like those of AEP will be discovered. Nonetheless, the fact that antigen presentation is inhibited by competition for substrate at all, favours AEP as the protease that selectively makes the first cut in tetanus toxin.

An exciting prospect is the as-yet-hypothetical involvement of discrete, possibly unique, sets of proteases in converting certain self-proteins into the class II MHC–peptide complexes that trigger an autoimmune response. By identifying such proteases — and AEP could be amongst them — we could selectively inhibit them to blunt the severity of an autoimmune attack, if not prevent it altogether. Given the malleability of protease inhibitors in the medicinal chemist's hand, proteases may turn out to be the preferred targets for development of small-molecule immunomodulators. □

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Superconductivity

An analogue of superfluid ^{3}He

Maurice Rice

Two letters to *Nature*[1,2] published in the past few months, and one in this issue[3] (page 658), report experiments that uniquely specify the unconventional superconductivity in strontium ruthenate (Sr_2RuO_4). They establish that it conforms to long-held views on how superconductivity driven by electron–electron (rather than electron–phonon) interactions should behave. These developments contrast with the heated debates that have swirled for a decade around the high-temperature copper oxide superconductors. Yet there are many similarities in the underlying electronic structures of the ruthenates and the copper oxides.

Shortly after the Bardeen, Cooper and Schrieffer (BCS) theory of conventional electron–phonon-driven superconductivity appeared in 1957, Kohn and Luttinger[4] proposed a generalization to electron–electron interactions. The BCS theory starts from a normal metallic state with its 'Fermi liquid' of mobile electrons, with their interactions well described by the perturbative Landau theory. As the temperature is lowered an effective attraction between the electrons near the Fermi level arises from the exchange of phonons, or lattice vibrations, which grows in strength and overcomes the Coulomb repulsion. This net attraction binds two electrons to form an isotropic spin-singlet Cooper pair in a state of zero angular momentum (that is, *s*-wave). The origin of superconductivity is the condensation of the centre of mass motion of these pairs to form a coherent quantum state.

Kohn and Luttinger[4] showed that even when the electron–electron interaction was predominantly repulsive it could still cause a subtle attraction, forming Cooper pairs in a higher angular momentum state (such as *p*-wave or *d*-wave). This attraction was estimated to be very weak in simple metals. As a result, any such unconventional superconducting state would be difficult to observe due to a very low transition temperature (T_c), and then only in highly perfect crystals. But the attraction should be higher in transition metals and other materials, where the electronic states are concentrated close to the ions, thereby strengthening the interactions between electrons. In particular, if these interactions are strong enough to drive the metal to the verge of magnetic order, then the attractions would be further heightened by the exchange of magnetic fluctuations. The discovery in the 1970s of just such *p*-wave Cooper pairing in the neutral Fermi-liquid, ^{3}He, stimulated the search for an electronic counterpart.

In the 1980s, superconductivity was discovered in a class of rare earth and actinide compounds known as heavy fermion metals. Here the relevant electronic states (4*f* and 5*f*) are even more compact and the proximity to magnetic order favours superconductivity (see ref. 5 for example). Surprisingly, the large class of transition metal oxides rarely shows superconductivity, although the variety of their spin and charge ordering attests to the presence of strong interactions.

Four years ago, Maeno and collaborators[6] succeeded in preparing high-quality Sr_2RuO_4 and found a metallic state with hallmarks of a Landau–Fermi liquid, and a superconducting transition at $T_c \sim 0.7$ K. The crystal structure is that of the $La_{2-x}Sr_xCuO_4$ copper oxide family. It consists of two-dimensional RuO_2 planes, and quantum coherence between the electrons in different planes occurs at $T < 50$ K. The most definitive

