100 YEARS AGO

Messrs. D. Schulte and Co. have submitted a sample of their self-lighting Bunsen burner, in which the well known property of finely divided platinum igniting under the influence of a stream of hydrogen is employed. The burner proper is of the usual type, but is furnished with a byepass tube at the side, controlled by a cross stopcock. At the top of the byepass, close to the open end of the burner, there is fitted a small bracket holding the bundle of several fine platinum filaments, so constructed that the thin stream of gas from the byepass tube impinges on the stretched wires… The arrangement works very readily, and if the old difficulties with regard to the durability of the delicate portions can be surmounted, the apparatus should be of considerable convenience to laboratory workers.

ALSO

At a sale recently held by Mr. Stevens in King Street, Covent Garden, a great auk's egg in fine condition was sold for two hundred guineas… This is a considerable falling-off from the three hundred guineas obtained for the last specimen sold by Mr. Stevens, the reason being attributed to the fact that several other fine examples are in the market.

From *Nature* 26 May 1904.

50 YEARS AGO

It has been shown that as a rule the deoxyribonucleic acid content of the interphasic nuclei of tissues of a given species corresponds to a constant equilibrium value, which is double that of the deoxyribonucleic acid content of the spermatic nuclei of the same species. Consequently, at each mitotic division, synthesis of deoxyribonucleic acid must take place in order that the quantity of this substance should be restored in the nuclei of the daughter cells at a 'normal' level… According to some authors, this occurs immediately before mitosis, so that the content reaches double that of the normal value: after division each nucleus of the daughter cells receives also a normal content. According to other authors, synthesis occurs soon after mitotic division when nuclei of the daughter cells which receive only half of the normal content restore the latter. We have undertaken the study of this question in the thyroid cell of the white rat… These measurements show clearly that in our material deoxyribonucleic acid is synthesized immediately before the onset of mitosis.

From *Nature* 29 May 1954.

the more stable the duplex. Eve is designed to be complementary to a relatively long unpaired region of indicator 4, whereas Alice is complementary only to a sub-sequence of Eve. So, Eve binds more stably with indicator 4 than with Alice. Also, the Alice and Bob oligonucleotides have (somewhat shorter) complementary sub-sequences, which are likely to form a duplex once Eve has bonded to indicator 4. The game of shifting allegiances plays out somewhat differently when diagnosing low, rather than high, concentrations of an indicator molecule, although the principles are similar.

Also needed is a mechanism for cleaving the guard in the presence of the Alice–Bob pair. This pair can bind to the guard (again, via bonding between complementary single-stranded regions of Alice and the guard, called sticky ends; Fig. 2c). One additional molecule, an enzyme called *Fok*I, recognizes a sequence pattern formed when the Alice–Bob pair is bound to the guard. *Fok*I then cleaves the guard from the hairpin loop, releasing the drug.

Unfortunately, the specific mechanisms proposed by Benenson *et al.*[2] would not work in a living cell: unwanted side effects of the cast of supporting molecules (particularly the *Fok*I enzyme) would be one major problem[4]. Nevertheless, getting an experiment of this scale to work *in vitro* is a real achievement. Perhaps more importantly, the work takes a conceptual step forward, by linking the development of molecular automata to antisense therapies. It is plausible that different molecular mechanisms can be found to create diagnostic automata in the cell, building on progress made so far in the use of antisense therapies or cellular computation[5,6]. Developing such mechanisms would certainly be a good direction for further research. ■

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Granular materials

The brazil nut effect — in reverse

Troy Shinbrot

In a box of mixed nuts, the brazils rise to the top. In granular mixtures in general, depending on their size and density, the 'brazil nuts' may sink instead. This reverse effect has now been explored further.

Every farmer can attest to the curious fact that the largest crop each spring is the boulders that appear, untended, on open fields. Common wisdom holds that this crop is loosened from the soil by frost heave, and rises because small pebbles can slip beneath large boulders, but not vice versa[1]. This is the 'brazil nut effect' — named for the fact that, in a container of mixed nuts, the brazil nuts always seem to rise to the top (Fig. 1). Because similar processes and effects occur in pharmaceutical, chemical and food processing, the problem of granular segregation has earned serious attention[2] — and now, in *Physical Review Letters*, Huerta and Ruiz-Suárez[3] add the latest piece of the puzzle.

The first complication to the simple picture of pebbles slipping beneath boulders (termed 'percolation') was the demonstration that a tapped bed of grains 'convects' in a regular pattern: a wide swath of grains rises in the centre of a container, and thin margins correspondingly sink[4]. According to the convection picture, large 'intruder' particles rise with the surrounding bed, and then find themselves simply unable to fit into narrow downwelling margins. This mechanism was confirmed by a clever experiment in which the convection rolls were reversed and, as predicted, large particles migrated to the bottom of vibrated beds[4]. Later confirmations came from magnetic-resonance-imaging experiments that conclusively demonstrated the presence of segregating convection rolls[5], and from meticulous computational comparisons that revealed that convection dominates over percolation in producing segregation in deep beds[6].

