100 YEARS AGO

Earthquakes. **By Clarence Edward Dutton. Major Dutton's work belongs to another category, and rather than telling us what earthquakes do, his main object has been to tell us what they are… Everything is discussed with a minimum of mathematics from a strictly scientific standpoint, whilst that which is sensational has properly been most carefully put under taboo. A justification for the exclusion of what is of practical importance, which gives not only to the man in the street but to Governments some inkling as to the use of earthquakes, is not so apparent. It is extremely likely that a Prime Minister may not care a twopenny-bit whether the inside of the world on which he lives is red hot stone or cold, while he might be extremely interested to know that seismograms may afford a satisfactory explanation for the interruption of his cablegrams. The importance of earthquake writings to communities who have been alarmed by accounts of disasters in foreign countries is self-evident, while it would at least be consoling to those who were suddenly cut off from the outer world by the failure of their cables to learn whether such failures were the result of an operation of war or of nature.**

From *Nature* 15 December 1904.

50 YEARS AGO

The structure of fibrous proteins has long been a subject of controversy. X-ray and electron microscope evidence has accumulated which suggests that single chains may not run the whole length of the fibril, but that the latter is made up of an aggregation of smaller parts of quite definite size. In collagen the sub-unit has been considered to be a protofibril of size about 640 × 12 A., although recently Schmitt has proposed a unit of about 2000 × 50 A., which he has named 'tropocollagen'. Striations of axial lengths about 210 A. (particularly in developing material) and 70 A. are also observed in electron micrographs of collagen. It is of interest to note that evidence for structure of size approximately 200 A. is found in α-keratin and 230 A. in fibrin, although the recurrence of this figure may be no more than coincidental. We have obtained X-ray diffraction evidence from dry collagen fibres which also suggests that the predominant 640 A. period is divided into sub-units of length about 210 A. **A. C. T. North, P. M. Cowan, J. T. Randall**

From *Nature* 18 December 1954.

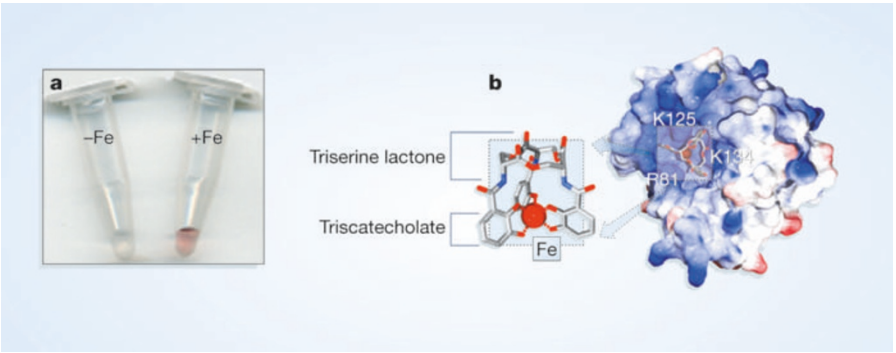

Figure 1 **Snatching bacterial iron.** a, **In the presence of iron, solutions of the lipocalin 2 protein, synthesized in the laboratory, are distinctively *rosé*; without iron, they are colourless[10]. This demonstration led to the discovery that a ligand for lipocalin 2 is bacterial enterochelin — a secreted iron-chelating molecule.** b, **Bacterial enterochelin is composed of a triserine lactone molecule, which has three catecholate groups. These groups, between them, chelate an iron atom or ion. The iron–enterochelin complex can in turn be buried in the calyx of lipocalin, between three positively charged amino acids (R81, K125 and K134, where R is arginine and K is lysine). Flo *et al.*[1] have now found that lipocalin 2 is necessary for mice to keep bacterial infections in check; it works by stealing bacterial iron. (Molecular models courtesy of R. K. Strong, Fred Hutchinson Cancer Research Center, Seattle.)**

Flo *et al.* reveal yet another mechanism: mammals can steal siderophores.

The authors first discovered that, during a bacterial infection, the mammalian liver, spleen and macrophages synthesize the lipocalin 2 protein, raising its concentration in the serum by log orders of magnitude. The lipocalins are a large family[9] that have attracted structural biologists' attention because, although they vary in amino-acid sequence, their three-dimensional structures are remarkably conserved. They are made up of strands of so-called β-sheets, which form a barrel or a cup-like structure, or calyx, that carries small chemicals. A well-known example is the retinol-binding protein, with its retinoic acid ligand. So what is the chemical carried by lipocalin 2? Two years ago, Goetz *et al.*[10] showed that iron-containing solutions of cloned lipocalin 2 are bright red (Fig. 1). Using several structural-analysis techniques, they tracked down the source of the red colour to the presence of iron-bound enterochelin.

The affinity of lipocalin 2 for enterochelin is very high (10^{-10} M), suggesting that this bacterial siderophore might be the authentic ligand (indeed, lipocalin 2 has been tentatively renamed siderocalin[10]). The idea is not so far-fetched — nitrophorin lipocalins (from the salivary gland of *Rhodnius prolixus*, the insect that spreads the parasite that causes Chagas' disease) were already known to carry iron-loaded haem groups[11]. And lipocalin from human tears binds to bacterial and fungal siderophores[12].

Nonetheless, all of this might have been dismissed as an artefact of the cloning of lipocalin 2. Instead, it seems that it actually revealed an *in vivo* function. Using mice in which lipocalin 2 had been knocked out, Flo *et al.* unequivocally show that the protein is essential for limiting the growth of common bacteria that produce enterochelin, but does not affect the growth of bacteria that rely on non-catecholate siderophores or other methods of iron acquisition. Eliminating lipocalin 2 increased bacterial colony counts by log orders of magnitude, and caused the rapid demise of the knockout mouse. Conversely, lipocalin 2 limited bacterial growth *in vitro* and *in vivo*, until reversed by excess siderophore. So lipocalin 2 directly regulates iron-dependent bacterial proliferation in mice — and probably, therefore, in humans.

These findings raise many issues for us to ponder. For instance, what happens to lipocalin 2 once it has chelated the siderophore and its iron? Recent work suggests[13] that the kidneys filter and reabsorb the complex, recycling its iron. This pathway protects the kidney tubules from stress, hinting that the function of lipocalin 2 does not stop with stealing iron from microbes — the iron-loaded protein may also have other activities in mammalian cells. Indeed, lipocalin 2 is produced in massive amounts by cells that are damaged by chemicals or oxygen depletion in the absence of bacterial infection. This suggests that the production of lipocalin 2 is either a stress response that was originally intended as a defence against bacteria, or perhaps a mechanism for shuttling an unidentified endogenous ligand into cells. That endogenous ligand might even be a mammalian version of the bacterial siderophore, although the existence of such molecules has not been confirmed[14].

Another possibility raised by the new findings is that many other lipocalins, whose functions are still unknown, are also iron carriers and provide an innate defence against microorganisms. And perhaps our most dangerous bacterial enemies, such as *Pseudomonas*, escape our control by making siderophores that are beyond the reach of our lipocalin-based surveillance mechanisms. Flo and colleagues' results[1] are an