100 YEARS AGO

It is naturally difficult to obtain direct evidence as to how birds rid themselves of the indigestible parts of the fruit they eat. It is a question to which I have given some attention from its bearing on the dispersal of seeds. I have found large quantities of the seeds of hawthorn, dog-rose, mistletoe and ivy evidently voided by birds, as I incline to think generally as faeces, especially in the case of the hawthorn and ivy. Some large bird, I suppose the rook, consumes ivy berries largely in the spring, and gets rid of the seeds in what appears to be a mass of excrementitious matter. Many of these have not lost their vitality, and germinate readily in the same season. I have some thriving ivy plants obtained from such seed sown in 1896 and numerous seedlings this year of similar origin, the seed being sown on April 28, and coming up on June 7. I do not think much stress need be laid on the fact that much of the fruit swallowed is voided undigested, though the mistle-seeds I found were in a mass something like a lump of frog-spawn, with much of the pulp of the berry still adhering to each seed. I fancy birds and beasts, like many human beings, frequently swallow greedily far more than is good for them, especially when they light upon an abundant supply after enforced abstinence.

From *Nature* 15 December 1898.

50 YEARS AGO

In recent discussions on blinking, it has been taken for granted that, in a physical experiment, an object cannot be kept under continuous observation. The difficulty, however, is easily overcome. It is easy to acquire the habit of blinking the eyes alternately and, provided the period is made slightly shorter than that associated with normal blinking, no discomfort results. I have used this technique in the laboratory for more than twenty years, and have always assumed that it was generally known; but this, apparently, is not the case.

From *Nature* 18 December 1948.

Many more abstracts like these can be found in *A Bedside Nature: Genius and Eccentricity in Science, 1869–1953*, a 266-page book edited by Walter Gratzer. Contact Lisa O'Rourke. e-mail: l.orourke@nature.com

proof of the sharp Fermi surface in the normal state, which is central to the perturbative Landau theory, is the observation of periodic oscillations in the magnetization as the magnetic field is varied, known as de Haas–van Alphen oscillations. Mackenzie *et al.*[7] succeeded in observing these oscillations and determined the shape of the Fermi surface, which agreed with band-structure calculations. The effective electron masses are unusually enhanced (factors of 3–5), indicating a strongly interacting Fermi liquid. The formal valence is Ru^{4+}, implying four electrons in bands of predominantly 4*d* character with {xy, yz, zx} symmetry, all of which contribute to give three Fermi surface sheets with cylindrical topology.

The Ru^{4+} ion can be viewed as two holes in the 4*d*-complex and by Hund's rule their spins align parallel to give a triplet, $S = 1$, ion. Furthermore, the related cubic compound $SrRuO_3$ is a ferromagnetic metal. Such considerations led myself and Sigrist[8] to speculate that the electrons in the Cooper pairs would have aligned spins leading to triplet superconductivity, and an odd orbital (for example, *p*-wave) wavefunction, analogous to ^{3}He and contrasting with the spin singlet *d*-wave pairing in the copper oxides.

Experiments determining the symmetry are now at hand. Luke *et al.*[1] performed spin-resonance experiments on muons implanted in Sr_2RuO_4, which are a sensitive test for induced magnetic fields in the superconducting state. The observation of such fields shows that the angular momentum of the Cooper pairs is not quenched by the crystal environment, and that the superconducting state has a broken time-reversal symmetry. Ishida *et al.*[3] show that the Knight shift of the NMR peaks (which measures spin susceptibility) of oxygen nuclei remains unaffected by the transition to superconductivity. This is a clear sign of triplet pairing, because singlet pairing necessarily has a vanishing spin susceptibility as $T \rightarrow 0$ K.

There is another twist to the story. Specific-heat measurements[9] showed that only about half of the Fermi surface had an energy gap in the superconducting state. A characteristic of Cooper pairs is that they can always scatter around a Fermi surface, conserving energy and momentum. As a result the whole Fermi surface should participate in electron pairing and possess an energy gap. Agterberg *et al.*[10] suggested that the highly planar character of Sr_2RuO_4 would prevent scattering between {xy} and {yz, zx} sheets of the Fermi surface owing to their differing parities under reflection (that is, $z \rightarrow -z$). The question then is, which sheets are involved in the superconductivity?

