patients to produce antibodies that react with cells containing mutant p53 (ref. 14).

Inside cells, p53 is bound to other proteins that negatively regulate it[4]. For example, the MDM2 protein binds to p53 inside the nucleus, enabling p53 to be exported from the nucleus into the hands of a protein-degrading machinery known as the proteosome. In some types of cancer (liposarcomas, for example), p53 is normal but there are too many copies of the MDM2 gene, so there is more MDM2 protein around to inactivate p53. The E6 protein from human papilloma viruses has a similar function, leading to cervical cancer. Drugs that interfere with the binding of MDM2 or E6 to p53 might free p53 from these protein shackles, suppressing sarcomas or cervical cancers[15].

The strategy outlined by Raj *et al.*[3] is likewise directed not towards p53 itself, but (in this case) towards the consequences of p53 action (Fig. 1). The authors infected cultured cells with adeno-associated virus (AAV), and found that this activates the p53 checkpoint, presumably because the unusual genome of AAV, which contains single-stranded DNA and DNA hairpins, mimics damaged DNA. Indeed, a DNA molecule corresponding to the AAV hairpin, but which contains no genes, had the same effect[3]. Cells containing normal p53 paused in the G2 phase to rid themselves of the AAV genome, and then began dividing again. But cells without functional p53 could not maintain their arrest in the G2 phase, and instead began a catastrophic nuclear division that led to cell death. The AAV strategy also proved successful in shrinking experimentally induced cancers in mice.

This approach might be more specific than standard DNA-damaging drugs, which interact with a plethora of cellular constituents and have diverse toxic effects. It would not matter if AAV entered normal cells, because these cells have functional p53. One problem, however, is that the virus is inactivated and non-infectious; because it cannot spread from cell to cell, it must be delivered specifically to almost every cancer cell.

There is a viral-based strategy that potentially solves part of this delivery problem[16]. The ONYX-015 adenovirus was originally developed as an anticancer agent that can replicate only in p53-deficient cells, killing them directly. Although the replicative abilities of this virus are more complex than once thought[17], the idea of a live virus that can infect p53-deficient cancer cells but cannot multiply in normal cells is attractive. Infection of only a few cancer cells could theoretically spread to the whole cancer. But there are drawbacks[17]. It is not trivial to infect even a small fraction of tumour cells by systemic administration (for example, by injecting adenoviruses intravenously), and the host's immune system may fight back. Immune reaction to the inactivated AAV might not be such a problem[3].

No cancer patient should expect any of these innovative approaches to cure them in the near future. But continued research into the structure of p53, the proteins to which it binds and the pathways that it controls should eventually lead to the maturation of one or more of these strategies — each of which has the potential to benefit millions. ■

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1. Baker, S. J. *et al. Science* **244,** 217–221 (1989).
2. Nigro, J. M. *et al. Nature* **342,** 705–708 (1989).
3. Raj, K., Ogsten, P. & Beard, C. *Nature* **412,** 914–917 (2001).
4. Vogelstein, B., Lane, D. & Levine, A. J. *Nature* **408,** 307–310 (2000).
5. Mauro, M. J. & Druker, B. J. *Oncologist* **6,** 233–238 (2001).
6. Waldman, T., Lengauer, C., Kinzler, K. W. & Vogelstein, B. *Nature* **381,** 713–716 (1996).
7. Diggle, C. P. *et al. Int. J. Cancer* **93,** 199–203 (2001).
8. Lane, D. P. *Nature* **358,** 15–16 (1992).
9. Roth, J. A. *et al. Semin. Radiother. Oncol.* **10,** 333–342 (2000).
10. Selivanova, G. *et al. Semin. Cancer Biol.* **8,** 369–378 (1998).
11. Foster, B. A., Coffey, H. A., Morin, M. J. & Rastinejad, F. *Science* **286,** 2507–2510 (1999).
12. Watanabe, T. & Sullenger, B. A. *Proc. Natl Acad. Sci. USA* **97,** 8490–8494 (2000).
13. Da Costa, L. T. *et al. Proc. Natl Acad. Sci. USA* **93,** 4192–4196 (1996).
14. Noguchi, Y., Richards, E. C., Chen, Y. T. & Old, L. J. *Proc. Natl Acad. Sci. USA* **92,** 2219–2223 (1995).
15. Hietanen, S., Lain, S., Krausz, E., Blattner, C. & Lane, D. P. *Proc. Natl Acad. Sci. USA* **97,** 8501–8506 (2000).
16. Bischoff, J. R. *et al. Science* **274,** 373–376 (1996).
17. Dix, B. R., Edwards, S. J. & Braithwaite, A. W. *J. Virol.* **75,** 5443–5447 (2001).

