healthy tissues to reach the site of infection. Compared with conventional antibiotics, the relatively large — typically with a mass of more than 2K — and often highly positively charged antimicrobial peptides penetrate tissues slowly and are costly to produce. So initial applications of such peptides have been limited to topical preparations (creams, ointments and mouth rinses) that require small quantities of drug and less tissue penetration[9,10]. Further improvements to these antibiotics are likely, but it is difficult to design them rationally because of the complexity of their interactions with membranes and with each other.

Clearly, it was desirable for researchers to extend their search beyond the common natural peptide structures. In living organisms, L-isoform amino acids are the building blocks that make up peptides and proteins. The mirror-image D-amino acids are rare, especially in peptides of animal origin. Ghadiri *et al.*[11] previously synthesized rings consisting of six or eight alternating D- and L-amino acids; these rings included three consecutive hydrophilic amino acids and a stretch of alternating hydrophobic amino acids, L-tryptophan and D-leucine. In lipid membranes, the rings stacked into tubes that made the membranes permeable to molecules up to 10K in size.

The group's current study[2] was stimulated by the observation that one of these ring peptides showed antimicrobial activity towards several common bacteria. Starting with this peptide, the authors systematically replaced the three amino acids in the hydrophilic stretch with different amino acids. The substitutions altered the peptide's *in vitro* activity towards both *S. aureus* and another commonly encountered pathogenic bacterium, *Escherichia coli*, as well as its toxicity, as measured by its ability to damage red blood cells. Several of the peptides made bacterial membranes permeable and rapidly killed target bacteria.

On the basis of these *in vitro* results, Fernandez-Lopez *et al.*[2] chose three peptides for testing in mice that were infected with *S. aureus*. The peptides were very effective at clearing the infection, without substantial toxic side effects. Although the authors do not report detailed studies of how well these peptides penetrated the mouse tissues, it is encouraging that, in these preliminary experiments, the peptides were effective even when injected under the skin into tissue far from the site of infection.

The proposed mechanism of action for these peptides resembles that of magainins and other natural antimicrobial peptides that form structures known as α-helices in membranes[7–9]. These α-helical peptides fold up in the microbial membrane into their active shape, an amphipathic cylinder stabilized by hydrogen bonds. Fernandez-Lopez *et al.* suggest that their ring peptides stack to form the same shape. In all cases, clusters of cylinders then form a pore through which small molecules can leak into and out of the microbe (Fig. 1).

One advantage of these new synthetic ring peptides is that they are much smaller than the α-helical ones, and this should increase their ability to penetrate tissues. But the presence of D-amino acids precludes the production of these peptides by available biosynthetic methods, and increases the cost of chemical synthesis — an important consideration given that these antibiotics might be required in amounts of the order of grams per dose. Non-peptide ring compounds with similar stacking and amphipathic properties might have some advantages over these peptides.

The development of a new antibiotic is a long and uncertain process. Many structural modifications have to be explored to increase activity, improve penetration and eliminate toxicity. Technological advances are frequently necessary so that the candidate peptide can be produced at an acceptable cost. Extensive testing in animals and humans often brings up unforeseen problems. But, in the face of increasing microbial resistance to existing antibiotics, every new lead is welcome news. ■

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Dyslexia

Talk of two theories

Franck Ramus

One possible reason why people with dyslexia have problems in learning to read is that some neuronal pathways involved in vision and hearing are damaged. That theory may need to be revised.

Regardless of how intelligent they are, people with developmental dyslexia have difficulty in learning to read, a characteristic first described more than a century ago[1]. Dyslexia is now known to be a hereditary neurological disorder that affects a huge number of people — about 5% of the global population — but its underlying basis is still hotly debated. At two recent meetings*, however, the reasons for the disagreement became clearer.

The prevailing view of dyslexia involves the idea that learning an alphabetic writing system requires the brain to map letters to mental representations of the corresponding basic speech sounds (phonemes). The phonological-deficit hypothesis (Fig. 1a, overleaf) holds that people with dyslexia have specific problems in representing or recalling those sounds — hence the problems with mapping them onto letters. The theory is supported by observations that people with dyslexia have difficulty in retaining speech in short-term memory, and in consciously segmenting speech into phonemes (for example, deleting or substituting phonemes from words)[2].

But this view — that the cognitive basis of dyslexia is purely phonological — has been challenged by the discovery that people with this disorder also have an array of subtle sensory defects. For example, they fare less well than control subjects in several auditory tasks that require the perception of brief or rapid speech and non-speech sounds[3]. They also seem to have difficulties with several visual tasks, such as those that involve the perception of motion[4]. Moreover, there is evidence that the brains of some dyslexics have subtle neurological abnormalities in certain areas of the visual and auditory systems — the so-called magnocellular pathways[5]. Researchers who support the magnocellular theory (Fig. 1b) do not dispute the phonological-deficit hypothesis. Rather, they contend that phonological problems are caused by a basic deficiency in hearing sounds, and that a visual deficit might independently contribute to reading problems.

