When a tick takes hold

One of the less pleasant aspects of walking in many parts of the bush, or indeed strolling in some woody suburbs of our coastal cities, is the chance of later finding a tick or two latched onto your skin and busy sucking your blood.

About 70 species of ticks live in Australia, but only 13 of these are known to bite humans. Five may cause serious effects in their victims.

Broadly speaking, ticks can cause two types of problems: a range of unpleasant symptoms, including eventual paralysis, brought about by tick-injected toxins; or allergic effects of varying severity caused by the 'over-reaction' of the body's own immune system when confronted with specific foreign components from the tick. These 'allergens' — antigens that cause an allergic response — may not necessarily be chemically toxic in their own right or cause any damage other than through the allergic reactions that they stimulate in some people.

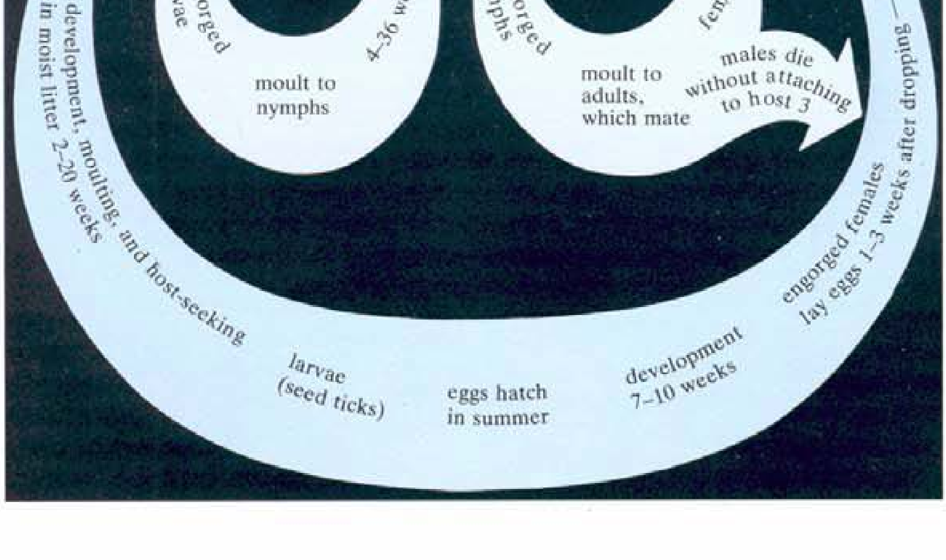
(Another potential problem with ticks is that they can also be the unwitting carriers of various disease-causing microbes, of which more in the box on page 17.)

Scientists have devoted a considerable amount of research to one particularly dangerous but common species of Australian tick — the so-called Australian paralysis or scrub tick, *Ixodes holocyclus*, which has the distinction of being one of the most toxic in the world. The creature occurs in moist habitats along the eastern coast of Australia from northern Queensland down to Lakes Entrance in Victoria. (Two related, but less well-studied, species of paralysis tick — *I. cornuatus* and *I. hirsti* — occur in southern Victoria and Tasmania, while Western Australia, as far as we know, has no paralysing ticks, although a related species, parasitic on numbats, does occur.)

The paralysis tick's principal hosts are bandicoots, either the long-nosed (*Perameles nasuta*) or the northern brown (*Isoodon macrourus*), but the parasite will happily attach to a variety of other wildlife hosts, including birds, and also to livestock, domestic pets, and you or me.

Tick paralysis in animals is usually fatal, and at least 20 known fatal cases in humans

Duration of the Australian paralysis tick's life cycle varies, but is usually about a year.



The itchy legacy of a bush-walk: tick-bites on a leg.

occurred in New South Wales between 1900 and 1945. Since then, there have been no further fatalities, but cases of paralysis still happen each year.

