100 YEARS AGO

The *British Medical Journal* for March 19 contains an important paper by Dr. Luigi Sambon, on the "Etiology of Sunstroke." Dr. Sambon adopts what at first appears a somewhat startling theory, namely, that sunstroke is not due to excessive heat or exposure to the sun, but is an infectious disease due to a specific organism. The author's case rests on three lines of argument. He begins by showing that excessive heat does not produce the disease; stokers, miners, and iron-workers are exposed to temperatures higher than those of any known climate. ... Dr. Sambon next discusses the geographical distribution of the disease, and proves that the areas in which it is endemic are strictly defined. It is very common in the low-lying regions of the Eastern United States, between the Appalachians and the Atlantic; it is unknown in Europe; it extends along the Nile Valley, Red Sea, and Persian Gulf .... Another peculiar feature of the disease explicable on the infection theory is the occurrence of epidemics, which may decimate hospital wards and not affect men exposed to greater heat and sun. Dr. Sambon concludes that the distribution, etiology, morbid anatomy, and epidemic character of the disease together demonstrate its organic origin.
From *Nature* 31 March 1898.

50 YEARS AGO

... one of the few serious complaints raised to-day against the young scientist graduate refers to his alleged inability to express findings in a written report. ... The main trouble seems to arise from the fact that often the young scientific worker has no love for writing. Whatever disciplinarians may say, it is doubtful whether anyone makes a real success of a task which gives him no sort of satisfaction. Enthusiastic and hard-working experimenters show an obvious reluctance to produce reports by the appointed day, and require a surprising length of time to produce a very simple memorandum. Even if the results, when ultimately completed, were perfect, the obvious disinclination to use the pen in the communication of ideas reveals an unsatisfactory state of affairs. This aversion to writing is often shown by men who are extremely successful in explaining their ideas by word of mouth.
From *Nature* 3 April 1948.

Molecular endocrinology

Steroids tickle cells inside and out

Didier Picard

On reaching a cell, an extracellular signal can either knock on the door (the plasma membrane), or it can just walk in. Most hydrophilic signals such as peptides are unable to cross the membrane, and they signal through specific, membrane-bound receptors. But steroid hormones are cholesterol derivatives and, being lipophilic, they are thought to cross membranes readily.

The first intracellular steroid receptors were discovered in the 1960s, and many receptors (along with other members of the intracellular receptor superfamily) were cloned in the 1980s and '90s. The central dogma of steroid signalling thus became that steroids signal through intracellular receptors, which are hormone-regulated transcription factors. But, in their excitement, researchers may have underestimated nature's wizardry — because steroids *can* reach specific receptors inside cells and elicit changes in gene expression ('genomic effects'), this does not mean that they always have to.

And they don't. On page 509 of this issue, Grazzini *et al.*[1] describe a transcription-independent signalling pathway of the steroid progesterone. Progesterone is essential for maintaining pregnancy in mammals, and it has the opposite effect to oxytocin, a nonapeptide that induces uterine contractions and may contribute to the onset of labour and parturition. Grazzini *et al.* show that progesterone inhibits oxytocin signalling by binding to the membrane-bound oxytocin receptor. It binds with an affinity (20 nM) that is considerably lower than its binding to the intracellular progesterone receptor (<1 nM). But this is compatible with the astronomical concentration of progesterone during pregnancy (500 nM).

Does progesterone really act on the outside of the cell? Undoubtedly it does, because the authors found that progesterone tethered to a membrane-impenetrable carrier protein also worked. Progesterone binding reduced the number of oxytocin receptors that were available to bind oxytocin (and, thereby, relay the oxytocin signal into the cell). The oxytocin receptor belongs to the large class of membrane-bound receptors that relay their signals through guanine-nucleotide-binding (G) proteins to intracellular target proteins such as phospholipase C. Grazzini *et al.* found that progesterone inhibits two functional effects of oxytocin signalling: the production of the second messenger inositol-1,4,5-trisphosphate, and an increase in the concentration of intracellular Ca^{2+}. By recording the changes in the Ca^{2+} concentration, they showed that inhibition takes place in less than a minute and is readily reversible.

