lond. B* **353,** 1295–1306 (1998).
2. Wojciulik, E. & Kanwisher, N. *Vis. Cogn.* **5,** 157–181 (1998).
3. Mattingley, J. B., Rich, A. N., Yelland, G. & Bradshaw, J. L. *Nature* **410,** 580–582 (2001).
4. Friedman-Hill, S., Robertson, L. C. & Treisman, A. *Science* **269,** 853–855 (1995).
5. Robertson, L. C., Treisman, A., Friedman-Hill, S. & Grabowecky, M. *J. Cogn. Neurosci.* **9,** 295–317 (1997).
6. Baron-Cohen, S. & Harrison, J. E. (eds) *Synaesthesia: Classic and Contemporary Readings* (Blackwell, Cambridge, MA, 1997).
7. Dixon, M. J., Smilek, D., Cudahy, C. & Merikle, P. M. *Nature* **406,** 365 (2000).
8. Desimone, R., Stanley, J. S., Moran, J. & Ungerleider, L. G. *Vision Res.* **25,** 441–452 (1985).
9. Baron-Cohen, S., Harrison, J., Goldstein, L. H. & Wyke, M. *Perception* **22,** 419–426 (1993).

Palaeontology

Chinese salamanders tell tales

Robert Carroll

A palaeontological treasure trove of over 500 specimens will help in understanding the evolutionary history of salamanders and their relationships with other amphibians.

On page 574 of this issue[1], Gao and Shubin report the discovery of hundreds of superbly preserved salamander skeletons from a 150-million-year-old pond deposit in China. The specimens include both larval and adult stages. They will help to answer questions about the evolutionary relationships and geographical distribution of the 10 living families of salamanders, as well as about the ancestry of salamanders — the order Caudata (urodeles) — as a whole. The urodeles are one of three orders that comprise the modern amphibians, the others being frogs and a limbless group known as the caecilians. The age of this deposit is based on radiometric dating and association with other fossils common to the Upper Jurassic (see Fig. 1 for timescale).

More than 500 specimens were collected from an area of less than 10 m^2 that had been buried by a volcanic eruption. The specimens include two species whose growth stages illustrate the main life-history strategies of modern salamanders. One exhibits the pattern of metamorphosis common to many living amphibians: aquatic larvae possessing external gills, with the gills being