Neutron scattering experiments by Riseman *et al.*[2] provide the answer. Agterberg[11] calculated that, in a magnetic field, the vortex lattice of flux lines that penetrate the material should unusually have square symmetry, whose orientation depended on which Fermi surface sheets are involved in superconductivity. Riseman *et al.* confirm the square symmetry, and from its orientation it follows that the pairing is occurring on the {xy}-sheets. The results yield a complete description of the superconducting state — it is a two-dimensional analogue of the A-phase, one of the two distinct superfluid phases observed in ^{3}He.

So what have we learned? In a Landau–Fermi liquid, spin fluctuations can strengthen the pairing attraction, but it remains weak. Simultaneously, the mass enhancement lowers the characteristic energy scale of the attraction. As a result T_c is low. This combination of low T_c and unconventional superconductivity makes for extreme sensitivity to sample defects. Indeed, in the Sr_2RuO_4-system a residual resistivity under 1 $\mu\Omega$cm is required to observe superconductivity[12]. Presumably many more unconventional superconductors could be found among the transition metal oxides if only they could be made perfect enough.

Although it is pleasing to see the original theory of superconductivity driven by electron–electron interactions verified, this route doesn't lead to high T_c. The copper oxides have a much higher T_c than the ruthenates; so what sets them apart? It cannot be the nearly two-dimensional character or the presence of strong spin fluctuations. These features are common to both. One difference lies in the formation in ruthenates of a well-defined Landau–Fermi liquid in the normal state ($T > T_c$). As emphasized by Anderson and others, such Landau character breaks down in the copper oxides. But this is a symptom rather than the cause of the

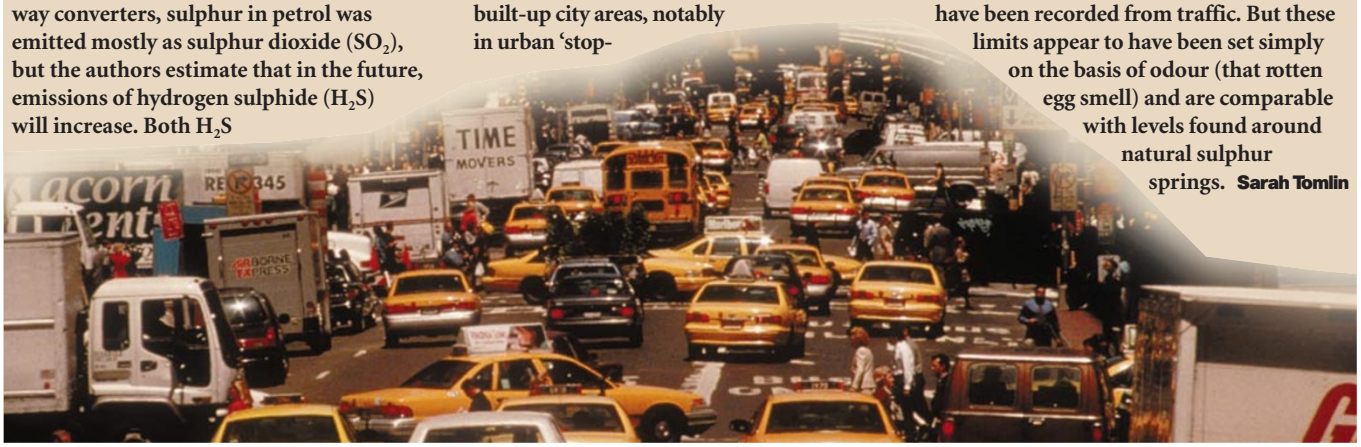
Atmospheric chemistry

Smelly cats

Since January 1993, all new cars in the European Union have had to be fitted with a three-way catalytic converter. Although three-way converters will lower emissions of certain harmful chemicals, such as oxides of nitrogen, S.F. Watts and C.N. Roberts raise the question of whether they may result in a shift in the balance of sulphur species, especially in cities (*Atmospheric Environment* 33, 169–170; 1999). Before the introduction of three-way converters, sulphur in petrol was emitted mostly as sulphur dioxide (SO_2), but the authors estimate that in the future, emissions of hydrogen sulphide (H_2S) will increase. Both H_2S and SO_2 are respiratory toxins, but only levels of SO_2 are regularly monitored.

