HOW TO MAKE A TAPEWORM

In the evolution of animal body plans, tapeworms may not be thought of as examples of radical design, but their transformation from free-living flatworms into highly reduced, reproductive 'machines' involved a remarkable journey that has left biologists unable to make heads or tails of their anatomy. By studying their diversity, development and genomes, Museum biologist **Dr Peter Olson** explains how tapeworms can shed light on the mechanisms that produce animal diversity, and at the same time contribute to the fight against disease.

In many ways the iconic parasite, the tapeworm is best known for one thing: its long, segmented body. We fear this powerhouse of growth, as once inside us it extends and extends, segment by segment, winding its way through our gut absorbing the nutrients from the food we eat. But those segments are also a wonderfully adapted anatomical feature. The first true tapeworms weren't segmented at all, and as they evolved and diversified came the ability to develop multiple sets of reproductive organs in a single worm, allowing a great increase in the number of eggs produced. It was a step towards becoming reproductive 'machines'.

Tapeworms, like all parasites, are extreme r-strategists: they produce an enormous quantity of offspring while investing nothing in their care. These parasites simply release their young into the wide open environment, which then complete their life cycles by being transferred through the food web from one organism to another. Few of the offspring survive to sexual maturity so the need for a very large number of them to be produced is a tremendous evolutionary pressure.

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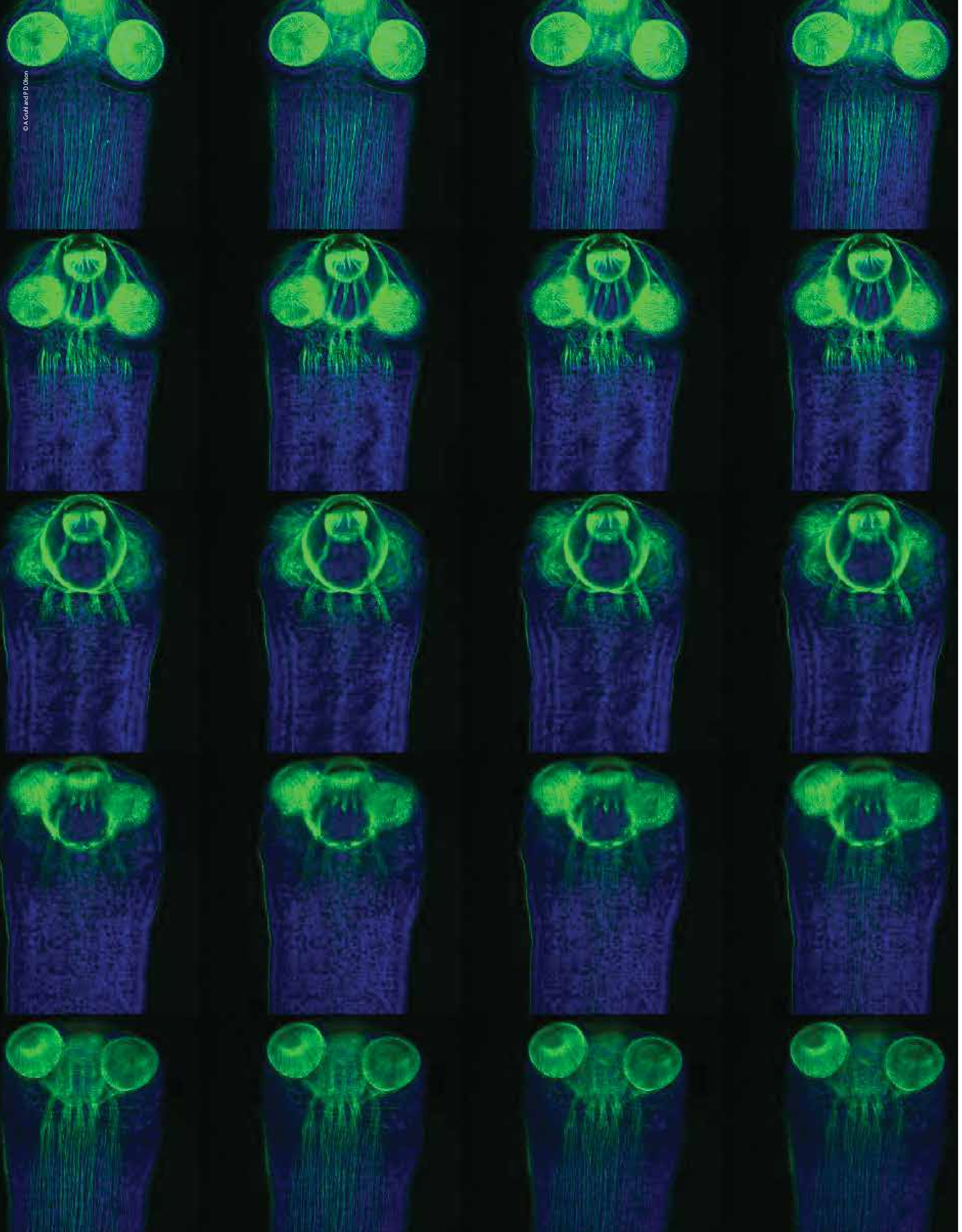