The pharmacology also held surprises and definitely put intracellular receptors off-side. The synthetic progesterone R5020 and the politically infamous anti-progesterone

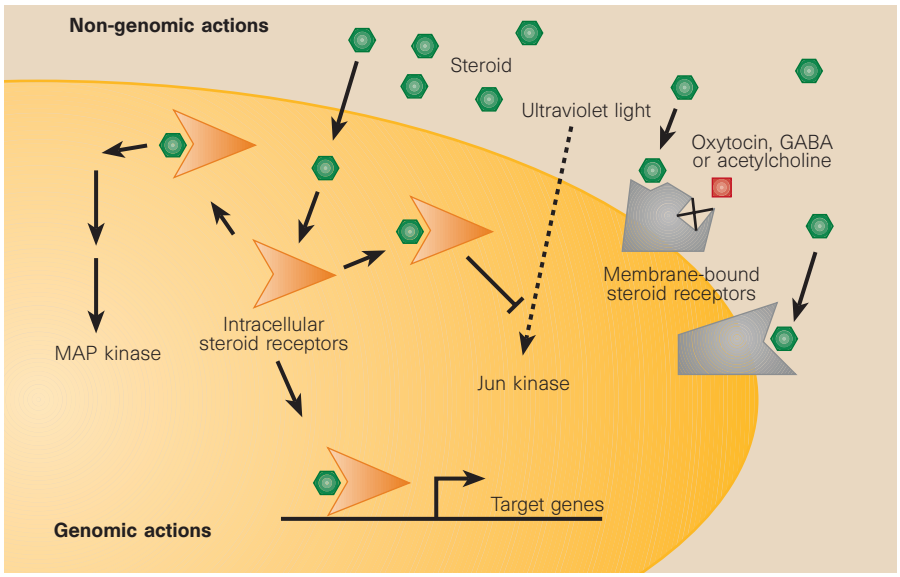


Figure 1 **The diverse mechanisms of steroid signalling. Steroids signal either through membrane-bound or intracellular receptors. Using membrane-bound receptors, they can modulate signalling of the receptor for another signal such as oxytocin, as described by Grazzini *et al.*[1]. Or they can elicit a signal by themselves through a specific receptor. Intracellular receptors are ligand-regulated transcription factors, although non-genomic actions have also been reported. These include activation of the mitogen-activated protein (MAP) kinase signalling cascade[5], and inhibition of the activation of Jun kinase[6].**

RU486 (the 'morning after' pill) also inhibit the rat oxytocin receptor, although other classes of steroids, including oestrogen and glucocorticoid, cannot. But the authors found that the human oxytocin receptor was not inhibited by progesterone or any of the other above-mentioned ligands. Instead, the inhibitory steroid for the human receptor turned out to be the progesterone metabolite 5β-dihydroprogesterone.

How does it work? Progesterone could bind the oxytocin receptor at an allosteric effector site, inducing a conformational change that prevents oxytocin from binding to its own binding site. To test this, the molecular details need to be characterized and compared to those in other steroid-modulated systems. Indeed, this is not the first example of a non-genomic effect. As-yet uncharacterized receptors seem to mediate steroid signalling in a variety of biological processes[2], and both stimulatory and inhibitory effects of progesterone and its derivatives have been described on receptors for the neurotransmitters GABA, NMDA (*N*-methyl-D-aspartate) and acetylcholine[2–4]. The work of Grazzini *et al.*[1] extends this phenomenon from these ligand-gated ion channels to G-protein-coupled receptors. Moreover, the olfactory receptors in our nose belong to this class, so is it possible that sex-specific differences in the steroid milieu in the olfactory epithelium itself contribute to the proverbially keener sense of smell of women?

Steroids do not stop here. Once inside a cell, they affect signalling pathways in a transcription-independent fashion through their cognate intracellular steroid receptors. For example, the oestrogen receptor can activate the mitogen-activated protein kinase signalling pathway[5] that is normally turned on by peptide factors. And the glucocorticoid receptor can interfere with the activation of a related signalling pathway that is involved in the response to ultraviolet and inflammatory signals[6] (Fig. 1).

The bewildering diversity of steroid actions — both inside and outside cells — suggests that it should be possible to develop therapeutic drugs that specifically affect only one mode of action. For instance, compounds that mimic the inhibitory effect of progesterone (or 5β-dihydroprogesterone in humans) could help to antagonize the effects of oxytocin in pre-term labour, but with fewer side-effects than the currently used beta-mimetic drugs. □

Didier Picard is in the Département de Biologie Cellulaire, Université de Genève, Sciences 3, 1211 Genève 4, Switzerland.
e-mail: Picard@cellbio.unige.ch

1. Grazzini, E., Guillon, G., Mouillac, B. & Zingg, H. H. *Nature* **392,** 509–512 (1998).
2. Wehling, M. *Annu. Rev. Physiol.* **59,** 365–393 (1997).
3. Baulieu, E.-E. *Recent Prog. Horm. Res.* **52,** 1–32 (1997).
4. Valera, S., Ballivet, M. & Bertrand, D. *Proc. Natl Acad. Sci. USA* **89,** 9949–9953 (1992).
5. Migliaccio, A. *et al. EMBO J.* **15,** 1292–1300 (1996).
6. Caelles, C., González-Sancho, J. M. & Muñoz, A. *Genes Dev.* **11,** 3351–3364 (1997).

