RECENT ADVANCES IN BIOMEDICAL SCIENCE

Deputy Editor **Andrew Blann** summarises some articles recently published in the *British Journal of Biomedical Science*.

Cancer and cardiovascular disease are the leading killers in the Western world. Recent papers in the journal reflect this.

Molecular genetics and cancer

Three papers using molecular genetics have focused on cancer, a disease that caused 25% of all deaths in England and Wales in 2021, the most common form being of the lung and bronchus (19% of cancer deaths). Ji and colleagues obtained paired malignant lung adenocarcinoma tissue and adjacent normal tissues from 129 patients. Low levels of the long non-coding RNA (lncRNA) species CARD8-AS1 were found in the malignant tissues, and levels were linked to tumour size, stage, lymph node metastases and, crucially, to survival. Further *in vitro* experiments pointed to a link with another non-coding micro-RNA – miR650, the authors suggesting that high levels of CARD8-AS1 suppress tumorigenesis, in that miR650 itself part-regulates second messengers such as Bcl-2 and Bax. This fits with other data showing that miR-650 is upregulated in lung cancer and can promote tumour cell proliferation and invasion. These data point to the potential use of this molecule in diagnosis and management, in that those with the lowest CARD8-AS1 expression may need more focused treatment.

Also from China, and with a similar design, Pan *et al.* looked at another lncRNA – LINC01929, but in non-small cell lung cancer, the most common form of this disease, and which has the poorest prognosis, finding levels to be over two-fold higher in 143 samples of malignant tissues than in adjacent normal tissues. As before, levels were linked to the stage of the cancer and to overall survival ($p=0.006$), which in multivariate analysis exceed the predictive value of tumour stage ($p=0.039$), once more pointing to potential clinical value. Again, this is in agreement with the previous lung cancer paper, and other tissue culture data pointed to the lncRNA species acting as a "sponge" for another miRNA molecule – miR1179, suggesting a more direct role of the latter in carcinogenesis. This is pertinent as miR1179 inhibits the growth and invasion of cancer cells by targeting an oncogene.

Infection with *H pylori*, and high intake of salt and of alcohol do not fully explain all causes of gastric cancer, a disease that

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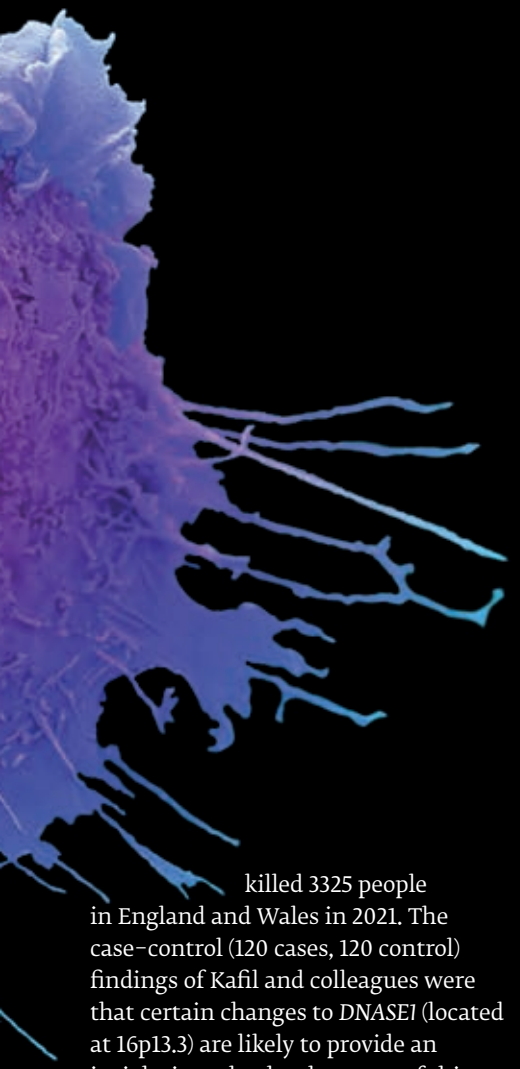
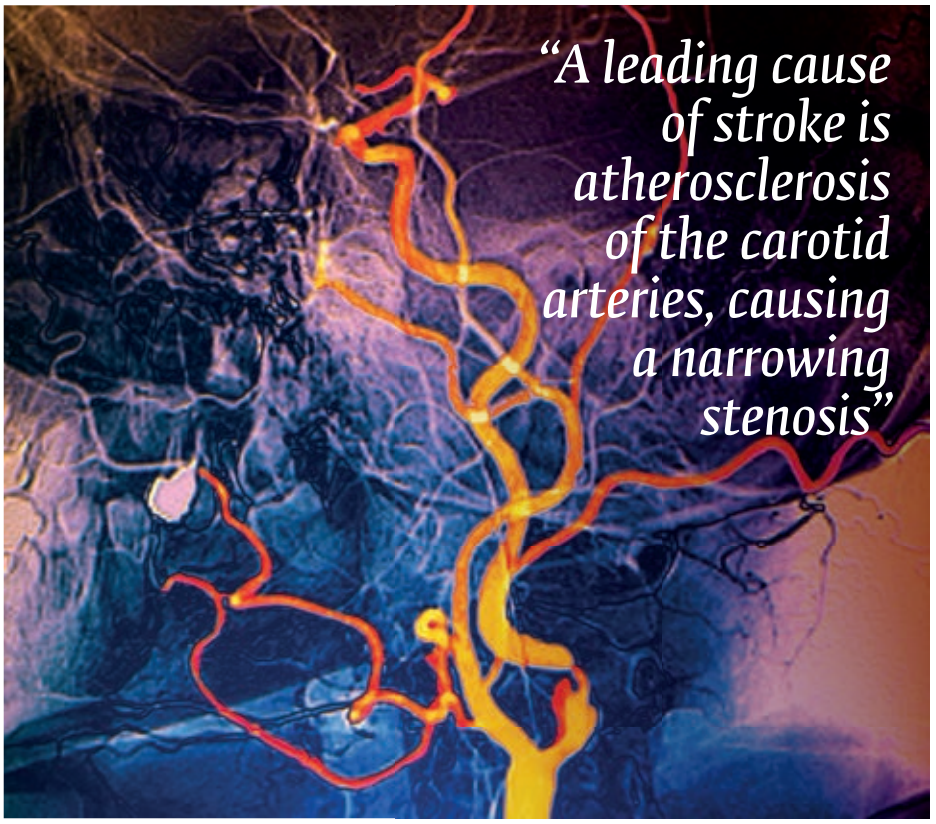