Quantum optics

Photons yield to peer pressure

Paul Kwiat

In 1960 the invention of the laser allowed classical light to be amplified inside a cavity. New experiments show that photons in a special quantum state can also be amplified.

Quantum entanglement between two particles means that measuring the behaviour of one instantly determines the behaviour of the other, even when they are physically far apart. Erwin Schrödinger once described this peculiar connection as "*the* characteristic trait of quantum mechanics, the one that enforces its entire departure from classical lines of thought". Now, on page 887 of this issue, Lamas-Linares, Howell and Bouwmeester[1] report some of the first basic experiments on amplifying entangled photons through a process analogous to that occurring in lasers. Because entanglement is a key ingredient in many quantum information procedures, such as quantum computing, teleportation and cryptography, a method for reliably producing entangled states of several photons could have significant ramifications, especially for quantum communications using optical techniques.

Entanglement describes a system with several components in which the individual parts carry no information but nevertheless share quantum correlations with each other that are stronger than those allowed by classical physics. For example, photons can be polarized — the polarization describes the oscillation direction of the electric field associated with a light wave. Polarization filters, such as Polaroid sunglasses, will let through photons polarized in one plane but block those polarized at right angles, and so can be used to measure photon polarization. If two photons have entangled polarizations, each photon individually would appear completely unpolarized (with no particular oscillation direction) and yet measuring the polarization of one completely determines the polarization of the other. It is as if you flipped two coins, each of which was equally likely to come up heads or tails, and yet they always gave the same results — that is, both heads or both tails.

Although normal coins do not behave like this, it has been known for some time how to produce pairs of photons that do display such bizarre quantum-mechanical correlations[2,3]. Ultraviolet photons sent into a nonlinear optical crystal will sometimes split into two infrared daughter photons (a process known as 'spontaneous downconversion'), each travelling in its own beam, which are polarization entangled. Unfortunately, the likelihood of each photon splitting in this way is less than 1 in 10 billion. So even though typical experiments use pulses that have several billion ultraviolet photons in them, often not even one will lead to a downconversion pair. The chance of two of them splitting, which can lead to an entangled quartet, is much smaller still: previous experiments have reported four-photon counting rates of only 1 to 2 events per minute[4–6] (out of 5 billion pulses per minute).

Lamas-Linares *et al.* have significantly increased this rate by using the entangled output of one crystal as a seed for 'growing' more entanglement in another crystal (actually the same one, used a second time). Without the seeding the second crystal would produce an entangled beam of about the same brightness as the first crystal. By adding the seed photons, one might naively expect production rates simply equal to the sum of the rates for each process individually (that is, a doubling of the

