sive effect of horizontal connections that decays with distance. This finding agrees with the authors' own model — that a cell's dendritic arbor overlaps with nearby cortical columns — as well as with the functional topography of laterally projecting inhibitory neurons[8].

The observed suppression marks angular discontinuities at the level of the primary visual cortex. This information is then available to the higher brain areas that are specialized for more complex and elaborate analyses. Das and Gilbert's finding adds another side to the modern view that the response field of a neuron in the primary visual cortex reflects the functional state of an extended cortical network. Excitation and inhibition subtly interact in analysing an object centred on the 'classical' receptive field, and this analysis is modulated by contextual information from an extended surrounding[9–11].

Cells with drastically different orientation specificities are effectively connected by inhibitory circuits over distances of up to 800 μm (ref. 8). But the functional significance of these connections seems to differ depending on whether non-overlapping or overlapping receptive fields are involved. Cells at different sides of a pinwheel (Fig. 1) represent different parts of the visual space[11] — that is, they have non-overlapping receptive fields — so inhibitory horizontal connections provide contextual information about the visual scene[1]. But cells located at similar distances, yet not separated by a pinwheel, have overlapping receptive fields. In that case, the inhibitory circuitry strongly suppresses the cell's response to any lines at the centre of the receptive field that have different orientations to the preferred one. The result is a sharper orientation tuning[12].

This specific effect was demonstrated by Crook *et al.*[13] when columns with an orientation specificity at right angles to that of recorded cells were reversibly inactivated at a distance of 500–700 μm. This inactivation released the recorded cells from 'cross-orientation' suppression, meaning that they could respond to the orientations represented in the inactivated column[12]. It seems, then, that the continuously debated cross-orientation inhibition[14] can contribute functionally to different computations within the cortex. The same inhibitory cortical circuitry can probably sharpen orientation tuning locally[12], and provide higher-level contextual information from spatially distinct regions[1]. This suggests that the same structures in the cortex can be functionally exploited for very different tasks — here, in analysing distinct features depending on the position of a neuron within the orientation map of the primary visual cortex. □

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Carbohydrate chemistry

Sugars out in the open

Ole Hindsgaul

Structural knowledge of naturally occurring, biologically important molecules is at the very foundation of modern biochemistry and biology. When an unprecedented and unanticipated type of molecular structure is suddenly discovered, one therefore imagines that either 'the microscope has got bigger', or that someone was lucky and stumbled onto something, or paid exceptional attention to detail. In the case of Vinogradov and Bock — who, in *Angewandte Chemie International Edition* (**38,** 671–674; 1999) report the discovery of a new type of sugar–sugar linkage in bacterial polysaccharides — all three events occurred simultaneously.

The procedures for determining the primary sequences of DNA and proteins or peptides are well known from textbooks, and commercial instruments are available that perform the required chemistry and analysis. This is not so in the case of oligosaccharides and polysaccharides. Polynucleic acids (such as DNA and RNA) and proteins are assembled from a limited number of monomers, whereas hundreds are available for building polysaccharides. Further, carbohydrate polymers do not have to be linear but can be branched, and the joining of sugar units together in glycosidic linkages involves the creation of a new stereochemical centre at the point of attachment.

Free sugars are known to exist predominantly in interconverting cyclic forms; the stable six-membered rings are called pyranoses, and the less stable five-membered rings are known as furanoses (Fig. 1). The carbon C-1 is asymmetric, so there are two possible configurations for each ring depending on whether the OH group is below (α-configuration) or above (β-configuration) the plane of the ring. For almost all sugars in solution, much less than 1% of the open-chain aldehyde form (that which contains a carbonyl group — a carbon and oxygen connected by a double bond) is present at equilibrium (Fig. 1). It is therefore not surprising that the biosynthesis of oligosaccharides and polysaccharides involves enzymes that act on the cyclic forms of sugars.