Condensed-matter physics

Stripes of a different stripe

A. J. Millis

In some materials, the electronic charge density organizes itself into stripes. Stripe physics has been of intense interest to condensed-matter physicists, as an example of a non-trivial ordering phenomenon, and because of its possible connection to high-temperature superconductivity. On page 473 of this issue[1], Mori *et al.* report a novel paired stripe order. Their work opens a new window onto stripe physics and onto the fundamental issue of the interplay between hybridization and interactions.

Hybridization, the overlap of electron wavefunctions centred on different sites, is a quantum-mechanical effect that allows electrons to hop from one atom to another, thus tending to spread the electronic density uniformly through the solid. In contrast, interactions of electrons with one another and with displacements of the atoms in the solid tend to promote non-uniform charge distributions. If hybridization is dominant, a conventional metal (such as aluminium) or insulator (such as diamond) results. But if interactions are dominant, charge ordering may occur: in a charge-ordered state the electrons arrange themselves in a pattern with periodicity differing from that of the underlying lattice. The precise pattern is determined by the nature of the interactions and by the residual effects of hybridization.

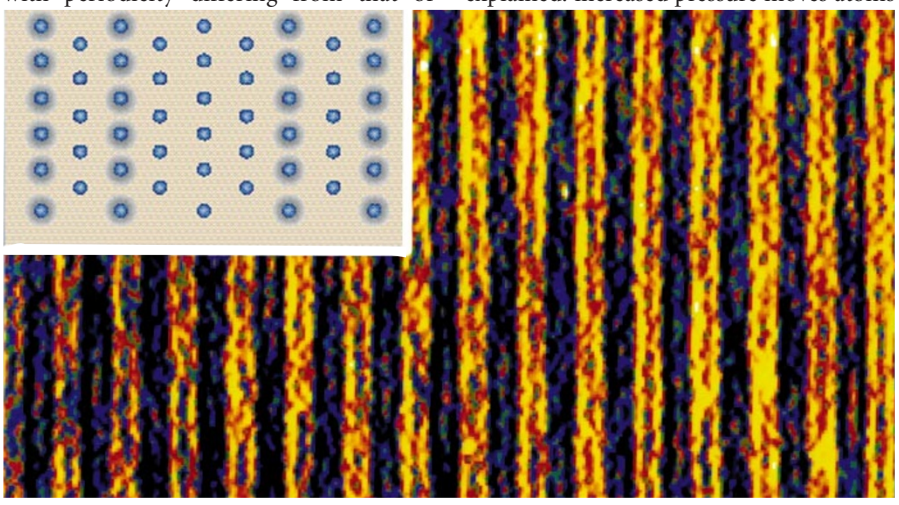
In many circumstances the charge ordering takes the form of stripes (Fig. 1), which seem to be the best compromise between the localizing effect of interactions and the delocalizing effect of hybridization. Along the stripe, the charge density is constant except for the variation imposed by the periodicity of the underlying lattice; perpendicular to the stripe, the charge density varies with a period different from that of the lattice.

Stripe order has been discovered in materials closely related to the high-temperature superconductors[2], and theorists have proposed that superconducting compounds should be regarded as 'quantum fluctuating stripe phases'[3] in which the hybridization is not large enough to prevent stripes from forming, but does cause their positions to fluctuate so strongly that no static order occurs.

Stripe phases have been difficult to study quantitatively, in part because in most materials the balance between hybridization and interaction can be varied only by changing the chemical composition, which introduces a host of extraneous complications.

The new work of Mori and co-workers promises to change this situation. They studied $La_{1-x}Ca_xMnO_3$, one of the 'colossal magnetoresistance' manganites, so-called because an applied magnetic field can change their resistivity by a factor which can be as large as several thousand. That property might be technologically useful, but from the standpoint of basic physics the manganites' most interesting feature is that their quantum-mechanical hybridization can be varied over a wide range by applying pressure or a magnetic field.

The variation with pressure is simply explained: increased pressure moves atoms



S. MORI *ET AL.*

Figure 1 **Stripe pairs in the manganite $La_{1-x}Ca_xMnO_3$. An electron diffraction image shows the overall structure of the stripe phase; the schematic inset shows a close-up. Itinerant electrons (diffuse clouds) may hop from manganese site to manganese site, but at low temperature are localized into pairs of lines.**