Previous Scanning electron micrograph of the mouse tapeworm *Hymenolepis microstoma*. This species is used as a model for laboratory research and is one of the first four tapeworms to have its entire genome sequenced. **Left** Optical sections through the scolex (head) of the mouse tapeworm. These specimens were stained using fluorescent antibodies specific to the muscles (green) and cell nuclei (blue).

This is where the advantage of segmentation is key. The early unsegmented tapeworms were reproductively quite prolific, but if a continuous chain of segments is produced, each bearing a set of reproductive organs, the output increases phenomenally, such that it has come to dominate the form tapeworms take today. But looking at their close relations, neither the tapeworm's immediate parasitic cousins the flukes, nor the more distantly related free-living flatworms, have segmented bodies. In fact, the closest segmented relatives are the annelids, including earthworms. But the annelids are so distantly related that this similarity in body plan is unlikely to have arisen through shared inheritance. Tapeworms must have evolved their own novel mechanism to become segmented.

HEADS OR TAILS

One hundred years ago biologists were still debating exactly what the tapeworm's segmented body represented. Was it a colony of animals joined together or just one individual? Part of the problem is that it's hard to tell which end of the worm is the head and which the tail. Indeed, as it develops from larva to adult the tapeworm's body effectively reverses along its head-to-tail axis so the head of the adult develops from the tail of the larva. Whether its 'head' can even be described as such is debatable as in the course of its evolution the head has been reduced to such a simple structure all it's good for is holding on inside the host's gut. In the transformation from free-living worms into obligate parasites wholly dependent on the host for survival, they also lost their guts and sensory organs. But their simple body plan and highly reduced anatomy is more than just a novelty, and more than just a case study in parasitism. They offer a unique opportunity to look at how genes that shape the development and anatomy of all animals are used to produce entirely new forms.

EXPLORING THE GENOME

To gain insight into how the tapeworm could change so much over its evolutionary history, biologists must consider its genome, studying not only how its genes relate to other animals but the processes involved in changing their anatomy. The first step is to characterise the genome itself, cataloguing and identifying every gene. In collaboration with leading researchers at the Wellcome Trust Sanger Institute in Cambridge, Museum researchers last year published their findings on the complete genomes of four tapeworm species in a report to the journal *Nature* (Tsai et al. 2013. 496:57-63), describing more than 10,000 genes. Three of the species sequenced are responsible for the most serious and prevalent tapeworm diseases of humans (see page 39), whereas the fourth is used as a model for research.

With this comprehensive directory of genes in place, the next step was to pinpoint which genes are involved in which aspect of the animal's development. The trouble is, nowhere in these vast stretches of data do we find explicit instructions on how to put the animal together or make it function. There are a lot of genes, but not all are active as such. The process of finding out which gene does what is done by sequencing expressed genes, those that are turned on when and where a certain function is performed. The identifiers are short-lived pieces of genetic material known as messenger RNA (mRNA), which act as templates for protein synthesis. Where a gene is being copied into mRNA it must therefore be in use. So it's the mRNA that biologists look for, acting as genetic signals for the processes that are happening.

For example, as a tapeworm grows, new segments are formed in the neck region. If we compare the genes in this area to genes in older, more mature segments further along the body we can determine the genes expressed specifically in the neck and infer that these are involved in producing new segments. Likewise this approach can identify changes in gene expression in response to a stimulus, like a novel drug or the host's immune system, and there are laboratories now actively pursuing these lines of investigation.

