patterns wouldn't form unless the emissions had retained the orbital's phase.

Esat and colleagues' experiment is reminiscent of Young's double-slit experiment[1], in which the patterns formed by the interference of light proved that light is a wave. But, in contrast to Young's experiment, the emission patterns observed by Esat *et al.* can be explained only if the electron wavefunction has a different sign depending on whether it is emitted from the top right or top left corners of the molecule. The relative phases of the electrons emitted from different sites of the molecule can thus be worked out from the spatial distribution patterns of the emission current.

The authors used an established method for moving atoms and molecules[4] to produce their device. A complementary approach has previously been reported[5] in which electrons are coherently emitted from carbon nanotubes. The physics underpinning the emission process is the same in both systems, but the approaches used to realize it are completely different: Esat and colleagues' method can be thought of as a 'bottom-up' approach, in which the emitter is constructed from scratch, whereas the nanotube method was a 'top-down' approach in which nanotubes were painstakingly processed to allow the interference patterns to be observed and studied. The structures of Esat and colleagues' emitters are therefore much more precisely defined and reproducible.

The emission of electrons from a molecular device could, in principle, be triggered and steered using a laser, as was recently demonstrated for larger emitters[6]. This would require the stability of the molecular emitters to be improved, but would be another step towards the development of phase control. Molecular emitters might eventually find applications in devices such as electron microscopes, detectors that identify the phase or spin of electrons, or even quantum computers. ■

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MEDICAL RESEARCH

Weighing in on weight loss linked to cancer

Weight loss and tissue wasting often occur in pancreatic cancer. Analyses of human and mouse data reveal a mechanism behind these events, and raise the question of whether tissue wasting affects cancer survival rates. SEE LETTER P.600

J. MATTHIAS LÖHR

An early symptom of pancreatic cancer is a profound loss in weight that can precede disease diagnosis by months[1]. Weight loss also occurs in other types of cancer, and is often associated with severe illness and a reduced quality of life. On page 600, Danai *et al.*[2] report an analysis of pancreatic cancer, using mouse models and clinical data, that illuminates the consequences of weight loss for cancer outcomes.

Cachexia, the term used to describe the cancer-linked symptom of severe weight loss, has been recognized since at least the time of the ancient Greek physician Hippocrates. It is often a hallmark of cancers originating in the gut system[3], and might manifest in changes such as loss of fat (adipose) tissue or skeletal-muscle wasting, which could arise if the body is using up the nutrient stores in such tissues. Cachexia is particularly common in people who have a type of cancer called pancreatic ductal adenocarcinoma. The mechanisms driving cachexia are not the same in all tumours[4], but whether there are different types of cachexia depending on the tumour type or the stage of the cancer at which weight loss occurs remains to be determined.

Two key mechanisms[4] thought to drive cachexia are the breakdown of molecules in a process called catabolism, and inflammation, which is controlled by the body's immune system. The pancreas secretes digestive enzymes that break down complex, calorie-rich food to provide the components needed for tissue growth and maintenance[5]; this catabolism-supporting function is known as its exocrine role. Exocrine-system impairment causes malnutrition that can lead to life-threatening tissue wasting. However, the degree to which pancreatic exocrine-system abnormalities contribute to human cachexia was unknown.

Human pancreatic cancer often occurs in a region of the organ that can obstruct the main pancreatic duct, hampering enzyme release. This can lead to a situation termed pancreatic exocrine insufficiency, which results in nutrient-absorption deficiencies and weight loss[6]. Cachexia in humans can be exacerbated if deficiencies occur in essential nutrients[7,8], for example long-chain fatty acids and vitamin D, whose uptake is facilitated by pancreatic enzymes such as lipase. The administration of fatty acids increases skeletal-muscle mass in people with pancreatic cancer, particularly when this supplementation is combined with pancreatic enzymes[9].

"This striking result indicates that cachexia does not drive cancer-associated mortality."

