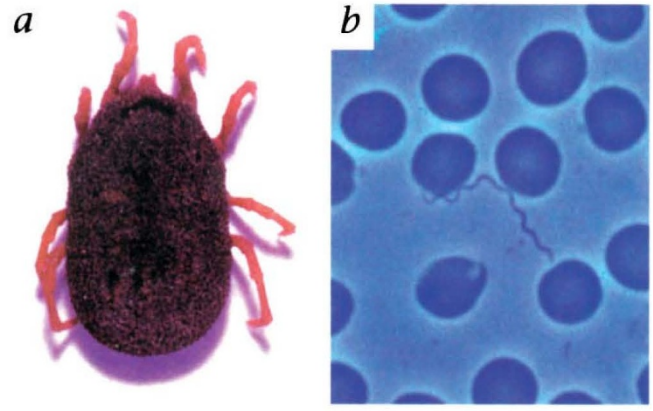

a, The soft tick *Ornithodoros turicata* is a vector of spirochetes of the species *Borrelia* that cause relapsing fever (magnification 7×). ***b***, A spirochete in a blood smear from a patient with relapsing fever (Wright's stain; magnification 1600×).

before the spirochetes entered the tick.

Temperature is one environmental variable that seems to affect VMP expression. Schwan and Hinnebusch found that lowering the temperature for spirochete cultivation from 37 °C to 23 °C (the typical temperature of ticks when not attached to mammals) increased the expression of VMP33 and decreased expression of mouse-associated VMP8. Although the authors do not characterize the function of either VMP33 or the mouse associated-VMPs, they suggest that these proteins may be important in transmission or colonization particularly because they are conserved among all *Borrelia* species.

The gene and promoter for the tick-associated VMP of *B. hermsii* are located on a different plasmid from the genes encoding the mouse-associated VMPs (ref. 7). How *B. hermsii* regulates expression of genes at two different loci is unknown. During serotype switching in the mouse, the expressed *vmp* gene is replaced by a different *vmp* gene on the same or different plasmids through DNA rearrangement[5]. In contrast, the gene for VMP33 does not undergo rearrangement: as expression from the tick-associated *vmp* locus increases, expression of the mouse-associated *vmp* gene appears to decrease (A.B., unpublished work).

The cyclical variation of VMP expression by *B. hermsii* is another example of a pathogen altering its phenotype as it moves from one type of host to another. Other infectious agents exhibiting such antigenic variation include those causing malaria, African trypanosomiasis and plague. *B. burgdorferi*, the etiologic agent of Lyme disease, expresses a completely different set of proteins in the tick and the mammal[8,9]. Outer surface protein (Osp) C, a *B. burgdorferi* protein that is homologous to VMP33 of *B. hermsii*[7], is preferentially expressed in mammalian blood at 37 °C instead of at 23 °C. Paradoxical though this seems, what VMP33 and OspC have in common (besides their sequence) is their association with tick salivary glands—the launching pads from which spirochetes invade their mammalian hosts. During the week-long blood meal of the *B. burgdorferi* tick vector, the spirochetes slowly travel from the intestine to the salivary glands, taking several days to reach their destination. Accordingly, expression of OspC is stimulated by the presence of blood in the tick intestine and the higher temperature close to the tick skin. On the other hand, *B. hermsii* spirochetes have to be present in the salivary glands of *Ornithodoros* ticks at the start of feeding because the tick blood meal only lasts an hour, too little time for the spirochetes to change surface antigens and move from the intestine to the salivary glands.

Several decades have passed since the last important studies of relapsing fever spirochetes in their tick vectors were published[10–12]. Why has a line of research initiated by Koch and other pioneering scientists been neglected for so long? One reason might be because ticks are a difficult experimental model to work with—life cycles measured in years make rearing them in the laboratory tedious and experiments lengthy. Moreover, research funding and the training infrastructure for the discipline of medical entomology dwindled after World War II, a response to the temporary victories of antibiotics and pesticides. This decline now appears to be short-sighted, particularly given the new threats posed by emerging and reemerging vector-borne infections, such as Lyme disease and malaria.

The article by Schwan and Hinnebusch as well as other recent studies may represent a turning point for scientific interest in (and research funding of) tick–pathogen interactions[13]. A renewed focus on the vectors of infection may yield new strategies to control and prevent arthropod-borne diseases. Contemporary investigators armed with the tools of molecular biology and genetics are successfully tackling problems that were first identified and described 50, 100, even 2,500 years ago.

1. Barbour, A.G. & Hayes, S.F. Biology of *Borrelia* species. *Microbiol Rev* **50**, 381–400 (1986).
2. Schwan, T.G. & Hinnebusch, B.J. Bloodstream versus tick-associated variants of a relapsing fever bacterium. *Science* **280**, 1938–1940 (1998).
3. Barbour, A.G. Linear DNA of *Borrelia* spp. and antigenic variation. *Trends Microbiol.* **1**, 236–239 (1994).
4. Stoenner, H.G., Dodd, T. & Larsen, C. Antigenic variation of *Borrelia hermsii*. *J. Exp. Med.* **156**, 1297–1311 (1982).
5. Kitten, T. & Barbour, A.G. Juxtaposition of expressed variable antigen genes with a conserved telomere in the bacterium *Borrelia hermsii*. *Proc. Natl. Acad. Sci. USA* **87**, 6077–6081 (1990).
6. Restrepo, B.I. & Barbour, A.G. Antigen diversity in the bacterium *Borrelia hermsii* through "somatic" mutations in rearranged *vmp* genes. *Cell* **78**, 867–876 (1994).
7. Carter, C.J., Bergstrom, S., Norris, S.J. & Barbour, A.G. A family of surface-exposed proteins of 20 kilodaltons in the genus *Borrelia*. *Infect Immun* **62**, 2792–2799 (1994).
8. Schwan, T.G., Piesman, J., Golde, W.T., Dolan, M.C. & Rosa, P.A. Induction of an outer surface protein on *Borrelia burgdorferi* during tick feeding. *Proc. Natl. Acad. Sci. USA* **92**, 2909–2913 (1995).
9. de Silva, A.M., Telford, S.R., Brunet, L.R., Barthold, S.W. & Fikrig, E. *Borrelia burgdorferi* OspA is an arthropod-specific transmission-blocking Lyme disease vaccine. *J. Exp. Med.* **183**, 271–275 (1996).
10. Davis, G.E. The relapsing fevers: tick–spirochete specificity studies. *Exp. Parasitol.* **1**, 406–410 (1952).
11. Burgdorfer, W. Analyse des Infektionsverlaufes bei *Ornithodorus moubata* und der natürlichen Uebertragung von *Spirochaeta duttoni*. *Acta Tropica* **8**, 196–262 (1951).
12. Aeschlimann, A. Développement embryonnaire d'*Ornithodorus moubata* (Murray) et transmission transovarienne de *Borrelia duttoni*. *Acta Tropica* **15**, 15–64 (1958).
13. Schwan, T.G. Ticks and *Borrelia*: model systems for investigating pathogen-arthropod interactions. *Infect. Agents Dis.* **5**, 167–181 (1996).

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The complete genome sequence of a fellow spirochete, *Treponema pallidum*, the bacterium that causes syphilis, appears in the July 17th issue of *Science*. The genome map compiled by Weinstock and Norris (University of Texas Health Sciences Center) and Fraser's group at The Institute for Genomic Research (Rockville, Maryland) identifies a number of novel *Treponema* genes, including 12 that encode surface membrane proteins which may be valuable as targets in vaccine development.

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