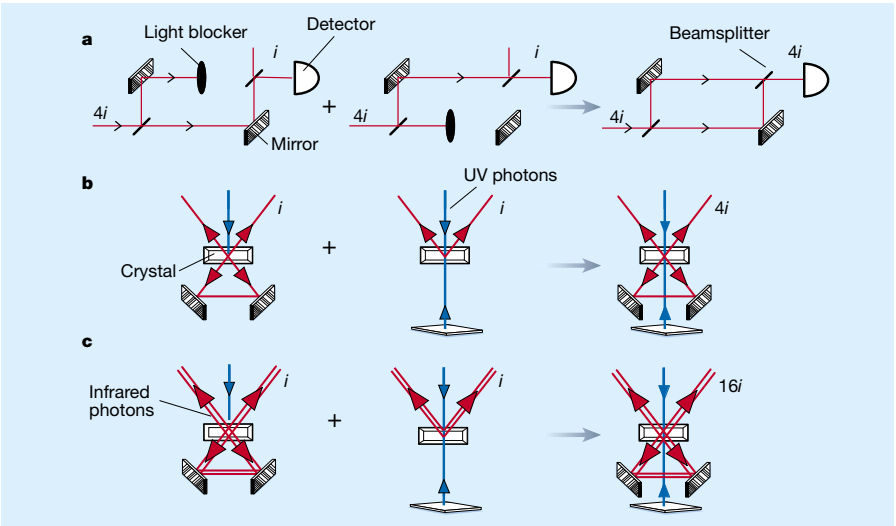

Figure 1 **In quantum mechanics, one plus one can equal zero, or four.** a, **An optical interferometer consists of two mirrors and two beamsplitters, which reflect half the light and transmit the rest. If we look at one output of the interferometer, with either path blocked we detect one-quarter of the light sent into the interferometer. If we call the contribution from each path *i*, we might expect that with both paths open the detector would see 2*i*. But in fact the intensity on the detector can range from 0 (if the contributions from the two paths interfere destructively) to 4*i* (if the contributions from the two paths interfere constructively).** b, **In a similar process, infrared downconversion pairs may be produced during the first passage of the ultraviolet (UV) photons through the crystal, or during their return passage. Because these indistinguishable processes can interfere, the final output intensity of pairs can vary from 0 to four times the pair intensity from a single passage through the crystal.** c, **Lamas-Lamares *et al.*[1] show that further enhancement is possible with the four-photon process — going through the crystal twice increases the rate of four-entangled photon production 16-fold.**

output of each crystal alone). Not so, thanks to the magic of quantum interference (Fig. 1a) and stimulated emission.

Because the two downconversion processes can interfere, the production of photon pairs can be enhanced by a factor of four (Fig. 1b). The enhancement of downconversion was first demonstrated in 1994 (ref. 7), but the new work extends this to pairs that are polarization entangled. Even more striking is the enhancement effect on four-photon processes (Fig. 1c). The simple interference analogy would again lead one to predict a maximum enhancement factor of four. But the enhancement for four-photon entanglement is higher still — a factor of sixteen — owing to the increased efficacy of stimulated emission as the number of photons increases. Loosely speaking, the photons experience more peer pressure when there are more photons to pressure them into conforming. Lamas-Linares *et al.*'s results clearly show the predicted enhancement, evidence that they have observed the stimulated emission of entangled radiation.

A word of caution: the extra enhancement by a factor of four of the quartet-photon state relative to the twin-photon state should not be misinterpreted to imply that creation of the former is more likely than creation of the latter. Lamas-Linares *et al.* report two-photon counting rates of over 10,000 per second, but four-photon counting rates of only 1 per second. Still, this is a 50-fold increase over the results of initial experiments done only a few years ago[4–6]. Equally important, the quality of the four-photon interference has seen a similar improvement — the interference contrast has been raised from about 85% to 97%.

The experiment of Lamas-Linares *et al.* is only a first step toward producing a 'laser' of entangled photons — strictly speaking, it is the analogue of a laser cavity in which the light is cycled just twice, instead of tens to hundreds of times. It will be interesting to see how far the technology can be pushed. Unfortunately, the entanglement is most visible only if a definite number of photons can be identified in each of the two beams. This becomes more and more difficult as the number increases (because of photon loss and detector inefficiency), and could limit the usefulness of the approach. Nevertheless, just as no one knew in 1960 all the possible applications of the optical laser, it can safely be said that the potential of an entangled-photon laser for quantum information applications is also largely unknown.