The generally accepted and well-supported mechanism for the synthesis of all polysaccharides is summarized in Fig. 2

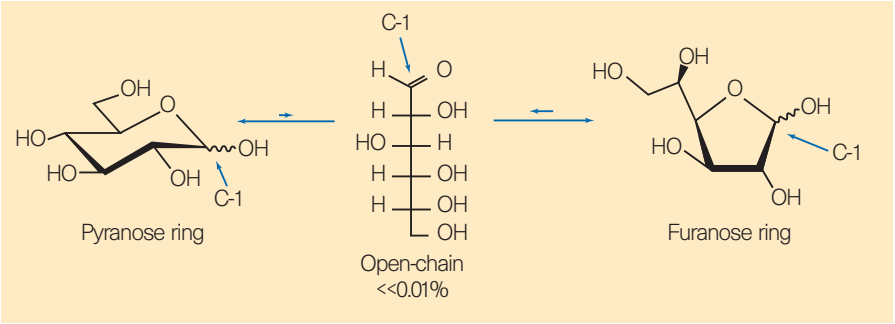

Figure 1 **The composition of free sugars in solution.**

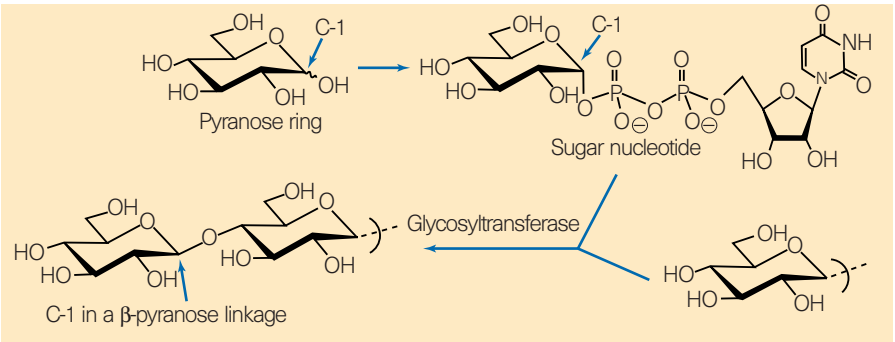

Figure 2 **Biosynthetic process for joining together two sugars in a glycosidic linkage.**

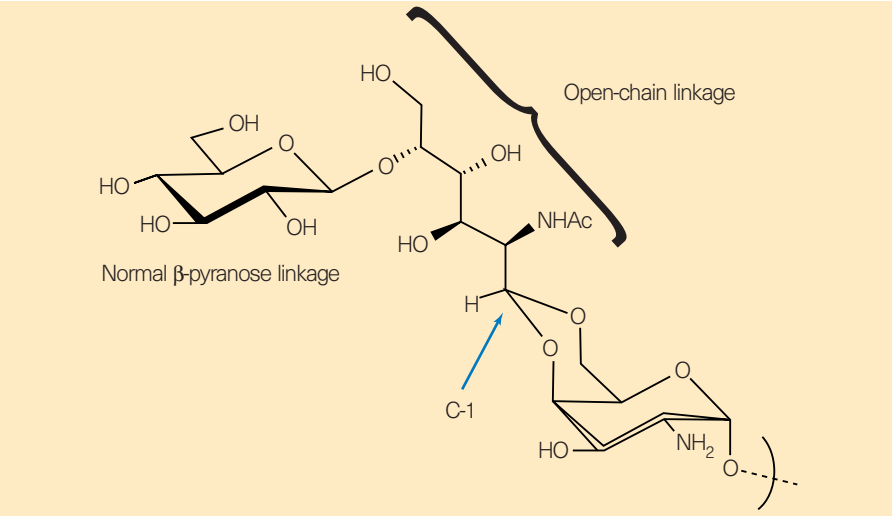

Figure 3 **A new type of glycosidic linkage. The 'open-chain' linkage was discovered by Vinogradov and Bock[1] in the cell wall of *Proteus* bacteria. NHAc denotes an N-acetyl group.**

(illustrated by the simple monosaccharide glucose). The cyclic pyranose form (or alternatively the cyclic furanose form) is phosphorylated at the C-1 hydroxyl group and ultimately converted to uridine diphosphate glucose, a high-energy sugar nucleotide. A glycosyltransferase enzyme then stereospecifically joins the cyclic pyranose to another sugar residue, for example in a β-pyranose linkage shown in Fig. 2. Repetition of this sequence using different sugar nucleotides and glycosyltransferases ultimately builds up the polysaccharides found in animals, bacteria and plants.

Vinogradov and Bock were fortunate to be at the right place at the right time. They were involved in a presumably routine study on the structure of the cell-wall polysaccharides of a poorly characterized *Proteus* microorganisim. Many such structural studies have been reported for other bacteria, fuelled by both the scientific challenge of tackling complexity and by the hope of generating polysaccharide-based vaccines. On this occasion the authors had access to state-of-the-art instrumentation (high-field nuclear magnetic resonance) and they paid meticulous attention to detail. They concluded that their structural data were inconsistent with all known sugar–sugar linkages. They had discovered the first example of an open-chain glycosidic linkage (Fig. 3).