The data are both few and preliminary. Nonetheless, roadside measurements of H_2S in Britain and the United States seem to indicate that it reaches higher levels in Britain. Watts and Roberts speculate that this is due to different driving conditions, and point to previous studies that identified situations that favour higher emissions of H_2S instead of SO_2. These include driving in built-up city areas, notably in urban 'stop-and-go' traffic, and the first 10–20 km of a journey after cold starting, when the engine is rich in fuel. In Britain, as many as 40% of all car journeys are under 5 km and with increasing traffic congestion, the situation is likely to get worse.

Not only are emission data scarce, but it is hard to evaluate the levels of exposure that are harmful to humans. Concentration levels have been set for occupational hazards that are many times lower than have been recorded from traffic. But these limits appear to have been set simply on the basis of odour (that rotten egg smell) and are comparable with levels found around natural sulphur springs. Sarah Tomlin



difference. Perhaps the key distinction is the antiferromagnetic nature of the spin fluctuations in the copper oxides, whereas in Sr_2RuO_4 they are ferromagnetic. Only in the antiferromagnetic case do resonant valence bonds with their special stabilization of singlet pairs form. Maybe details of the dispersion of the energy bands also play a role.

We now have a complete description of the unconventional superconductivity of Sr_2RuO_4. But it sharpens the most burning question in condensed matter physics today — just what is it that is so special about the high-T_c copper oxide superconductors? □

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Apoptosis

Death deceiver

Douglas R. Green

The simple fact that cancer cells survive beyond their normal 'die by' date has only in the past decade been incorporated into our understanding of tumorigenesis. How transformed cells evade death provides insights not only into cancer, but also into the molecular mechanisms of apoptotic cell death, which eliminates those normal cells that might turn cancerous. On page 699 of this issue, Pitti *et al.*[1] report a newly discovered mechanism that tumours use to avoid a death signal — the production of a soluble molecule which binds to, and neutralizes, a trigger for apoptosis.

Fas (also known as CD95 or Apo-1) acts as a receptor on many different types of cell. When bound by its ligand (Fas ligand; FasL), Fas delivers a signal that leads to cell death (Fig. 1a). This is an important pathway for apoptotic cell death, although it is only one of several[2]. Pitti *et al.* have now identified a molecule, which they call decoy receptor 3 (DcR3), that can also bind to FasL and block its binding to Fas. Moreover, DcR3 is genetically amplified in a number of lung and colon carcinomas, suggesting that Fas/FasL interactions limit cancer growth, and that cells expressing higher levels of DcR3 are more likely to become cancerous.

As well as amplified DcR3, transformed cells often produce a soluble form of Fas that can block the interaction between normal Fas and FasL[3]. Furthermore, Fas is mutated or downregulated in some cancers. These (and other) mechanisms interfere with the Fas pathway, which may then contribute to oncogenesis. In addition, although congenital defects in Fas expression or function cause a lymphoaccumulative syndrome, with accelerated autoimmune disorders, they are also associated with an increased risk of cancer in some individuals. These observations raise the intriguing possibility that Fas and FasL are tumour suppressors.

How, then, does FasL limit cancer such that its inhibition by DcR3 might favour the disease? Pitti *et al.*[1] suggest that when DcR3 binds FasL, tumours may be able to evade surveillance by cytotoxic lymphocytes, which express FasL and can kill Fas-positive target cells (Fig. 1b). If so, such immune surveillance represents the selection for DcR3 amplification in tumour cells. Although this is certainly a possibility, cytotoxic T cells have another potent killer mechanism at their disposal — they can release the contents of their cytotoxic granules, activating apoptosis downstream of Fas and other apoptotic pathways.