The research group that conducted the current study had previously[10] observed that tissue breakdown occurs before pancreatic-cancer diagnosis in humans and before the development of early-stage pancreatic cancer in mice. To continue their investigation, Danai and colleagues studied pancreatic cancer using genetically engineered mouse models of the condition[11,12], and they used transplantation experiments to test whether tumour location affects wasting. They found that if pancreatic-tumour cells were transplanted into mice beneath the skin surface, adipose-tissue wasting did not occur, whereas wasting did occur if the cells were transplanted into the pancreas. This finding indicates that some aspect of the pancreatic environment has a key role in this phenomenon, and is consistent with the results of a previous study[11]. However, that study also found that tissue wasting was promoted when tumour cells were introduced into the body cavity, suggesting that tumour presence at a non-pancreatic site can also trigger this phenomenon.

Danai and colleagues' metabolic investigations revealed that mice with pancreatic tumours used less oxygen and produced less carbon dioxide than did control mice lacking tumours. This suggested that the presence of the cancer might be linked to a decrease in the processes involved in food breakdown and nutrient adsorption. To investigate how the pancreatic-tumour environment might cause this early metabolic change and weight loss, the authors tested whether pancreatic exocrine insufficiency was responsible, given that this can occur in human pancreatic cancer[6]. When Danai and colleagues gave the mice pancreatic enzymes, the level of adipose-tissue wasting decreased, suggesting that pancreatic exocrine insufficiency has a causal role in cachexia (Fig. 1).

Danai and colleagues found that, although pancreatic-enzyme supplementation could limit the tissue wasting, the animals' survival rate did not improve. This striking

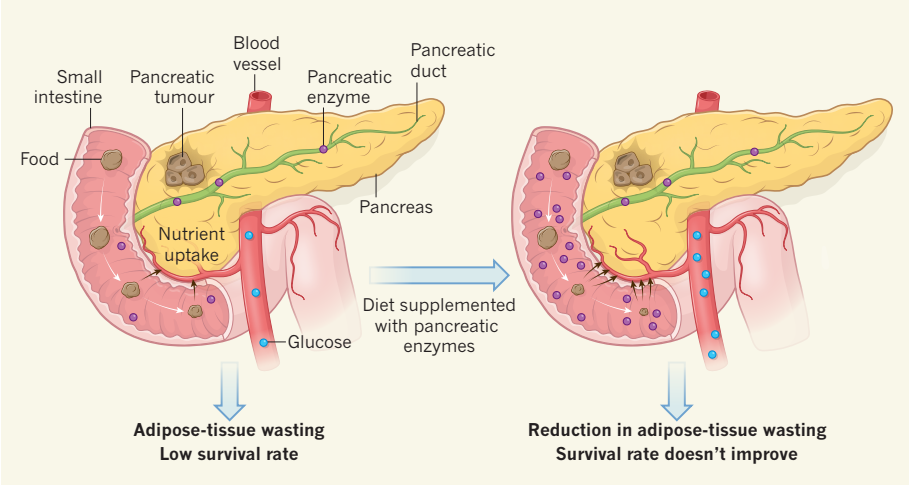

Figure 1 | Tissue wasting in pancreatic cancer. The pancreas secretes enzymes into the small intestine that aid the breakdown of food, enabling nutrients to be absorbed (black arrows). Abnormalities in this process can lead to weight loss and tissue wasting. Danai *et al.*[2] investigated the cause and consequences of the weight loss and adipose-tissue wasting that often occur early in pancreatic cancer. They observed that mice with pancreatic tumours had lower blood glucose levels, increased levels of adipose-tissue wasting and a decreased survival rate compared with control mice that did not have a pancreatic tumour. The authors tested whether feeding the mice pancreatic enzymes would result in any improvements, and found that it decreased adipose-tissue wasting and increased blood glucose. However, these changes did not increase the animals' survival rate, providing insights into the debate about whether weight loss is linked to cancer mortality.

result indicates that cachexia does not drive cancer-associated mortality. The result is also consistent with previous clinical evidence[6] that pancreatic-enzyme supplements do not improve survival in pancreatic cancer. Moreover, when Danai *et al.* analysed clinical data to assess adipose-tissue wasting in 782 people with pancreatic cancer, they found that wasting did not correlate with poorer survival rates. However, it was previously reported[13] that the loss of skeletal muscle and adipose tissue is linked to worse cancer survival rates, so Danai and colleagues' results call into question the idea that cachexia affects survival.