With the benefit of hindsight, the existence of open-chain glycosidic linkages involving sugar C-1 aldehydes makes perfect chemical sense. After all, aldehydes, such as benzaldehyde, have been extensively used as protecting groups in sugar chemistry. Moreover, pyruvate acetals (ketone compounds containing a carbonyl group that have reacted with sugar diols) are known to exist in microorganisms. But the reason open-chain glycosidic linkages have never even been considered is undoubtedly because we were all taught that sugars in nature are cyclic.

The bacterial polysaccharides found to contain these new linkages may or may not have important biological functions. They may make an important contribution to the stability of the cell walls, or they could be important cell-wall antigens. They could even be virulence factors, or they could simply be unnecessary evolutionary baggage. But what is far more intriguing is that their biosynthesis requires the existence of a brand new class of enzymes, because the known biosynthetic pathways for polysaccharides use cyclic sugar nucleotides. It is tempting to speculate that the biosynthesis of open-chain glycosidic linkages may in fact involve the addition of a cyclic sugar followed by the action of a glycosidase cleaving enzyme, whose mechanism involves an open-chain intermediate. Such intermediates have been hypothesized, but never identified. It will be interesting to see just how common the open-chain glycosidic linkage is, now that we know that it exists and therefore know how to look for it. □

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Developmental neurobiology

Decoding the Reelin signal

Isabelle Bar and André M. Goffinet

Back in 1995, the *reeler* gene was cloned and its protein product was christened Reelin[1]. Since then, the Reelin signalling pathway — which is involved in brain development — has been progressively unravelled. The latest, most unexpected, twist is now reported in *Cell*, where Trommsdorff *et al.*[2] show that mice lacking both the very low density lipoprotein (VLDL) receptor and apolipoprotein E receptor-2 (ApoE-R2) genes have the same characteristics as mice that lack Reelin.

During development, neurons generated along the cerebral ventricles migrate through the tissue, then settle into rigorously defined patterns before deploying their dendrites and axons to connect with other cells. Particularly exquisite patterns are formed in the cerebellum, inferior olive, hippocampus and, most of all, in the six-layered cerebral cortex and its precursor, the embryonic cortical plate (Fig. 1a, overleaf). But these patterns are disturbed in *reeler* mutant mice, which have been studied as a model of abnormal brain development for 50 years (reviewed in ref. 3).

Reelin is a large glycoprotein[1] found in the extracellular matrix that is secreted by, and surrounds, cells. Reelin is secreted by a variety of neurons, most notably by Cajal–Retzius cells in the cortical marginal zone, and by cerebellar granule cells. But it is not expressed by those neurons that show disrupted patterns (the *reeler* phenotype), such as cortical-plate neurons or cerebellar Purkinje cells. This suggests that Reelin acts at a distance on target cells, via the extracellular matrix. Two years ago, it was shown that the *reeler* phenotype can also result from mutations of mouse Disabled-1 (Dab1). This phosphotyrosine protein, which resides in the cytoplasm, is thought to interact with tyrosine kinases of the Src and Abl families[4–6]. Unlike Reelin, Dab1 is expressed in the neurons that manifest the *reeler* phenotype, suggesting that it is a key element of the response to a Reelin signal. Indeed, phosphorylation of Dab1 is decreased in Reelin-deficient embryos, but increased when Reelin is added to neuronal cultures[7]. Until now, the molecules in the cell membrane that sense the presence of Reelin in the extracellular matrix and relay this signal to the cell via Dab1 have been a mystery.

Enter Trommsdorff and colleagues[2]. Mice with single mutations in the VLDL receptor gene have some abnormalities in neuronal patterning, and single mutants of the ApoE-R2 gene show subtle alterations in cortical development. But the double mutants develop a drastic malformation that is identical to the *reeler* phenotype, suggesting that the functions of the VLDL receptor and ApoE-R2 overlap. Both proteins are expressed in cells that contain Dab1 — cortical-plate neurons and Purkinje cells, for example — although ApoE-R2 is also found deeper in the tissue. The VLDL receptor and ApoE-R2 proteins belong to a small family that also includes the low density lipoprotein receptor of Nobel fame, megalin and the