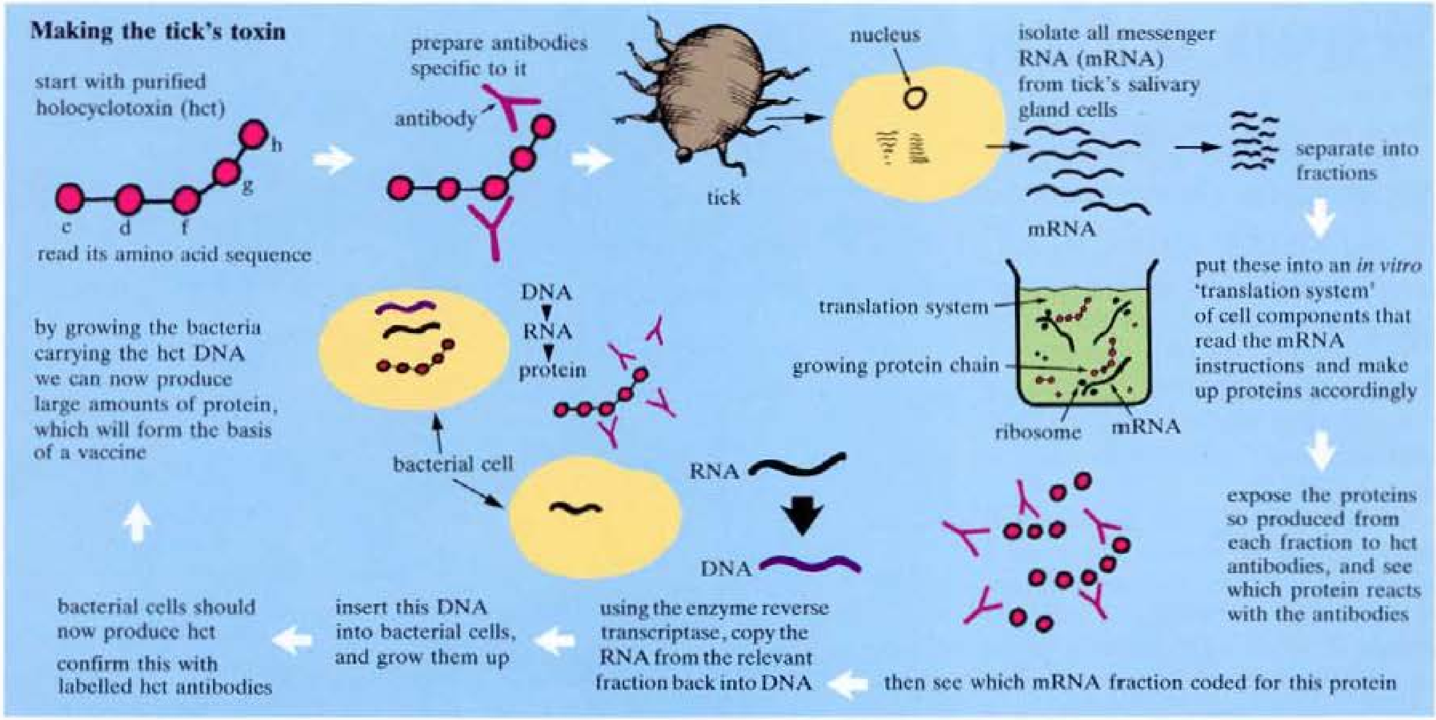
The symptoms move up the body, and start with unsteadiness in walking and tiredness, followed by weakness in the arms, vision disturbances, difficulty in swallowing, and, finally, difficulty in breathing, which can lead to death. Localised paralysis, such as in the face, can also occasionally occur.

Attached ticks do not feed continuously, although the rate at which they increase in size may suggest so. Periods of blood-sucking alternate with times of salivation, during which excess water from the host's blood is expelled in the parasite's saliva, along with substances designed to increase the host's blood flow to the area of attachment and to prevent clotting.

The paralysis toxin also enters at these times, but it is not produced in large amounts until the tick has been on the host for 4–5 days. Therefore, human paralysis is relatively rare, because we would generally notice and remove the tick before 5 days had elapsed. But animals are not so fortunate.

Toxin

Paralysis in livestock and pets is quite a problem in tick-infested areas, which is why Dr Bernard Stone and his colleagues at the CSIRO Division of Tropical Animal Production in Brisbane are attempting to produce a vaccine. Of course, such an achievement



Scientists are using genetic engineering techniques to produce holocyclotoxin, the Australian paralysis tick's toxin.

does not happen overnight, and the work has been in progress for several years. *Ecos* carried a report on it in 1983 (issue 43); since then, the CSIRO team have started work on producing the toxin by means of genetic engineering.

