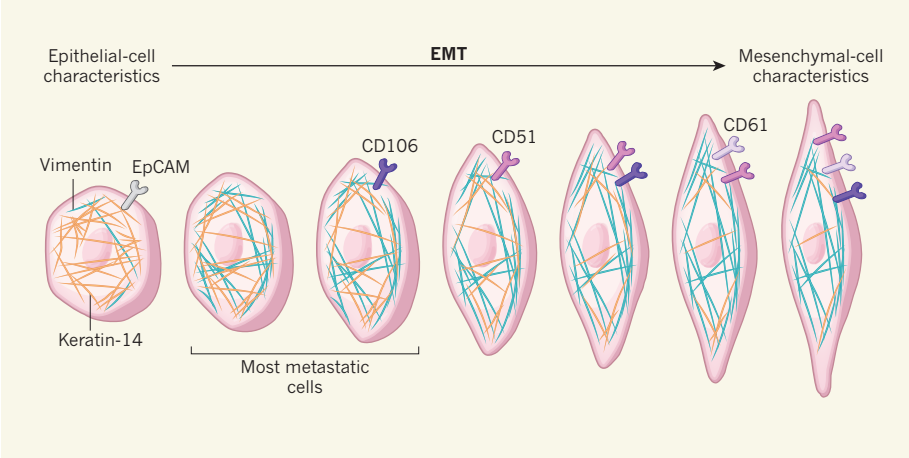

Figure 1 | Populations of cancer cells in transition states. Cancers that arise from epithelial cells often contain some tumour cells that have acquired mesenchymal-cell characteristics, such as an elongated shape and the expression of genes associated with mesenchymal cells. This change is termed the epithelial-to-mesenchymal transition (EMT). Whether this transition occurs as a gradual, continuous change or by discrete stages is debated. Pastushenko *et al.*[1] report mouse studies consistent with the latter, in which they identified cell populations *in vivo* that represent stable, distinct intermediates in this transition. The authors analysed cells that do not express the epithelial-cell receptor protein EpCAM, and isolated cell populations on the basis of their expression of the mesenchymal-cell receptor proteins CD51, CD61 and CD106. They monitored the level of proteins characteristic of the epithelial-cell state (such as keratin-14, yellow) or of the mesenchymal-cell state (such as vimentin, blue), and found cells that exhibited a hybrid of epithelial and mesenchymal characteristics. Cells that expressed EpCAM had low levels of vimentin and high levels of keratin-14. Once EpCAM expression was lost, the level of vimentin increased sharply and the level of keratin-14 declined incrementally as cell populations became more mesenchymal in character. The authors identified two cell populations that were the most likely to spread and form tumours elsewhere in the process called metastasis.

This finding might have clinical relevance. The authors' work therefore provides a platform for future investigations of this phenomenon in other cancer models, including studies of the regulatory networks that control these states. Such investigations might improve understanding of the molecular and cellular features that underlie the tumour-cell capabilities associated with these states.

Do these subpopulations exhibit behaviours that might offer therapeutic opportunities? One of the authors' most striking findings, made in the mouse skin-carcinoma and mammary-tumour models, is that when comparing these cell subpopulations, two of them stood out as having a substantially higher metastatic potential (Fig. 1). This raises the question of whether these highly metastatic cells could be specifically targeted with drugs to arrest tumour progression. Interestingly, none of the stable subpopulations was superior to the others in terms of tumour-initiating capability or proliferation rate. Also, each of the subpopulations that had acquired mesenchymal characteristics exceeded the metastatic capabilities of the epithelial-cell population. These findings are relevant to current debates in this field, which include the question of whether a cycle of EMT followed by MET is required for successful metastatic colonization of a secondary location[6,11].

The authors' work reveals the progressive acquisition of EMT features in EMT hybrid cells, supporting the previously proposed[8] idea of stable transitional states. A process of stepwise change is supported by Pastushenko and colleagues' data, indicating that distinct transcriptional and signalling processes govern intermediate aspects of EMT. The different cell subpopulations had characteristic transcriptional signatures regulated by distinct transcription-factor proteins, underscoring the reproducible and meticulously regulated nature of these hybrid cells.

Although these hybrid cell populations are a stable presence in tumours, the authors found that these cells also maintain a high degree of plasticity, given their ability to undergo MET and revert back to an epithelial-cell state. However, the authors found that the cell subpopulations that were best at undergoing MET during tumour metastasis to the lung in mice were not the most metastatic populations, which will fuel the debate[6] about whether MET is a requirement for metastasis.

Elucidation of the circuitry and signalling feedback loops that might stabilize[7,12] these distinct cellular states will be a worthy goal for future work. Studies of such cellular intermediates in patients' tumours, circulating tumour cells and metastases would be an ideal way to extend this work in a clinical context. If EMT states can be characterized for a wide range of human tumours, this might offer a way to enhance personalized approaches for cancer treatment. The development of specific technologies to identify human EMT states might allow clinicians to predict a tumour's metastatic potential and thereby plan the most effective treatment regimen. ■

50 Years Ago

Can experiments with bacteria or strips of gut help to explain the behaviour of the drug addict? Are drugs sought because of their special pharmacological properties, or as a form of social currency? … Such were the questions tackled at a symposium on the scientific basis of drug dependence … Sir Aubrey Lewis reviewed past attitudes and terminology. Although "physical" dependence could be reliably defined, "psychological" dependence was a dangerously woolly concept. Thus psychogenic polydipsia might be cited to prove water a drug of dependence. He underlined the need for a sense of proportion by quoting the scathing denunciation, by two authorities a generation ago, of the danger to mankind of that menacing beverage, tea.

From *Nature* 27 April 1968

100 Years Ago

A disease known as "trench fever" has been very frequent among the troops on the Western front. It is characterised by recurrent attacks of fever of short duration … and followed generally by acute pain in the shins and frequently by dilatation and disordered action of the heart. A committee … was instituted to investigate the causation and spread of the disease … various circumstances implicated the louse, and experiments were made on this hypothesis. Lice were allowed to feed on patients in all stages of the disease, and were then allowed to bite healthy volunteers; the result was negative. Next the excreta of lice similarly infected were applied to a scarified area of skin, and in from six to ten days after, all the five volunteers … developed trench fever. From these experiments it is evident that the bite alone of the louse does not produce trench fever, but that when the excreta of infected lice are scratched into the skin the disease is produced.

From *Nature* 25 April 1918