Over the past decade, however, our understanding of the segregation of large particles in vibrated beds has been challenged by experiments revealing that although large heavy 'intruder' particles can indeed rise in vibrated beds of finer grains, equally large light intruders can sink, contrary to expectation and common experience. Now termed the 'reverse brazil nut effect', this observation[7], made by myself and Fernando Muzzio, is explained by neither the convection nor the percolation description. It is so counterintuitive that a reviewer of the original manuscript reporting the effect insisted that it could not be correct; and the


MAXIMILIAN STOCK LTD/SPL

Figure 1 **Nuts: why do brazils always rise to the top?**

manuscript editor at *Physical Review Letters* conscientiously (if sceptically) tested the effect in his office using a jar of sand, a large plastic pin (a light intruder) and a steel nut (a heavy intruder). Since this impromptu confirmation, particle-dynamics simulations (subsequently validated experimentally[8]) have verified that the reverse brazil nut (RBN) effect appears under ideal *in silico* conditions, and that multiple intruders also separate in the curious RBN manner[9].

In fact the RBN effect turned out to be even more complex than realized at first. Subsequent experiments showed that there are actually separate size and density influences at work in a tapped bed[10]. On the one hand, for intruders of a fixed density there is a distinct size threshold above which intruders rise, and below which they sink. On the other hand, intruders of a fixed size rise with a speed that grows and then diminishes non-monotonically as the intruder density is increased. To complicate matters still further, there have been numerous commentaries on the RBN effect, some of which question whether the effect even exists, or whether it is actually a computational artefact[11].

Huerta and Ruiz-Suárez[3] have shown that there are actually two distinct regimes of segregation: one seen at higher frequencies of vibration (50 Hz), in which the bed becomes fluidized and ordinary buoyancy prevails (heavy intruders sink but light ones float); the other at low frequencies (5 Hz), in which intruder inertia and bed convection conspire to produce either the ordinary or the reverse brazil nut effect, depending on intruder size and density. This result concurs with much earlier findings that there is a transition at vibration frequencies of about 20 Hz, below which dissimilar-size particles segregate and above which they mix[12].

Interestingly, this transition coincides with the frequency at which the surface first forms heaps driven by air flow (pumped by piston-like container motion against the granular bed), suggesting that the transition between ordinary buoyancy and the RBN effect is tied to air flow. This hypothesis has also been investigated recently, but the dual roles of grain and air dynamics remain entangled[10,13]. Huerta and Ruiz-Suárez[3] propose that this entanglement might only occur in beds of very small particles, which seems to agree with the *in silico* air-free duplications of the effect. But this leaves us with enduring difficulties in understanding the interplay between intruder size and density — and now bed particle size and vibration speed — and why, to begin with, convection does not prevail to entrain intruders irrespective of such details.

The RBN effect is sure to provide fruit for future exploration and debate. We find ourselves facing the situation anticipated by Mark Twain: "The researches of many commentators have already thrown much darkness on this subject, and it is probable that, if they continue, we shall soon know nothing at all about it." Although farmers can count on continuing harvests of heavy boulders under any segregation model, it remains to be seen whether — and how — pharmaceutical engineers should expect their granular formulations to mix or separate. ■

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Genome sequencing

Differences with the relatives

Jean Weissenbach

One of the chimpanzee's chromosomes has been sequenced to near-completion. What can this accomplishment tell us about how we have come to look and act so differently from our chimp relatives?

There are good reasons to continue the endeavour to accumulate genome sequence data from the passengers of Noah's Ark. As illustrated on page 382 of this issue[1], genome sequences can serve to address basic evolutionary issues — the power of this approach depending to a large extent on the amount and quality of data available.

The rationale for sequencing the genome of the chimpanzee (*Pan troglodytes*; Fig. 1, overleaf) has been explained on numerous occasions (see ref. 2 for a review), and a publicly funded effort, involving some of the large US sequencing centres, has already produced a draft assembly of the whole sequence[3]. But this initial assembly still contains many gaps and ambiguities that present difficulties for some types of analysis.

In an independent effort[1], a consortium of Old World humans has now sequenced chimpanzee chromosome 22 to a degree of completion and accuracy equivalent to that of the human genome assembly in its present version. The quality of this chimp chromosome sequence is therefore good enough to allow reliable comparisons with its human counterpart (chromosome 21). A chimpanzee chromosome provides a unique angle from which to look at the human genome and to draw conclusions about its recent evolution, because the sequences of