The authors[1] suggest that this work may lead to some new form of quantum cryptography, with higher transmission rates than are presently available using entangled photon twins[8–10]. I think this is unlikely, both because any loss will reduce the entanglement, and because the generation rate of these multiple-pair pulses is so much lower than the generation rate of single-pair polarization-entangled photons. Entanglement might also be used to improve the signal-to-

100 YEARS AGO

Mr. W. W. Davis has a paper in "Studies from the Yale Psychological Laboratory"… on some relationships between temperament and effects of exercise. His tests and observations are scarcely sufficient to establish very definite relations, but the conclusions at which he arrives are not without interest. The observations suggest that nervous persons, in training for the development of strength, require light practice, and phlegmatic persons require vigorous practice. The phlegmatic type of temperament is apparently characterised by the presence of much reserve energy of muscle and nerve cell. The nervous type has less reserve energy but a greater ability to use the energy at hand. It is not difficult to apply these principles to practical physical training. They make necessary on the part of the trainer a knowledge, secured either by means of observation or experiment, of the temperament of each man under his charge.
From *Nature* 29 August 1901.

50 YEARS AGO

The ground-state of the hydrogen atom is a hyperfine doublet the splitting of which, determined by the method of atomic beams, is 1,420.405 Mc./sec. Transitions occur between the upper ($F=1$) and lower ($F=0$) components by magnetic dipole radiation or absorption. The possibility of detecting this transition in the spectrum of galactic radiation, first suggested by H. C. van de Hulst, has remained one of the challenging problems of radio-astronomy. In interstellar regions not too near hot stars, hydrogen atoms are relatively abundant, there being, according to the usual estimate, about one atom per cm. Most of these atoms should be in the ground-state. The detectability of the hyperfine transition hinges on the question whether the temperature which characterizes the distribution of population over the hyperfine doublet — which for want of a better name we shall call the hydrogen 'spin temperature' — is lower than, equal to, or greater than the temperature which characterizes the background radiation field in this part of the galactic radio spectrum. If the spin temperature is lower than the temperature of the radiation field, the hyperfine line ought to appear in absorption; if it is higher, one would expect a 'bright' line; while if the temperatures are the same no line could be detected… We can now report success in observing this line.
From *Nature* 1 September 1951.

noise ratio of interferometric devices, such as those used in precision measurements. But at the moment the main value of the research is in giving physicists an ever more complex playground of quantum states; learning how best to use them is the next step. In attempting to build an entangled photon laser (light amplification by stimulated emission of radiation), Lamas-Linares *et al.* have pushed the frontier of exotic quantum-state generation. And what's more, they did it with EASE — entanglement amplification by stimulated emission. ■

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1. Lamas-Linares, A., Howell, J. C. & Bouwmeester, D. *Nature* **412,** 887–890 (2001).
2. Freedman, S. J. & Clauser, J. F. *Phys. Rev. Lett.* **28,** 938–941 (1972).
3. Kwiat, P. G. *et al. Phys. Rev. Lett.* **75,** 4337–4341 (1995).
4. Bouwmeester, D. *et al. Nature* **390,** 575–579 (1997).
5. Ou, Z. Y., Rhee, J.-K. & Wang, L. J. *Phys. Rev. Lett.* **83,** 959–962 (1999).
6. Pan, J. -W. *et al. Nature* **403,** 515–519 (2000).
7. Herzog, T. J, Rarity, J. G., Weinfurter, H. & Zeilinger, A. *Phys. Rev. Lett.* **72,** 629–632 (1994).
8. Jennewein, T. *et al. Phys. Rev. Lett.* **84,** 4729–4732 (2000).
9. Naik, D. S. *et al. Phys. Rev. Lett.* **84,** 4733–4736 (2000).
10. Tittel, W. *et al. Phys. Rev. Lett.* **84,** 4737–4740 (2000).