However, the magnocellular theory is itself now facing criticism. In several studies, auditory processing has not been found to be impaired[6,7]. Moreover, although groups of people with dyslexia and control groups sometimes show significant differences in both visual tasks (J. Stein, J. Talcott, Univ. Oxford; K. Pammer, Univ. Newcastle) and auditory tasks (P. Tallal, Rutgers Univ.; C.

**The Fifth British Dyslexia Association International Conference*, University of York, UK, 18–21 April 2001. http://www.bdainternationalconference.org/
Sensory Bases of Reading and Language Disorders, University of Essex, UK, 27–30 May 2001. http://www.essex.ac.uk/psychology/symposium2001/

100 YEARS AGO

Only a few decades ago the real nature of tuberculosis was unknown to us: it was regarded as a consequence, as the expression, so to speak, of social misery, and, as this supposed cause could not be got rid of by simple means, people relied on the probable gradual improvement of social conditions, and did nothing. All this is altered now. We know that social misery does indeed go far to foster tuberculosis, but the real cause of the disease is a parasite — that is, a visible and palpable enemy, which we can pursue and annihilate… Such a conflict requires the cooperation of many, if possible of all, medical men, shoulder to shoulder with the State and the whole population; but now the moment when such cooperation is possible seems to have come… If we are continually guided in this enterprise by the spirit of genuine preventive medical science, if we utilise the experience gained in conflict with other pestilences, and aim, with clear recognition of the purpose and resolute avoidance of wrong roads, at striking the evil at its root, then the battle against tuberculosis, which has been so energetically begun, cannot fail to have a victorious issue. Robert Koch

From *Nature* 25 July 1901.

50 YEARS AGO

The year 1950 was a good one for studying the movements of swifts (*Apus apus*), and during the year the movements of forty thousand birds were recorded: a report on the observations has been made by H. G. Hurrell and recently described in *British Birds* (44, No. 5; May 1951)… Swifts appear to penetrate the country from the south and work northwards. Arrivals over many years average a day or two earlier in the south than in the south-east. The east coast as a rule is reached rather late and usually in such small numbers that there is little to indicate any spring passage of swifts from the British Isles to other countries. It is difficult to say when the arrival period ends because movements which have a migratory appearance may take place at any time while swifts are in Britain. Large movements occur in June and early July. These are thought to be undertaken because unfavourable weather forces the swift to seek regions with more adequate food supplies; the food of the swift is adversely affected by the passage of a cyclone or depression.

From *Nature* 28 July 1951.

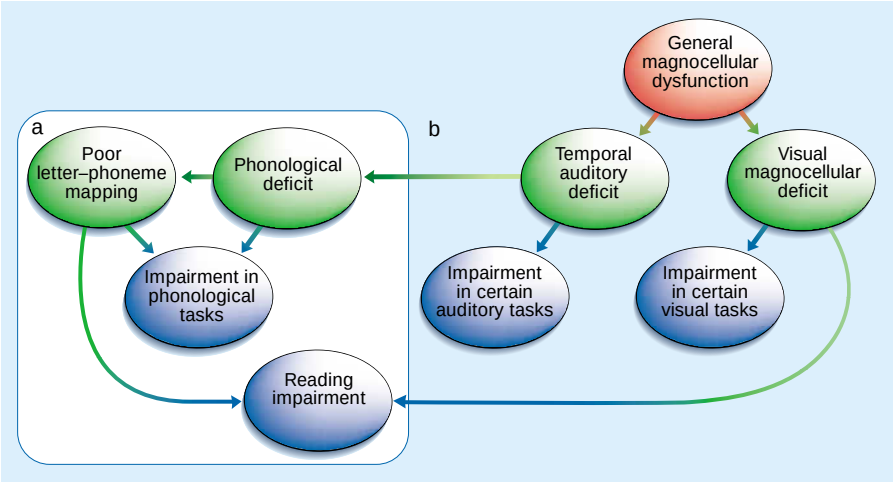

Figure 1 **The phonological and magnocellular explanations for dyslexia. Ovals represent impairments at the neurological (red), cognitive (green) or behavioural (blue) levels; arrows represent causal connections.** a, **The phonological theory holds that the core cognitive deficit lies in the ability to represent or recall speech sounds (phonological representations). This results in defects in mentally mapping letters to phonemes, and leads to reading impairments and problems with phonological tasks. The neurological basis for the phonological deficit, however, is not yet known.** b, **The magnocellular theory is based on the division of the visual system into two neuronal pathways: the magnocellular and parvocellular pathways. This theory holds that the magnocellular system is abnormal in people with dyslexia, causing difficulties in some aspects of visual perception and in binocular control that may cause a reading impairment. In addition, similar impairments in the auditory system are suggested to cause a deficit in processing the rapid temporal properties of sounds, leading to the phonological deficit.**