As well as regulating exocrine function, the pancreas has endocrine functions — it produces hormones that regulate metabolism. A key component of the endocrine system produced by the pancreas is the hormone insulin. Insulin facilitates glucose uptake into cells, and its absence can cause diabetes. Diabetes can sometimes precede pancreatic-cancer diagnosis by a year or two, and might be a red flag of trouble ahead[14]. Moreover, abnormal glucose metabolism might contribute to adipose- and skeletal-tissue wasting[15], and diabetes can cause exocrine insufficiency[16].

Danai and colleagues observed lower insulin and glucose levels in the blood of their model mice compared with the levels in control mice, and this decrease in insulin and glucose might lead to increased breakdown of stored fats, which could, in turn, increase the level of tissue wasting. This potential connection between the endocrine and exocrine systems and weight loss is supported by studies in the fruit fly *Drosophila melanogaster*[17].

Much remains to be understood about the role of the exocrine and endocrine systems in pancreatic cancer. One way to address this might be to perform detailed gene- and protein-expression analyses to determine the signalling crosstalk between transplanted cancer cells and the surrounding healthy pancreas in the mouse model used by the authors. Another potential avenue of research would be to investigate pancreatic exocrine insufficiency at the time of cancer diagnosis, especially in people whose tumours do not block the main pancreatic duct.

The authors did not investigate the role of inflammation in cancer-associated weight loss, but this is tricky to investigate because pancreatic tumours are associated with immunosuppression caused by factors such as the protein TGF-β. Inhibiting TGF-β reduced cachexia in a mouse model of pancreatic cancer[18], and there is circumstantial evidence that low-level inflammation contributes to pancreatic-exocrine insufficiency[19]. These observations provide tantalizing hints that inflammation warrants further investigation in this context.

It is worth considering whether other mechanisms might contribute to cachexia. For example, appetite loss might in turn reduce enzyme output, so dietary intake could be another key factor. As work such as that of Danai and colleagues improves our understanding of cachexia, the condition comes into focus as a distinct entity, rather than merely an early symptom of cancer. A goal for future research should be to delineate the interactions between exocrine and endocrine function and inflammation in cachexia. Although Danai and colleagues' results cast doubt on whether

50 Years Ago

The resignation of two matrons within a short space of time suggests that discontent among hospital staff is on the increase … matrons simply do not wield today the power they used to. Together with senior nurses they are assuming more and more responsibility, but their opinions are not being taken into account. It would not be a gross exaggeration to say that the concept of an all-powerful, dictatorial matron is fast disappearing, and this is perhaps no bad thing, because no individual can successfully carry the burden of running a hospital. But the answer does not lie in the appointment of honorary members of hospital committees who may be highly capable managers and administrators in their own right, but who have no real knowledge of the problems of nursing staff. What seems to be happening is that these "amateurs" … are overriding the people with professional knowledge.

From *Nature* 29 June 1968

100 Years Ago

Every boy and girl at school who "does science" now learns that metric units are the universal medium of scientific expression, and is practised in their use … A boy goes home at the end of term and tells his father that he has been doing science, weighing in grams, measuring lengths in centimetres, pressures in millimetres of mercury, and temperatures in degrees centigrade. Surely the most natural remark for any naturally minded parent to make is that his boy need not pay any attention to that, because, if it had any bearing at all upon practical life, he would certainly have been taught to use pounds or grains, inches, and Fahrenheit degrees, and not the outlandish things that nobody uses after he has left school.

From *Nature* 27 June 1918

cachexia affects survival in cancer, if progress could be made to stop tissue wasting, it would substantially alleviate the disease burden for patients. ■

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In retrospect

Twenty years of network science

The idea that everyone in the world is connected to everyone else by just six degrees of separation was explained by the 'small-world' network model 20 years ago. What seemed to be a niche finding turned out to have huge consequences.

