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50 & 100 YEARS AGO

50 YEARS AGO

Physics and Applied Mathematics — The contributions to this excellent survey were originally given as lectures at a symposium arranged in 1954... where a number of the leading physicists in the United States explained the recent advances in their own fields... Thus, H. A. Bethe mentions the plans then being made by Reines and Cowan to detect the neutrino by inverse beta-decay; C. H. Townes explains the principle of the 'maser' (as yet unnamed), being rather guarded as to whether it will eventually work usefully... W. Shockley gives a fairly elementary but full description of transistor physics... I. I. Rabi discusses atomic structure, emphasizing the importance of recent work on positronium... V. F. Weisskopf analyses the complicated pattern of the elementary particles, and forecasts more to come as cosmotron work in the ultra-high energy range continues... E. U. Condon, on physics and the engineer... [directs] attention to the shortage of high-school science teachers. This last appears to be a feature of the times, and not restricted to any one country; one wonders if it really is the only problem that is quite unapproachable by the methods of operational research, for there must be some way of averting the impending academic dust-bowl.

From *Nature* 3 August 1957.

100 YEARS AGO

The experiments which have been in progress in the Congo State for some time past in training the African elephant for domestic work are progressing satisfactorily. During the first three months of the present year, eight young elephants were captured, bringing the stud up to a total of thirty. At first the wild elephants suffer in health on confinement, but this depression soon passes off. Similar experiments are being made in the British territory of Uganda, but so far the results there are uncertain.

From *Nature* 1 August 1907.

In the small sample set studied by Soda *et al.*, mutations in *ALK* were mutually exclusive with *K-RAS* and *EGFR* mutations.

So far, the tyrosine kinase inhibitors gefitinib (Iressa) and erlotinib (Tarceva) are the only effective targeted therapies for lung cancer and are approved in different countries; these drugs seem to be most effective for the treatment of NSCLC patients with *EGFR* mutations[8–10]. Soda and colleagues present evidence that ALK inhibition is physiologically feasible, showing that mouse BA/F3 cells that were transformed with the *EML4–ALK* fusion gene can be specifically killed with an ALK inhibitor. The potential therapeutic use of such inhibitors would be of particular interest if the *EML4–ALK* fusions are often found in smoker NSCLC patients; this is because gefitinib/erlotinib are most effective for non-smoker NSCLC patients whose tumours are most probably due to *EGFR* mutations.

Until recently, chromosomal rearrangements have mainly been linked to blood-related cancers and seldom to solid tumours. However, the discovery of *TMPRSS2–ERG* and *TMPRSS2–ETV1* fusion genes in prostate cancer[11,12], and now the implication that the *EML4–ALK* fusion gene is involved in lung cancer, indicate that activated fusion genes associated with chromosomal rearrangements are probably both common and important in solid tumours. Developing systematic genome-wide approaches for discovery and diagnosis using these gene fusions will probably provide a leap forward in our understanding of the causes of solid-tumour cancers. ■

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MAGNETISM

Managed mess

Zachary Fisk

The presence of non-magnetic atoms can create a random internal field in magnetic crystals. Tuning that field from outside allows the intrinsic magnetic properties of the material to be precisely controlled.

The eccentric inventor and industrialist Diet Smith — financier of Dick Tracy's crime-fighting gadgetry (Fig. 1) — noted long ago that "he who controls magnetism controls the Universe". And efforts to control magnetism continue to make progress, as Silevitch *et al.* ably demonstrate in this issue[1] (page 567). These authors use a combination of chemical impurities and an external, variable magnetic field to manipulate the innate magnetism of a crystalline ferromagnet.

In a material with magnetic ordering, the directions of the magnetic moments that reside on every atom have a regular pattern. Among such materials, one expects ferromagnets (the atomic moments of which are all oriented in the same direction, even in the absence of an external magnetic field) to be simpler than antiferromagnets (which have some or all adjacent moments pointing in non-parallel directions). But being simpler is not the same as being simple. The physics of some ferromagnets is simpler than that of others, and the genius of he who wishes to control magnetism lies in finding these materials.

Silevitch and colleagues' choice[1] is the insulating ferromagnet $LiHoF_4$ (ref. 2). Magnetically, the $LiHoF_4$ crystal can be thought of as a three-dimensional stack of planar sheets of bar magnets made of holmium (Ho) atoms, which carry an intrinsic atomic magnetic moment. Each of these bar magnets can be oriented only with its north pole pointing at right angles — either up or down — to the plane of the sheets. This arrangement is known as an Ising system. Below this material's critical Curie temperature for ferromagnetic ordering — 1.53 kelvin — all of the north poles point in the same direction. The simplicity of this material is due partly to the fact that the dominant magnetic coupling between the atomic magnets is exactly the same as the dipole–dipole interaction of bar ferromagnets seen in basic school experiments.

The authors disturb this perfect simplicity by 'diluting' their crystal, replacing some of the holmium atoms in the crystal lattice with atoms of the non-magnetic, but chemically almost equivalent, element yttrium (Y), so that only a fraction x of the original holmium is left. The resulting material has the chemical formula $LiHo_xY_{1-x}F_4$. This breaking of the symmetry

Figure 1 | Speaking clock. Dick Tracy's two-way wrist radio was the most obvious consummation of his backer's faith in the power of magnetism.

surrounding each holmium site leads to 'off-diagonal' coupling of spin components between them, which results in a spatially random internal magnetic field[3]. At the heart of Silevitch and colleagues' work lies the insight that they can control the amplitude of this random field — and so use it as an experimental variable — by applying an external magnetic field in the plane of the holmium bar magnets.