Witton, Univ. Oxford), it is becoming apparent that these group effects result from only a minority (typically one-third) of the dyslexic participants. The remaining two-thirds fare normally (S. Rosen, Univ. College London). Other teams have failed to find significant differences between dyslexic and control groups, but usually discover a few people in the dyslexic group who do have sensory defects (Y. Griffiths, M. Snowling, Univ. York; S. Heath, Univ. Western Australia; M. Van Ingelghem, KU Leuven; S. Amitay, Hebrew Univ. Jerusalem). So, although most studies have shown that some dyslexic people have sensory deficits, the prevalence and significance of such deficits remain uncertain.

One consideration is the tasks used to investigate these defects. Given that attention and general cognitive abilities are involved in sensory tasks, it is not surprising that differences in auditory and visual processing can sometimes be explained by differences in non-verbal intelligence (M. Ahissar, K. Banai, Hebrew Univ. Jerusalem). Likewise, verbal skills, such as verbal short-term memory, may influence performance. A typical task requires a person to judge the order of events: two, three or four stimuli are presented one after the other, and the subject must recall the order of the stimuli, or say which one was different from the others.

Clearly, this task requires storing the stimuli in short-term memory, which might involve a verbal strategy; subjects might mentally rehearse the words 'high, low' so as to remember that they heard a high tone followed by a low tone. Yet many people with dyslexia also have problems with verbal short-term memory — a characteristic of the phonological deficit. Indeed, when people are explicitly instructed to use a verbal strategy in this task, control subjects fare better than before, whereas dyslexics perform more poorly (C. Marshall, Univ. York). Similarly, dyslexics have difficulty in discriminating between some visual stimuli when presented sequentially, but not when presented simultaneously (G. Ben Yehuda, Hebrew Univ. Jerusalem). Perhaps, then, the presumed sensory deficits actually reflect strategic differences.

Even when sensory deficits are found, they do not always appear in the ways predicted by the magnocellular theory. For instance, the magnocellular visual pathway is most sensitive to stimuli of low spatial frequencies, presented under low lighting and at low contrast. So one would predict visual defects in dyslexics to be most apparent under these conditions (for example, when having to detect gratings of thick light-grey and dark-grey stripes appearing on a screen in the dark). Yet people with dyslexia typically fare worse than control subjects at all spatial frequencies (that is, whether stripes are thin or thick)[8] (G. Ben Yehuda), as well as at tasks in which frequencies are not entirely controlled and contrast and lighting are high (M. Bradshaw, Univ. Surrey; M. Van Ingelghem). Similarly, the theory predicts that the auditory impairment will be limited

to rapid or brief sounds, but dyslexics sometimes fare normally when sound frequencies change rapidly[9,10], and badly when they change slowly[11]. At best, the implication is that the magnocellular theory needs some revision.

More worrying is that there is little evidence for a link between these simple sensory deficits and phonology and reading. Indeed, no magnocellular deficit has been found in people who have a reading impairment as a result of eye strain or visual distortion (A. Wilkins, Univ. Essex). Similarly, performance in auditory tasks does not seem to predict performance in speech processing (C. Watson, Indiana Univ.; C. Marshall). Moreover, a study of twins showed that phonological impairments are highly heritable, whereas auditory deficits are more likely to be due to environmental factors[12]. Of course, as the auditory system is a major source of input to the phonological system, any auditory defects are likely to affect phonological processing (M. Merzenich, Univ. California, San Francisco). But the question here is whether the auditory deficit suffered by some dyslexics is of the type and magnitude to cause the kind of phonological deficit that in turn causes a reading impairment.