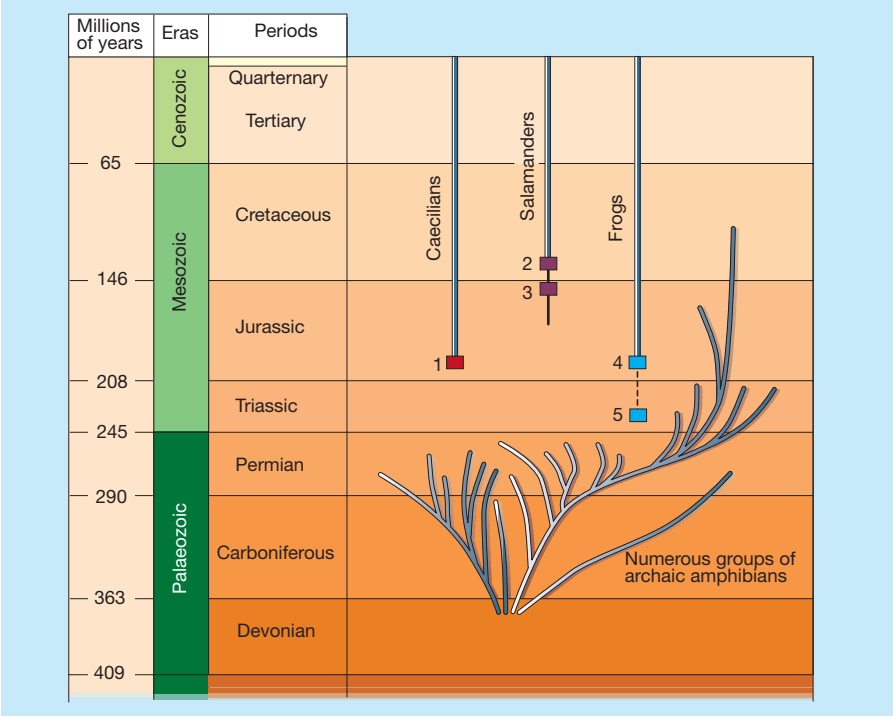

Figure 1 **Geological timescale showing the overall pattern of amphibian evolution, and the time of occurrence of the fossils discussed by Gao and Shubin[1] and shown in Fig. 2. 1, *Eocaecilia micropodia*. 2, *Valdotriton gracilis*. 3, The newly described[1] Chinese species. 4, *Prosalirus bitis*. 5, A Lower Triassic amphibian, close to the ancestry of frogs.**

lost in larger, more fully ossified specimens that are presumed to be terrestrial. The second species, like members of many modern salamander families, was apparently neotenic — that is, it reached sexual maturity without metamorphosing into a fully terrestrial form. That some examples of this species had reached maturity can be seen from the high level of ossification of the bones in the wrists and ankles. But the gill supports are also ossified, indicating that the creature still relied on external gills for aquatic respiration.

The fossils are immediately recognizable as salamanders from their body and limb proportions, as well as from details of the skull anatomy. They also share with modern salamanders a unique aspect of limb development, in which the two most anterior elements of the distal row of bones in the wrist and ankle are fused to form a single bone, known as the basal commune, that supports the first two digits. No group of vertebrates other than salamanders has this specific configuration.

The closest relationships of the Chinese specimens with living salamanders lie within the most primitive families, the Hynobiidae and Cryptobranchidae, which together constitute the superfamily Cryptobranchoidea. The Chinese fossils and cryptobranchoids share the retention of several bones that are lost in more advanced salamanders (including the lacrimal bone, which bears the lacrimal duct, and a separate angular bone in the lower jaw). But the fossil specimens appear to be even more primitive in their retention of a separate coronoid bone in the adult and the presence of more than three caudal vertebrae bearing ribs. Given the close affinities of the Jurassic species with the cryptobranchoids, Gao and Shubin argue that the initial radiation of all later salamander lineages occurred in Asia, before they spread to Europe and North America.

The primitive position of the Chinese species is evident from Gao and Shubin's phylogenetic analysis, which combines skeletal data from fossils and modern families with molecular evidence from living amphibians. But the consensus trees provide little resolution of the specific pattern of interrelationships of the more advanced families. Further study of these and other Mesozoic salamanders from China should allow the sequences in which the families diverged to be more reliably established.

The ancestry of salamanders remains highly contentious, and the newly discovered fossils should help here, too. It is generally accepted that salamanders shared