Having catalogued the tapeworm's genome and established which genes >

> Tapeworms, like all parasites, are extreme r-strategists: producing an enormous quantity of offspring

are functioning where and at what point in development, researchers from the Museum and Oxford Zoology Department have set their sights on the genes responsible for co-ordinating shape and form as animals grow. This particular class of developmental genes functions to turn other genes on and off, acting like molecular switches in the genome. This same process is at the heart of the diversity of form seen in the entire animal kingdom, and tapeworms show the largest loss of developmental genes of any animal examined to date. Specifically, those genes involved in an animal developing a head are mostly lacking from the tapeworm's genome, a reflection of their greatly reduced body plan. In contrast to this overall loss, tapeworms show an increase in other types of genes, particularly those involved in combating the immune defences, which are essential for the parasite to survive.

THE CANCER COMPARISON

As well as the far-reaching implications for how an animal develops its form, developmental genes are also key to biomedical research. These genetic switches work with signalling molecules that allow cells to communicate across different parts of the body. And it is these molecules and processes that most anti-helminthic drugs (those that work to rid the body of parasitic worms) are designed to target.

Whereas most adult tapeworm infections are readily treatable, some larval infections have parallels to cancer. Both can proliferate throughout the body, including critical organ systems such as the central nervous system, and both require a form of targeting the disease with surgery or drugs without damaging surrounding tissues. Tapeworms rely on immunological cues from their host animal for their development and where the host's immune system is compromised the growth of the tapeworm can more closely resemble the way a tumour grows than the way an animal does. A major impetus for sequencing tapeworm genomes is to find specific targets for chemotherapy. By identifying genes that code for proteins known to be inhibited by pre-existing drugs, researchers can inhibit the growth of tapeworms. In research so far, a surprising discovery has been that many of the targets discovered were the same as those used to control the growth of tumours. Thus not only is the spread of the disease similar to that of cancer in some cases, but potentially the treatment is, too.

The tapeworm and its genome will take much more deciphering, but what we know is that this unusual animal has become extraordinarily specialised over the course of its evolution, resulting in the loss of many genes common to free-living animals. Aspects of their biology that have perplexed biologists for more than a century are being addressed using techniques that were impossible only a decade before. This work can tell us how genes produce novelty in animal form and goes hand in hand with controlling the diseases they cause. Not bad for a worm.

More information on tapeworms and their genomes at **www.olsonlab.com**, **www.nhm.ac.uk/nature-online/species-of-the-day/scientific-advances/disease/hymenolepis-microstoma/index**, **www.sanger.ac.uk/research/projects/parasitegenomics**

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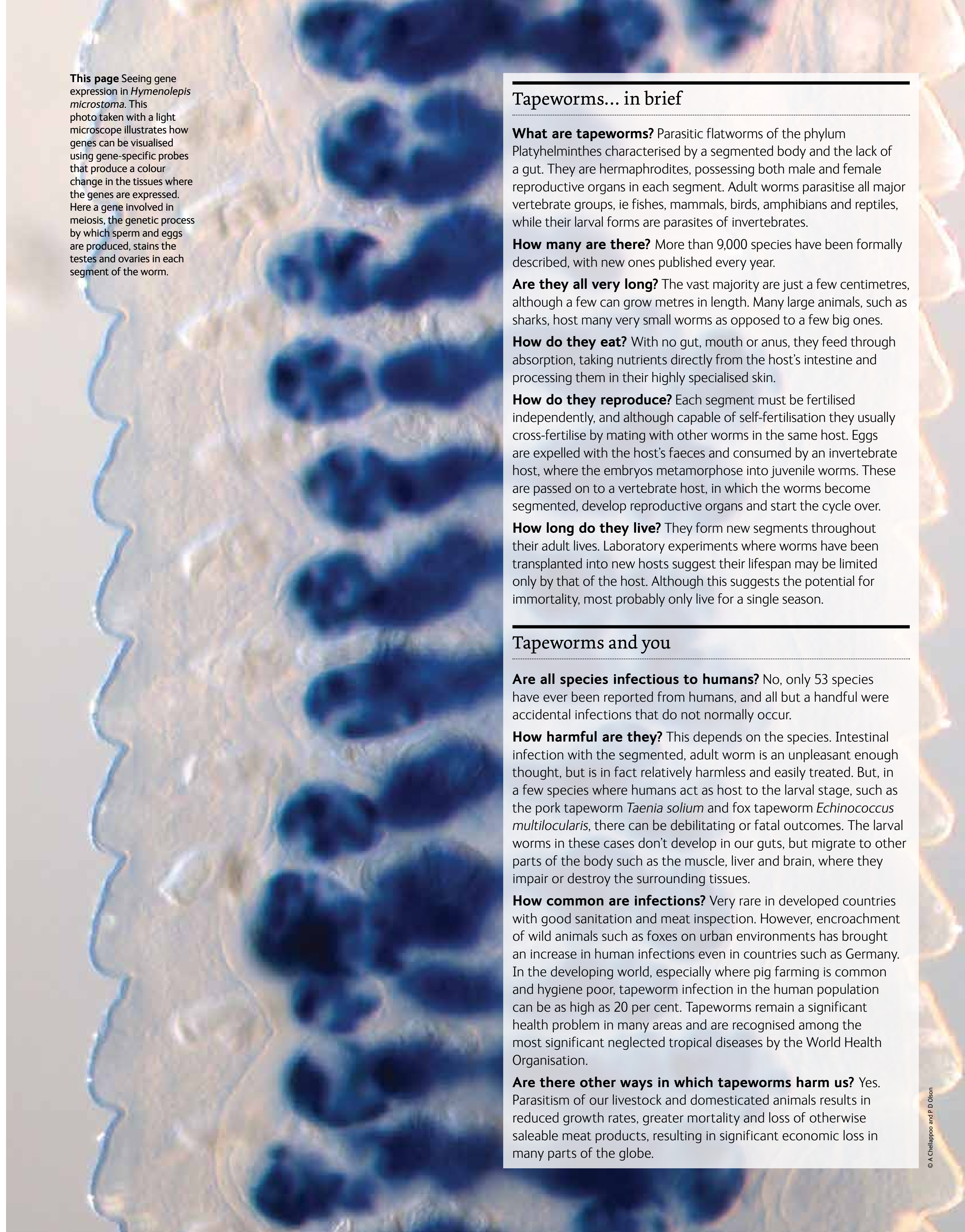