Dr Jim Aylward of the Division has isolated and purified the toxin from salivary gland extracts — an essential first step. The team is calling the substance holocyclotoxin, after the tick's species name. It is a protein that acts on the junction between nerves and muscles.

Usually, a nerve-ending releases molecules of a transmitter substance — acetylcholine is a common one — that diffuse across a minute space or junction to attach to a muscle's outer membrane, bringing about a change in its permeability to certain ions, and so triggering the firing of the muscle.

Various compounds can induce paralysis by interfering with this process: for example, curare — the potent poison that South American Indians used on arrow-tips — blocks the receptor sites for acetylcholine on the muscle membrane. Other substances, such as organophosphorus insecticides, inhibit the enzyme that normally breaks down acetylcholine, with the disastrous result that any muscle activated by a nerve remains in a state of full contraction — permanently switched on by the acetylcholine — and the victim dies in a rigid paralysis.

However, holocyclotoxin gives rise to a flaccid paralysis, and we now know that it does so by interfering with the release of the transmitter acetylcholine from the end of the nerve cell. The paralysis, if not severe enough to cause death by respiratory or cardiac failure, will disappear with time. Interestingly, laboratory studies on isolated muscles have revealed that holocyclotoxin has more effect at higher temperatures;

What makes a tick tick?

Ticks are not insects — they're arachnids, the class of creatures that also includes spiders, mites, and scorpions.

Arachnids have the dubious honour of perhaps being the layperson's most hated class in the giant and ubiquitous phylum Arthropoda (insects and crustaceans are other classes of arthropod). Like nearly all arachnids, ticks have a basic body plan that includes eight legs. (Insects have six legs.)

Mites and ticks together form an order within the arachnids. Most mites are tiny (0·2–2 mm in length) and live in soil or on vegetation. But many, such as the human scabies mite, are parasitic on the skin of vertebrates.

Ticks are generally larger than mites, some of them reaching a length of 2–3 cm. Their size varies according to whether they have taken their fill of blood (all of them are external parasites, feeding on blood). The female of *Ixodes holocyclus* is only about 4 mm at attachment, but enlarges to about 20 mm and may weigh as much as 1 g when fully engorged after a few days of feeding. Many mites and ticks act as vectors for various disease-causing organisms (see the box on page 17).

Two types of tick exist — soft and hard. In the soft ones, the large sack-like body hides the mouthparts and the bases of the legs; hard ticks, including *Ixodes* species, have projecting mouthparts and a hard shiny shield.

Soft ticks tend to live in colonies near their host's sleeping place, usually hiding by day, but emerging periodically when their host is present to take a meal; they generally produce relatively few eggs. Hard ticks usually spend longer on their hosts, after which the engorged female drops off to lay literally thousands of eggs. The larvae from these climb up vegetation and wait for a suitable host to pass by: the majority of them have no luck and eventually die, but their large numbers ensure successful reproduction.

Zoologists have described about 800 tick species world-wide. Most produce substances to 'cement' themselves to the host, and then establish a feeding lesion that receives tissue fluids and blood. The salivary secretions of the tick often contain pharmacologically active compounds that

At top, the back of a female of the Australian paralysis tick, *Ixodes holocyclus*, and, below, a view of its underside.

conversely, the paralysis may be the more easily reversed the lower the temperature becomes.

Vaccine

Now that the scientists have isolated the toxin from the many molecules present in the tick saliva, they need to produce it in large quantities as the basis for a vaccine. A suitably modified toxin molecule can be injected into animals and, without causing a paralysis, will stimulate the formation of antibodies that will react against the real toxin. The team has already demonstrated this in the laboratory; now they need ways of making enough toxin for a commercial product.

Dr Robert Don of the Division is using genetic engineering — inserting the gene coding for manufacture of the toxin into bacteria, which proliferate and produce the chemical — to procure large enough quantities for vaccine development. This is a great advance on previous attempts (reported in *Ecos* 43), which involved laboriously collecting the toxic secretions of ticks feeding on a liquid through an artificial membrane. Such methods also had the disadvantage of not giving a pure toxin to work with.