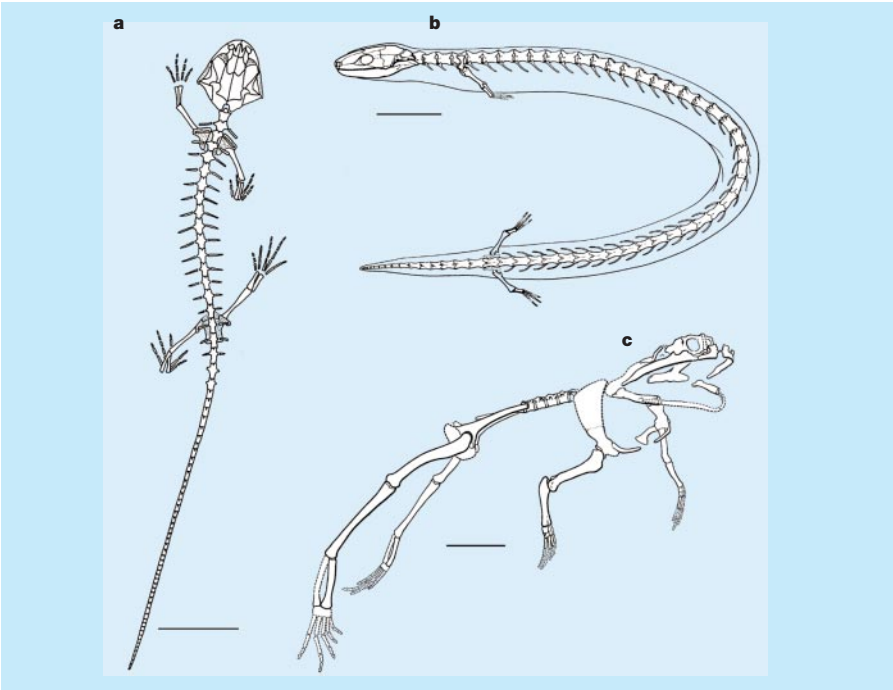

Figure 2 **Comparison of the body proportions and limb structures of a fossil salamander, caecilian and frog.** a, ***Valdotriton gracilis*[8], a salamander from the Lower Cretaceous of Spain. This species broadly resembles the Upper Jurassic salamander, described by Gao and Shubin[1], which underwent metamorphosis from an aquatic larval stage to a terrestrial adult.** b, **A caecilian (*Eocaecilia micropodia*) and,** c, **a frog (*Prosalirus bitis*) from the Lower Jurassic of Arizona. The distinct anatomy and way of life of Jurassic salamanders, caecilians and frogs, and the presence of a putative frog ancestor from the Lower Triassic, suggest that separate ancestral lineages for all three orders should be sought among Palaeozoic amphibians. Scale bars are 1 cm. Parts** a, b **and** c **are reproduced from refs 8, 5 and 4, respectively.**

with frogs and caecilians (which have greatly elongated bodies but lack limbs, and are restricted to the wet tropics) an immediate common ancestry that was distinct from that of all other terrestrial vertebrates. But the various hypotheses about the Palaeozoic ancestry of salamanders differ considerably[2,3].

The Chinese fossils and living cryptobranchoids show a host of features that indicate a long period of evolution after they had diverged from the ancestors of frogs and caecilians. The limb proportions of primitive salamanders are similar to those of most Palaeozoic amphibians, but they show no evidence of the jumping habit of frogs or the snake-like body of caecilians that were already established by the Lower Jurassic[4,5] (Fig. 2). Whereas frogs had evolved a highly derived tadpole by the Lower Cretaceous, with a distinctive filtering apparatus for feeding on microscopic plant material, salamanders retained gradual metamorphosis without a distinct change in diet between the larvae and adults.

The high degree of adaptive and structural divergence of the modern amphibian orders does not necessarily mean that they did not ultimately have a common ancestry. But it does point to the importance of establishing the specific ancestry of each of the three lineages, and how they may be related to the great diversity of Palaeozoic amphibians. In most aspects of their body proportions and feeding apparatus, primitive living salamanders resemble the Palaeozoic branchiosaurs[6] — small, immature amphibians with external gills. Like modern salamanders, many branchiosaurs were neotenic; this is a lifestyle that is not possible for frogs because they cannot reproduce before metamorphosis[7].

We have no fossil from the Upper Permian or Triassic to link the essentially modern salamanders of the Jurassic with any putative Palaeozoic ancestors. But the Chinese specimens now provide a way to compare the two — including not only the adult anatomy, but also the generally untapped information from larval stages and patterns of development that can also be studied in branchiosaurs. ■

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1. Gao, K.-Q. & Shubin, N. H. *Nature* **410,** 574–577 (2001).
2. Milner, A. *Herpetol. Monogr.* **7,** 8–27 (1993).
3. Laurin, M. & Reisz, R. in *Amniote Origins* (eds Sumida, S. S. & Martin, K. L. M.) 9–59 (Academic, San Diego, 1997).
4. Shubin, N. H. & Jenkins, F. A. *Nature* **377,** 49–52 (1995).
5. Jenkins, F. A. & Walsh, D. M. *Nature* **365,** 246–249 (1993).
6. Boy, J. A. & Sues, H.-D. in *Amphibian Biology* Vol. 4, *Palaeontology: The Evolutionary History of Amphibians* (eds Heatwole, H. & Carroll, R. L.) 1150–1197 (Surrey Beatty, Chipping Norton, New South Wales, 2000).
7. Wassersug, R. J. *Am. Zool.* **15,** 405–417 (1975).
8. Evans, S. E. & Milner, A. R. *Phil. Trans. R. Soc. Lond. B* **351,** 627–646 (1996).