This page Seeing gene expression in *Hymenolepis microstoma*. This photo taken with a light microscope illustrates how genes can be visualised using gene-specific probes that produce a colour change in the tissues where the genes are expressed. Here a gene involved in meiosis, the genetic process by which sperm and eggs are produced, stains the testes and ovaries in each segment of the worm.

Tapeworms… in brief

What are tapeworms? Parasitic flatworms of the phylum Platyhelminthes characterised by a segmented body and the lack of a gut. They are hermaphrodites, possessing both male and female reproductive organs in each segment. Adult worms parasitise all major vertebrate groups, ie fishes, mammals, birds, amphibians and reptiles, while their larval forms are parasites of invertebrates.

How many are there? More than 9,000 species have been formally described, with new ones published every year.

Are they all very long? The vast majority are just a few centimetres, although a few can grow metres in length. Many large animals, such as sharks, host many very small worms as opposed to a few big ones.

How do they eat? With no gut, mouth or anus, they feed through absorption, taking nutrients directly from the host's intestine and processing them in their highly specialised skin.

How do they reproduce? Each segment must be fertilised independently, and although capable of self-fertilisation they usually cross-fertilise by mating with other worms in the same host. Eggs are expelled with the host's faeces and consumed by an invertebrate host, where the embryos metamorphose into juvenile worms. These are passed on to a vertebrate host, in which the worms become segmented, develop reproductive organs and start the cycle over.

How long do they live? They form new segments throughout their adult lives. Laboratory experiments where worms have been transplanted into new hosts suggest their lifespan may be limited only by that of the host. Although this suggests the potential for immortality, most probably only live for a single season.

Tapeworms and you

Are all species infectious to humans? No, only 53 species have ever been reported from humans, and all but a handful were accidental infections that do not normally occur.

How harmful are they? This depends on the species. Intestinal infection with the segmented, adult worm is an unpleasant enough thought, but is in fact relatively harmless and easily treated. But, in a few species where humans act as host to the larval stage, such as the pork tapeworm *Taenia solium* and fox tapeworm *Echinococcus multilocularis*, there can be debilitating or fatal outcomes. The larval worms in these cases don't develop in our guts, but migrate to other parts of the body such as the muscle, liver and brain, where they impair or destroy the surrounding tissues.

How common are infections? Very rare in developed countries with good sanitation and meat inspection. However, encroachment of wild animals such as foxes on urban environments has brought an increase in human infections even in countries such as Germany. In the developing world, especially where pig farming is common and hygiene poor, tapeworm infection in the human population can be as high as 20 per cent. Tapeworms remain a significant health problem in many areas and are recognised among the most significant neglected tropical diseases by the World Health Organisation.

Are there other ways in which tapeworms harm us? Yes. Parasitism of our livestock and domesticated animals results in reduced growth rates, greater mortality and loss of otherwise saleable meat products, resulting in significant economic loss in many parts of the globe.