The tick team at CSIRO is collaborating with the Commonwealth Serum Laboratories and Coopers Animal Health Australia in the development of a commercial vaccine. Of course, the vaccine will not

increase blood flow to the region of attachment, and sometimes anticoagulants as well. They may also contain various enzymes. Taken together, these substances may cause local redness and itching, which differ from an allergic effect.

About 50 of the world's tick species can transfer toxins to their hosts. We don't know the real function of the toxins; those species that can't produce them don't seem to be any the worse off. The toxin might have evolved for another function — for example, local anaesthesia or prevention of blood clotting — perhaps only coincidentally affecting the nervous system of mammals as well, but once present it might have conferred an advantage, or at least no disadvantage, and so remained.

Dr Stone speculates that paralysis toxins, by reducing host movement, may make it easier for ticks to remain attached. However, it is worth noting that the native original hosts of *I. holocyclus* — such as bandicoots, possums, koalas, and some birds — are, as adults, usually immune to the paralysing effects of its toxin, suggesting a state of equilibrium has been reached over time. The more susceptible humans and their domestic animals are all relatively recent arrivals.

Ixodes holocyclus is an unusual tick in that only the female takes blood feeds; in most species, both sexes feed on their host. They come across each other on our warm skin (perhaps meeting over a blood meal) and copulate on the host. Then they drop off, and the female lays her eggs on vegetation a few days or weeks later.

In the case of *I. holocyclus*, the male is smaller than the female and has shorter mouthparts, incapable of piercing the skin of a mammal. To make up for his deficiency, he simply feeds on his partner, penetrating her skin and sucking juices directly from her abdomen — an interesting case of one parasite feeding on another.

As Jonathan Swift is alleged to have put it: 'Big fleas have little fleas upon their backs to bite 'em. Little fleas have smaller fleas and so *ad infinitum*.'

Even though fleas are insects and ticks are not, this ditty suggests they may have more in common than just a bad name and a propensity to suck blood.

stop ticks attaching: it will merely stimulate the host to produce antitoxin antibodies that, by binding to the toxin, will neutralise it and thereby prevent it exerting its effects on the nerve–muscle junction.

At present, veterinarians treating animals affected by the bite of the paralysis tick have to make do with an expensive antitoxin that they administer once the condition becomes apparent. The antitoxin preparation comes from the blood of dogs exposed to tick bites, and contains their natural antibodies to the toxin. Unfortunately, these canine antibodies themselves are foreign to other animals, and so can cause an unwanted reaction.

The high cost of antitoxin treatment and the fact that it is not protective mean that a vaccine — probably given annually to animals in tick-infested areas — is vastly preferable. The scientists are not considering the vaccine for human use, as cases of human tick paralysis are rare and, with quick killing of ticks, need not occur.

Allergies

Dr Stone has also turned his attention to a tick problem that troubles far more people than does paralysis, namely allergies. Reactions to tick bites constitute an occupational hazard for bush workers and campers in many parts of the country, as well as for inhabitants of suburbs such as those on Sydney's north shore where *I. holocyclus* is prevalent.

Reactions vary from mild effects around the area of the bite — which are probably not strictly allergic — to itching, swelling, and the development of blistering lesions. Other symptoms may include headache, rheumatoid pain, or, in severe cases, a frightening but rare manifestation of allergy called anaphylactic shock that may result in death.

The National Health and Medical Research Council helped finance Dr Stone in this world-first study of tick allergies. Dr Maryann Gauci assisted the work by devising tests to identify allergic individuals. These will help in clinical diagnosis of the problem of tick allergy, as well as in research.

Dr Gauci and Dr Stone, together with Professor Thong, a Queensland University clinical immunologist based at the Mater Hospital, found 50 volunteers in the Brisbane area. Some of these had suffered the attentions of the tick and showed allergic symptoms, while others showed none; still others had never been exposed to the tick. The scientists took blood samples and prepared sera from them. (Serum, a straw-coloured fluid, is blood without any red or white cells.)

They wanted to know whether a type of antibody from the serum called IgE, which is involved in this sort of allergic reaction, combined with tick components. This, if it happened, should be a clear indication of allergy to ticks.