Cardiovascular biology

Creating unique blood vessels

Peter Carmeliet

When tissues need more oxygen, they release molecules that encourage blood vessels to grow. The discovery of the first such molecule that is specific to one type of tissue has implications for cancer and heart failure.

On a farm, systems of hosepipes are used to deliver vital water to every field. Similarly, in our bodies, blood vessels deliver essential oxygen and nutrients to each organ. New blood vessels form when the endothelial cells that line the inside of the vessels, and the smooth-muscle cells that form a jacket around the outside, grow in response to specific signals. This process is known as angiogenesis and, when derailed, contributes to numerous diseases, including cancer, blindness in diabetics and arthritis[1].

One might assume that it would be irrelevant whether the blood vessels in different organs are alike or not, just as it would not matter what type of hosepipes irrigate the farm, as long as all fields receive the water they require. Yet, beyond their basic need for oxygen and nutrients, different tissues make different demands on their blood vessels. This suggests that, as well as the general signals (such as vascular endothelial growth factor, VEGF) that control angiogenesis in all organs[2–4], there should also be tissue-specific angiogenic molecules. On page 877 of this issue, LeCouter and colleagues[5] describe their discovery of the first such molecule. Their results imply that other tissue-specific angiogenic signals exist. If so, this would create many new — and probably safer — opportunities for stimulating or inhibiting angiogenesis in diseased tissues without affecting healthy organs (Box 1).

Because different tissues have distinct needs, the blood vessels that supply them also differ (Box 1). Take, for instance, the vessels in endocrine glands — organs such as ovaries and testes that produce steroid hormones involved in growth, metabolism, stress, reproduction and sexual development. These hormones must be able to reach the bloodstream, so vessels in endocrine glands are leaky and their endothelial cells contain fenestrations (tiny gaps through which fluid and small solutes can pass). In contrast, endothelial cells in the brain are tightly linked to each other and are engulfed by numerous periendothelial cells, which constitute a barrier that protects nerve cells from potentially toxic molecules from the blood.

VEGF is involved in the growth of fenestrated blood vessels. But, given that it is also expressed near non-fenestrated vessels, it cannot be the only factor involved. Moreover, when endothelial cells from endocrine glands are cultured in a dish, they lose their fenestrations. This plasticity suggests that endocrine glands produce signals that are essential to maintain the specificity and growth of their endothelial cells.

LeCouter *et al.*[5] have now identified such a molecule, which they call endocrine-gland-derived VEGF (EG-VEGF). This molecule functionally resembles and complements VEGF in its ability to induce the formation of endothelial fenestrations. However, EG-VEGF and VEGF are structurally dissimilar and probably work through different receptors. Moreover, VEGF affects endothelial cells non-selectively, and even acts on non-endothelial cells such as motor neurons[6]. EG-VEGF, on the other hand, affects only endothelial cells in endocrine glands. It is likely to be the first member of a large class of tissue-specific vascular growth factors.

Box 1 Blood-vessel growth factors

The properties of general and specific molecules that promote the growth of blood vessels (angiogenesis). Vascular endothelial growth factor (VEGF) is an example of a general molecule, produced by most tissues. Endocrine-gland-derived VEGF (EG-VEGF) is the first tissue-specific angiogenic molecule to be identified[5]; its discovery suggests that there may be others. Tissue-specific angiogenic molecules are needed because blood vessels differ. Bottom, blood vessels in endocrine glands need to be leaky, and have pores known as fenestrations through which hormones, produced by the endocrine glands, can enter the bloodstream. VEGF and EG-VEGF cooperate to induce the growth of fenestrated blood vessels[5]. Top, endothelial cells in the brain are very different: they do not have fenestrations, and are encased in an impenetrable layer of periendothelial cells (pericytes), which prevent potentially harmful molecules from leaking out of the blood. Different vessels vary in the number of pericytes per endothelial cell. P.C.