Could there be a hidden factor that might explain why the incidence of sensory deficits varies so much between studies? One factor might be the occurrence of other developmental disorders in the dyslexic population — many dyslexics also have specific-language impairment or attention-deficit disorder. There is a growing suspicion that sensory deficits might be found only in these people[6] (G. McArthur, Univ. Oxford; my own data). The implication is that groups of people with 'pure' dyslexia might be most relevant to understanding the causes of the reading impairment. Finally, the phonological-deficit theory also requires further investigation. Indeed, the greatest challenge is still to try to understand the precise nature of the phonological deficit and its biological cause. ■

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Planetary science

Uncool Callisto

Kristin A. Bennett

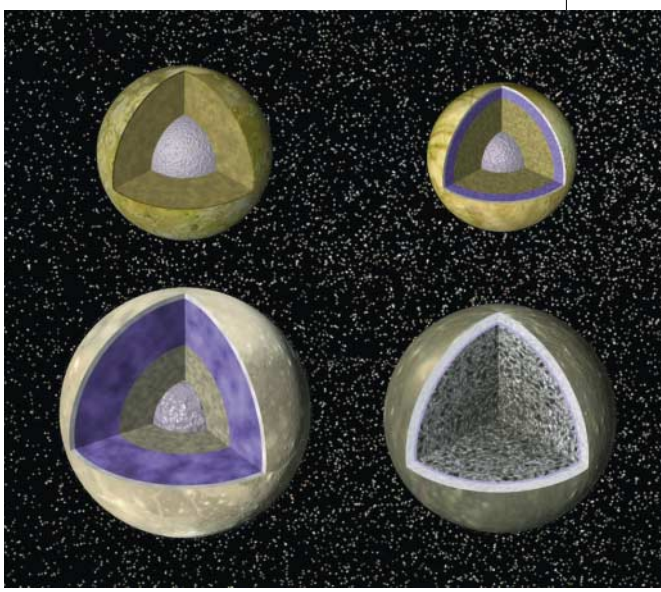
Models of heat convection suggested that any liquid on Callisto, one of Jupiter's moons, must be frozen. But those models did not take into account the different properties a surface layer of ice might have.

Jupiter's four largest moons, Io, Europa, Ganymede and Callisto, are known as the galilean satellites. These are dark and mostly dynamic worlds, and their present state and evolution can usefully be compared with Earth. For various reasons, Callisto has been seen as the least interesting of the four. But this may be no ugly duckling among the moons. As Ruiz points out on page 409 of this issue[1], if the different properties of ice under various conditions are taken into account, there may be a liquid ocean 150 km beneath Callisto's icy surface.

The galilean satellites are vast: Callisto, for instance, is the size of Mercury. And like planets they are thought to consist mainly of ice and rock, more or less differentiated into inner cores, convecting mantles and outer rigid crusts (Fig. 1), and are active to varying degrees. Of the four, Callisto has always been the odd one out. It seems to be a barely differentiated solid ball of ice and rock, covered by a rigid rim of ice. Around 80% of its surface is cratered and pitted, from which it is inferred that, unlike its companions, Callisto has been volcanically and tectonically dead almost since its origin[2]. Frankly, from a geologist's point of view, Callisto was boring. But Ruiz shows that an internal water-ice ocean ebbing and flowing under its surface is perfectly plausible.

Ruiz's theme, as stated in the title of his paper, is the "stability against freezing of an internal liquid-water ocean in Callisto". Magnetometer data[3] from the Galileo spacecraft show that Callisto has a variable magnetic field, which is most easily explained by a dynamo effect stemming from electronic conductivity of an electrolyte — water with a high salt content. But all other evidence suggested that any water would be frozen, because the heat to keep it warm would have long since been lost through convection. Ruiz's rigorous geophysical model, based on the properties of different forms of ice and water, shows that there can indeed be an ocean in Callisto's depths, even without a high salt content in the water to lower the freezing point. He calculates that a 'stagnant' outer ice shell on the moon would remain resistant to internal heat loss. The implication is that Callisto may have retained an ancient liquid ocean, now some 20 km thick.

To keep an ancient liquid-water ocean from freezing inside a body the size of Callisto, there must be both a heat source and a mechanism for impeding heat flow. Callisto is too far from the Sun to gain any solar heating, and there is no 'tidal heating' from the energy generated in a surface ocean by its orbit around Jupiter. So all heat is assumed to be generated by the decay of radioactive elements. One way to maintain a liquid ocean is by an antifreeze substance that reduces the freezing point of water ice. Another way would be if the outer ice layers are more rigid and resistant to heat flow out through them than has been assumed. Heat can be transferred through conduction or convection, and there have been numerous attempts with



NASA/JPL

Figure 1 **The galilean satellites. Clockwise from lower left: Ganymede, Io, Europa and Callisto. The surfaces are mosaics of images obtained in 1979 by the Voyager mission, and the interior characteristics are inferred from gravity- and magnetic-field measurements by the Galileo spacecraft. The satellites are shown according to their relative sizes (Callisto's radius is 2,403 km). All except Callisto have metallic cores of iron and nickel. Image taken from ref. 8.**