The scientists prepared 'cocktails' of tick antigens, either from extracts of whole ticks or from the salivary glands only. They then used sensitive immunological techniques to detect any reactions. These tests clearly distinguished between 'positive' and 'negative' sera — that is, serum from sufferers of allergy to the tick and that from non-responsive subjects. Furthermore, the tests could measure the degree of severity of the allergies. Volunteers who had had heavy exposure to ticks during their lives and had strong reactions to them showed up as having more tick-specific Ig-E than those who exhibited only small local reactions to bites.

The scientists also found that the salivary-gland extract of the ticks was a more concentrated source of allergens than the whole-body extract. This may seem obvious, but it confirms that the allergy is brought about by an injected substance in tick saliva, rather than by our skin's contact with substances in the 'skin' of the tick.

Now that we know that the allergen or allergens are in tick saliva, can we identify them? In theory, the answer is yes, and the CSIRO scientists have already succeeded in partially purifying the components of the salivary-gland extract.

They found that two proteins bound large amounts of Ig-E, and three others bound it in much smaller quantities. The two main proteins occurred in high concentrations in the nymph form of ticks and adult females, but not in eggs, larvae, or males. This is quite significant, because in *I. holocyclus* only the females and juveniles feed on mammalian hosts (see the box on page 14 for more about the males' strange feeding habits).

Therefore, the scientists speculate, the major allergens may well be enzymes associated with feeding. They differ from the main toxin, since the allergen is secreted as soon as the tick attaches while, as we already know, the main toxin doesn't appear for 4–5 days.

But even before we precisely identify the allergens, we can still use salivary-gland extract to desensitise allergic people, a procedure that involves injecting patients with small quantities of the allergen or allergen-containing extract, causing them to build up an immunity to ticks in a controlled manner.

***I. holocyclus* can cause a wide range of reactions in people.**

Effects, common and rare

tick-bite reactions	clinical description
small local	painful, itchy, and red lesion persisting for up to 3 days
large local	painful red lesion generally greater than 50 mm diameter and persisting for a week or more
anaphylactic	whole-body reactions including itching, swelling of the larynx, spasm of the bronchi, colic, high blood pressure, and even collapse within 1 hour after tick bite
atypical	large local reaction followed by headache, nausea, lethargy, and pain in the joints persisting for a week or more
tick paralysis	neuromuscular paralysis and respiratory failure
tick-borne infection	spotty rash; swollen, tender lymph glands; fevers; and painful joints

Tick off!

If you find one of these paralysis ticks on you — see the photos to help with identification — what should you do? In the case of this species, Dr Stone warns that, strange as it may seem, removing the offending creature(s) alive may dramatically worsen the allergic or paralysis symptoms! This contrasts with the effects of another well-studied paralysis tick that lives in North America.

In the case of 'our' tick, *Ixodes holocyclus*, Dr Stone postulates that molecules of toxin and allergen may remain relatively concentrated in the host's skin lesion while the tick is attached. If somebody forcibly removes the live tick, then the defensive wall that the body forms around the injury

Tick-borne diseases

Throughout the world, ticks transmit a variety of unpleasant diseases to humans (and other animals). None of these diseases passes from person to person; rather, each is maintained in reservoirs of various wild animals and only 'accidentally' transmitted to us. Interestingly, the ticks themselves seem to be unaffected by the pathogens that they carry.

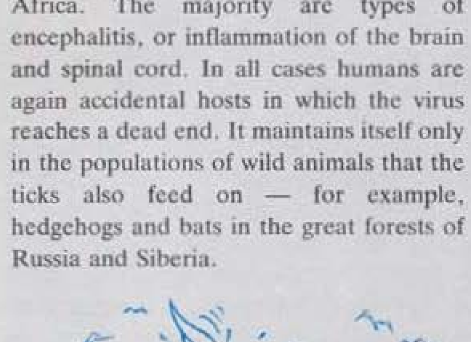
The rickettsiae — a rather unusual type of bacteria that grow within living cells — cause a group of related tick-borne diseases. All of these are characterised by fever, chills, headaches, and a skin rash. The most dangerous is the quaintly named Rocky Mountain spotted fever, which you can contract from ticks in North America. Untreated cases have a mortality rate of about 20% — even higher among old people. A similar, but milder, fever is transmitted by ticks in Mediterranean countries.