There are several other possibilities to explain how FasL restricts tumour growth. For instance, it is not only expressed on cytotoxic lymphocytes. Some tissues, such as the eye or testis, express FasL constitutively, and in other tissues (the intestinal epithelium, for example) FasL is inducibly expressed[4]. It is possible that tissue disruption caused by a tumour could trigger this expression and kill any Fas-sensitive transformed cells (Fig. 1c). Metastasis of lung melanoma has been shown to be suppressed by functional FasL (perhaps on the lung epithelium?) acting on tumour cells susceptible to Fas-mediated apoptosis[5].

But FasL need not come from surrounding cells, as many tumours (including non-lymphoid tumours) themselves express functional FasL. DNA-damaging agents can trigger FasL production[6], so increased expression of DcR3 might also be an adaptive response to cancer therapy (Fig. 1d). In a system designed to mimic the effects of chemotherapy on colon carcinoma cells, inhibition of FasL function preserved the ability of the cells to grow[7]. So increased expression of DcR3 may give tumour cells

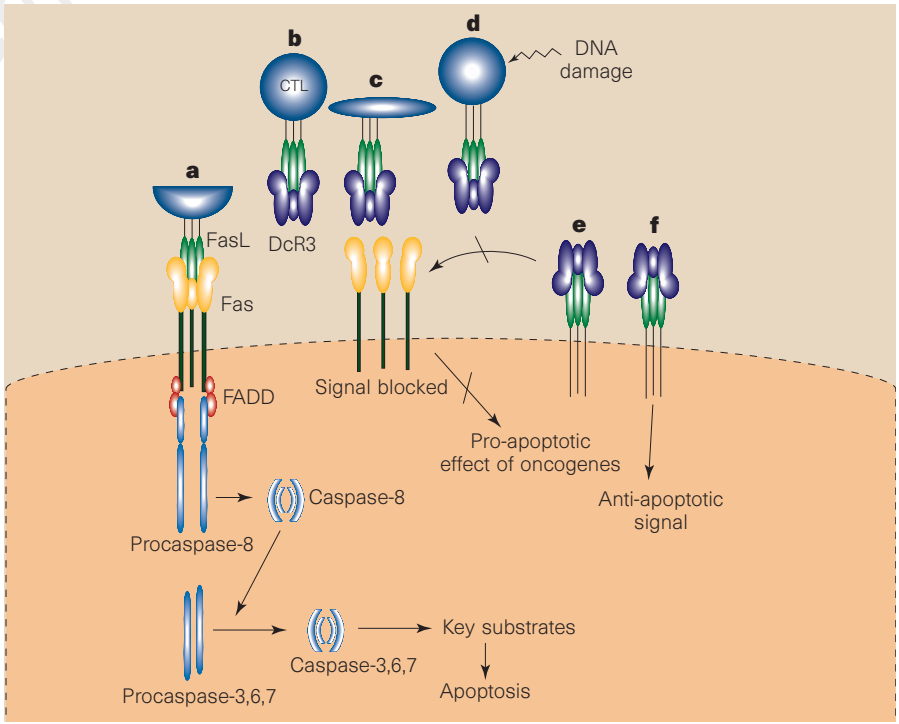

Figure 1 **How DcR3 promotes tumorigenesis.** a, **Normally, trimerization of FasL-bound Fas recruits the cytoplasmic adaptor molecule FADD which, in turn, recruits procaspase-8, the precursor of an initiator caspase (cysteine protease with aspartic-acid specificity) involved in apoptosis. Two procaspase-8 molecules process one another, and assemble to form the mature, active caspase. This cleaves and activates other caspases (directly or indirectly[2]), which then orchestrate apoptotic cell death.** b–f **Anti-tumorigenic measures that may be blocked by the binding of DcR3 to FasL.** b, **Cytotoxic lymphocytes (CTLs) express FasL.** c, **Surrounding cells express FasL in response to tumour infiltration.** d, **DNA damage by therapeutic agents induces expression of FasL on tumour cells, which may kill neighbouring cells.** e, **Fas/FasL signalling normally contributes to the pro-apoptotic effects of oncogenes (such as c-Myc).** f, **Ligation of FasL delivers an anti-apoptotic signal to the cell.**