The system thus created provides a playground in which to explore the changing behaviour of a magnetic material near critical points in response to variations in parameters such as temperature, magnetic field and pressure (this paper[1] concentrates on the first two of these variables). There are two different critical points of interest: the classical ferromagnetic Curie temperature, which occurs when the external field is zero; and the quantum critical point, which occurs when the Curie temperature has been driven to absolute zero by varying an experimental parameter such as the external magnetic field or the chemical doping.

The authors show that the immediate effect of yttrium substitution in $LiHoF_4$ is to depress the ferromagnetic Curie temperature linearly with decreasing holmium proportion, down to a proportion $x = 0.2$. Of particular interest is the effect of an applied magnetic field H on the material's magnetization M. This is defined by a parameter known as the magnetic susceptibility, $\chi = dM/dH$ (the rate of change of magnetization in a small applied magnetic field). In these experiments, χ also depends on the transverse applied field used to tune the random fields at the holmium sites.

Silevitch *et al.*[1] extract inverse exponential power-law dependencies for χ both as a function of temperature (at zero effective transverse magnetic field) and as a function of the effective transverse magnetic field (at the Curie temperature). A comparison of the pure compound ($x = 1$) with a diluted variant ($x = 0.44$) at zero applied magnetic field finds that the first power law is essentially unaltered, but that the second is considerably different in the diluted material. Remarkably, the authors find that this difference, which is the effect of random fields, can be parametrized in a modified Curie law, the standard expression that relates a material's magnetization to temperature and applied magnetic field. All that is needed are extra terms that take into account the suppression of magnetic order through chemical dilution and transverse fields, as well as the effects of quantum fluctuations and higher-order random field effects.

The immediate import of this work is twofold. First, the authors have shown how random field effects in a ferromagnet can be experimentally seen and tuned in a simple and standard laboratory measurement. Second, they have, for the first time, found a quantitative route into the realm of Griffiths singularities[4]. This term describes anomalies expected to occur in the magnetization (as a function of temperature at zero field) of randomly diluted Ising ferromagnets below the Curie temperature of the undiluted material. The extensive theoretical literature on the subject suggests that the difficulty in observing such singularities is caused by their being extremely weak, because they arise from isolated still-pure regions of the diluted system that occur with very low probability.

But these results[1] are also a prod to thinking about where else, and in what other related classes of material, such tuning of magnetic properties might be possible. The results could have relevance, for example, to the control of the magnetic domain boundaries, a focus of enormous research interest (see, for example, page 544). He who controls magnetism might not end up controlling the world, but will have a better handle on technologies so important in our information age. ■

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CANCER

An infernal triangle

Alberto Mantovani

Signals induced by sex hormones and inflammation have been viewed as different aspects of tumour development. But a three-way interaction between these two classes of signal and carcinogenesis has emerged.

In 1896, George Beatson discovered that surgical removal of the ovaries slows the growth of breast tumours, so revealing a link between sex steroid hormones and cancer of their target endocrine organs. Moreover, it has long been known that females are less susceptible to tumours at sites that are not conventional target organs of sex steroid hormones, such as the gastrointestinal tract[1]. Differences in drinking and smoking habits do not seem to fully account for these gender differences. Now, several studies open up unexpected vistas on the relationship between gender differences and cancer. They suggest that the inflammatory response, which is mediated by the innate, or nonspecific, immune system, might be an essential element of the action of sex steroid hormones.

Hepatocellular carcinoma, the most common type of liver cancer, is a frequent outcome of chronic inflammation triggered by hepatitis due to viral infection[2], with males being more susceptible to this tumour than females. Naugler *et al.*[3] have now explored the mechanisms underlying this gender difference. They started from the observation that, in response to injections of the carcinogen diethylnitrosamine, male mice had higher levels of a cell signalling compound (cytokine) known as interleukin-6 (IL-6), which is a marker as well as a mediator of chronic inflammation. The sex difference in susceptibility to cancer was absent in mice deficient in IL-6 and in the adaptor protein MyD88. The latter operates downstream of the Toll-like receptors that sense microbial invasion and tissue damage, or (in the form of the IL-1 receptor) act as amplifiers of inflammation.

The following picture emerges from *in vitro* work and from *in vivo* studies in mice (Fig. 1a). Carcinogen-induced tissue damage results in the release of debris, which in turn causes MyD88-dependent activation of Kupffer cells in the liver. These cells are a type of macrophage, a main player in the innate immune response. The cellular debris probably acts via Toll-like receptors, although this has not been formally proven. The Kupffer cells produce IL-6, which promotes liver injury, inflammation, compensatory cell proliferation, and carcinogenesis. In females, however, oestrogen steroid hormones act through gene transcription factors (such as NF-κB) to inhibit IL-6 production in Kupffer cells, and so to protect female mice from cancer. Curiously, tumour-necrosis factor, another cytokine, has been implicated in liver carcinogenesis[2,4,5] but is not involved in this gender difference.

Other investigations offer further evidence on the role of innate immune signalling in carcinogenesis. Mice deficient in MyD88 are relatively resistant to intestinal cancers, and