Rickettsiae also cause typhus (not to be confused with typhoid), which has similar symptoms to the spotted fevers. Typhus can be transmitted by lice and mites, as well as ticks. The severity of the disease is very variable.

In Australia, we have a fairly mild version called North Queensland tick typhus, which, incidentally, is not confined just to northern Queensland. It is caused by *Rickettsia australis* and transmitted by the Australian paralysis tick *Ixodes holocyclus*. Symptoms are low-grade fevers and a reaction at the tick-bite site, leading within about 10 days to the development of a raised black area called an eschar.

Fortunately, all these rickettsial diseases can now be well controlled by suitable antibiotics. But viral diseases cannot and, world-wide, ticks rate second only to mosquitoes as arthropod vectors of viruses.

Ticks carry about 12 known viral diseases, most of which occur in Asia and Africa. The majority are types of encephalitis, or inflammation of the brain and spinal cord. In all cases humans are again accidental hosts in which the virus reaches a dead end. It maintains itself only in the populations of wild animals that the ticks also feed on — for example, hedgehogs and bats in the great forests of Russia and Siberia.



In Australia, we know that ticks of sea-birds living on islands can carry at least one virus capable of infecting humans. There are suggestions that this and maybe other tick-borne viruses have actually caused human disease, but the reports have not been confirmed so we lack any hard evidence. Certainly scientists have noted that the migration of sea-birds may explain the world-wide distribution of some viruses and their tick vectors.

Recently, doctors have recognised a new tick-borne disease in the United States. Called Lyme disease, it takes its name from a small town in Connecticut where, in the summer and autumn of 1975, a group of children developed the painful symptoms of arthritis. At first, doctors thought they were dealing with juvenile rheumatoid arthritis, but the number of suffering children in Lyme and nearby towns was 100 times higher than the normal incidence of that complaint.

A year later, Dr Allen Steere of Yale University Medical School demonstrated that a tick normally living on deer transmitted the disease. The deer population has increased in America this century, and Lyme disease is a problem in pleasant suburbs where the inhabitants like to see the occasional wild deer wander across their lawns.

It was not until 1982 that researchers discovered that the causative organism was a spirochaete, a type of bacterium. (The spirochaetes are notorious because one of their number — *Treponema pallidum* — causes syphilis. However, Lyme disease is certainly not venereal and is seldom as severe as syphilis.) Early symptoms can include headaches, fevers, and flu-like muscle aches. These may subside of their own accord, but painful and swollen joints can develop later.

Now that it is recognised, the disease has been diagnosed throughout the United States, and has probably surpassed Rocky Mountain spotted fever as the country's most common tick-borne disease. Unfortunately, we now know that a similar affliction exists in Australia, several cases having been confirmed in the Hunter Valley, and four on the New South Wales south coast.

However, we don't yet know what acts as its vector here. Two tick species in the *Ixodes* genus transmit the disease in America, but neither occurs here. Whether or not our own *Ixodes* species are vectors remains unclear. It may be that insects, rather than ticks, are responsible, and sandflies and mosquitoes are under suspicion. Research to pin down the culprit carrier is now under way at Westmead Hospital in Sydney.

site may break, and toxin and allergen, which were previously 'bound' to various host cells, are probably released into the blood-stream in sufficiently large amounts to worsen the reaction. Furthermore, holding the tick to pull it out may squeeze out more saliva.

Dr Stone has discovered that, if you kill the tick *in situ*, the mouthparts shrink away from the host tissue and don't disturb the feeding lesion. He has found that 'personal' insect repellents containing pyrethrins or their synthetic counterparts quickly paralyse the tick, so preventing any further salivation. A very fitting death!

Roger Beckmann

More about the topic

Detection in allergic individuals of IgE specific for the Australian paralysis tick, *Ixodes holocyclus*. M. Gauci, B.F. Stone, and Y.H. Thong. *International Archives of Allergy and Applied Immunology*, 1988, **85**, 190–3.

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