ALESSANDRO VESPIGNANI

In 1998, Watts and Strogatz[1] introduced the 'small-world' model of networks, which describes the clustering and short separations of nodes found in many real-life networks. I still vividly remember the discussion I had with fellow statistical physicists at the time: the model was seen as sort of interesting, but seemed to be merely an exotic departure from the regular, lattice-like network structures we were used to. But the more the paper was assimilated by scientists from different fields, the more it became clear that it had deep implications for our understanding of dynamic behaviour and phase transitions in real-world phenomena ranging from contagion processes to information diffusion. It soon became apparent that the paper had ushered in a new era of research that would lead to the establishment of network science as a multidisciplinary field.

Before Watts and Strogatz published their paper, the archetypical network-generation algorithms were based on construction processes such as those described by the Erdös–Rényi model[2]. These processes are characterized by a lack of knowledge of the principles that guide the creation of connections (edges) between nodes in networks, and make the simple assumption that pairs of nodes can be connected at random with a given connection probability. Such a process generates random networks, in which the average path length between any two nodes in the network — measured as the smallest number of edges needed to connect the nodes — scales as the logarithm of the total number of nodes. In other words, randomness is sufficient to explain the small-world phenomenon popularized as 'six degrees of separation'[3,4]: the idea that everyone in the world is connected to everyone else through a chain of, at most, six mutual acquaintances.

However, random construction fell short of capturing the local cliquishness of nodes observed in real-world networks. Cliquishness is measured quantitatively by the clustering coefficient of a node, which is defined as the ratio of the number of links between a node's neighbours and the maximum number of such links. In real-world networks, node clustering is clearly exemplified by the axiom 'the friends of my friends are my friends': the probability of three people being friends with each other in a social network, for example, is generally much higher than would be predicted by a model network constructed using the simple, stochastic process.

To overcome the dichotomy between randomness and cliquishness, Watts and Strogatz proposed a model whose starting point is a regular network that has a large clustering coefficient. Stochasticity is then introduced by allowing links to be rewired at random between nodes, with a fixed probability of rewiring (p) for all links. By tuning p, the model effectively interpolates between a regular lattice ($p \to 0$) and a completely random network ($p \to 1$).

At very small p values, the resulting network is a regular lattice and therefore has a high clustering coefficient. However, even at small p, short cuts appear between distant nodes in the lattice, dramatically reducing the average shortest path length (Fig. 1). Watts and Strogatz showed that, depending on the number of nodes[5], it is possible to find networks that have a large clustering coefficient and short average distances between nodes for a broad range of p values, thus reconciling the small-world phenomenon with network cliquishness.

Watts and Strogatz's model was initially regarded simply as the explanation for six degrees of separation. But possibly its most important impact was to pave the way for

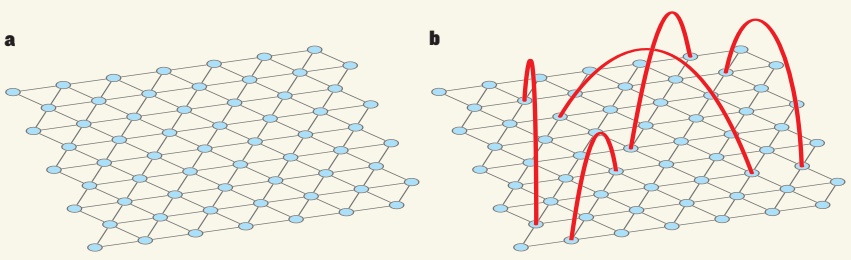

Figure 1 | The small-world network model. In 1998, Watts and Strogatz[1] described a model that helps to explain the structures of networks in the real world. **a**, They started with a regular network, depicted here as nodes connected in a triangular lattice in which each node is connected to six other nodes. **b**, They then allowed links between nodes to be rewired at random, with a fixed probability of rewiring for all links. As the probability increases, an increasing number of short cuts (red lines) connect distant nodes in the network. This generates the small-world effect: all nodes in the network can be connected by passing along a small number of links between nodes, but neighbouring nodes are connected to one another, forming clustered cliques. (Adapted from Samay/Vespignani.)