Cancer

Chromosome defects in the colon

David M. Livingston

A tumour-suppressor protein known as adenomatous polyposis coli malfunctions in many colon cancers. So too does chromosome segregation during cell division. These features may somehow be connected.

The cells of many colon cancers have the wrong number of chromosomes, as well as defects in a protein called adenomatous polyposis coli (APC). Writing in *Nature Cell Biology*, Fodde and colleagues[1] and Kaplan and co-workers[2] provide surprising evidence for a cause-and-effect relationship between these two phenomena. The key to the puzzle is that, as well as having numerous other roles, the functional APC protein docks at chromosomal regions called kinetochores during cell division. Failure to do this seems to result in defects in the segregation of chromosomes into two daughter cells during cell division, as well as abnormal chromosome numbers.

The APC protein is a tumour suppressor; in other words, it normally contributes to the suppression of cancerous cellular characteristics. According to doctrine, APC's tumour-suppressing function is intimately linked to its participation in the efficient turnover of β-catenin. This protein is a key component of the Wnt signalling pathway — a multistep process that is involved in controlling development and cell proliferation. The best evidence for this view of APC's function is that colon cancer cells either have mutations in APC that are associated with accumulation of β-catenin, or have mutations in β-catenin that promote its own accumulation. In the latter case, the colon tumour cells have normal APC.

But APC has other functions, too. It is also involved in regulating the functions of certain networks of molecules that make up the cellular cytoskeleton. For example, it interacts with the ends of growing microtubules (a type of cytoskeletal filament), a function that is mediated by its carboxy-terminal region[3–5]. This portion of APC is also, at least in part, dedicated to interactions with EB1 — a protein that also interacts with microtubules, including those associated with the spindle (the chromosome-segregating apparatus) and centrosomes (organelles that produce the spindle)[6–10].

Given the link between APC and microtubules, and the involvement of microtubules in the spindle, Fodde *et al.*[1] and Kaplan *et al.*[2] wondered whether there is a relationship between the defects in chromosome segregation seen in colon cancer cells bearing mutations in APC[11], and the APC–microtubule connection. They show that, in cells that are dividing, APC is located at the ends of spindle microtubules that associate with kinetochores (Fig. 1) — the chromosomal regions to which the spindle attaches. Indeed, APC itself interacts with kinetochores, and this depends on the presence of an intact spindle apparatus. The authors also generated mutations in APC in mouse embryonic stem cells, which are embryonic cells with the potential to develop into many other cell types. The mutant stem cells, too, had aberrant chromosome numbers and underwent defective chromosome segregation — abnormalities that were not detected in controls. So there seems to be a direct link between normal APC function and chromosome segregation.

A yeast analogue of the mammalian APC-binding protein EB1 is known to be involved in the function of the spindle and in chromosome segregation[12–16]. So Fodde *et al.* searched for, and found, interactions between EB1 and kinetochores in mouse embryonic stem cells. They went on to show that disruption of the formation of an APC–EB1 complex was associated with abnormal spindle formation and incorrect chromosome numbers. So EB1 probably provides at least part of the molecular connection between APC and normal spindle function.

But how might APC influence processes at the kinetochore–spindle interface? The assembly of a spindle is crucial for correct cell division, and a 'spindle-assembly checkpoint' ensures that cells do not attempt to segregate their chromosomes until a proper spindle is in place. Neither group of authors detected a role for APC in the spindle checkpoint. But Kaplan *et al.* do provide evidence that two enzymes that are involved in the checkpoint, BUB1 and BUB3, probably associate with APC. Moreover, *in vitro* these enzymes efficiently added phosphate groups to APC.

Even more telling, this reaction was enhanced markedly by previous phosphorylation of APC by glycogen synthase kinase-3β, a key participant in the Wnt signalling pathway. So it appears that APC communicates with 'professional' spindle-checkpoint proteins, and might be influenced by them in a Wnt-dependent manner. Given these observations, one feels compelled to ask whether APC has finally grown beyond its distinguished origins in the Wnt pathway