killed 3325 people in England and Wales in 2021. The case–control (120 cases, 120 control) findings of Kafil and colleagues were that certain changes to *DNASE1* (located at 16p13.3) are likely to provide an insight into the development of this neoplasm. The enzyme product of the gene has a role in apoptosis and is implicated in the carcinogenesis of numerous forms of cancer. They found that gastric cancer was linked to an SNP in one of the exons and to a genotype of the variable number tandem repeat in an intron, with odds ratio between 1.5 and 4.6. However, the combined genotype frequencies of these abnormalities brought a very high odds ratio of 20.57 (95% confidence interval 2.18–193.79). A practical aspect of this study was that it was performed on genomic DNA from a blood sample, and so may become a diagnostic and prognostic marker that the routine laboratory may one day adopt.

"Against usual findings, those with retinopathy needed less insulin"



"A leading cause of stroke is atherosclerosis of the carotid arteries, causing a narrowing stenosis"

Cardiovascular disease

The second most frequent case of death is cardiovascular disease (23% of deaths), and a leading cause of stroke (which killed almost 29,000 people in 2021 [almost 57,000 of heart disease]) is atherosclerosis of the carotid arteries, causing a narrowing stenosis. The degree of this stenosis, which can be detected by ultrasound, requiring a hospital visit, is linked directly to the risk of stroke, and so is a powerful risk factor. Seeking a laboratory marker of this risk, Li and Pan took a blood sample from 105 people with asymptomatic carotid artery stenosis, and from 101 controls, probing for levels of serum miRNA-206, as a previous study found reduced expression of this miRNA in atherosclerotic tissue samples. The researchers found that the level of serum miR-206 correlated strongly ($r = -0.83$, $p<0.0001$) with the degree of carotid stenosis, with a receiver operating characteristic area under the curve of an impressive 0.94 ($p<0.001$), and an odds ratio (95%) confidence interval of 0.34 (0.13–0.86)($p=0.02$) for carotid stenosis. Furthermore, in view of this, perhaps unsurprisingly, in a five-year follow-up study, those with low levels (and so a high degree of stenosis) had a much decreased risk of an adverse event (stroke, death, etc.) with a hazard ratio (95% confidence interval) of 0.046 (0.005-0.431)($p=0.007$), which exceedd all other clinical and laboratory data. A simple and quick blood test for this miRNA would be a useful tool in clinical assessment. (For PDF of an open-access review on lncRNAs and miRNAs in the *BJBS*, visit **bit.ly/BJBS_RNAs**)

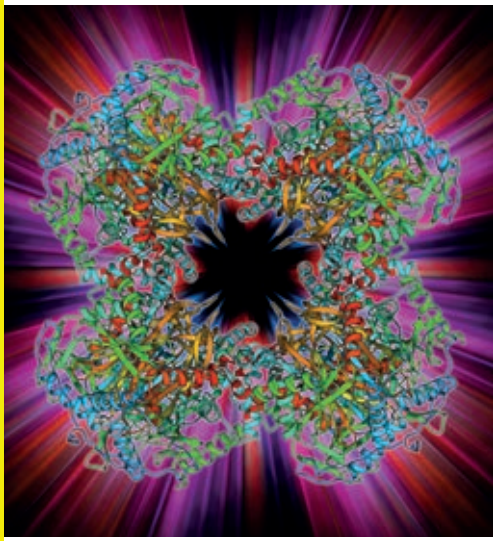
The major fatal complication of diabetes is, of course, cardiovascular, but the disease also causes considerable morbidity, one of which is retinopathy. Of the various candidate genes linked to the development of this condition, KCNJ11 (also known as Kir6.2, which codes for a subunit of a membrane protein part-regulating the passage of potassium) may have a role in certain forms of abnormal glucose metabolism. Alidoust *et al.* tested the hypothesis that a certain single nucleotide polymorphism (SNP) in KCNJ11 is linked to retinopathy in type 2 diabetes, but found no such association. This negative result is unlikely to be due to a

"A simple and quick blood test for this miRNA would be a useful tool"

false negative as our colleagues in Iran studied 234 patients without retinopathy, and 290 with the eye disease, and is counter to a report from China where a positive link was indeed reported. It follows that there must be other reasons for the link in the Chinese report– genetics clearly comes to mind, perhaps in a multi-hit process. Interestingly, and against usual findings, those with retinopathy needed less insulin (59.3% v 70.5%, p<0.01).

Other diseases

Most haematologists and biochemists will be aware of pyruvate kinase deficiency, but there are other defects in this metabolic pathway. Pyruvate dehydrogenase, with other enzymes, forms a complex in the mitochondrion, the enzyme deficiency causing an extremely rare metabolic condition, with around 500 cases reported in the literature. Generally appearing in the newborn, clinical signs include microcephaly (a small head), and later there is often mental retardation, blindness and spasticity. Karissa and colleagues reviewed the pathology and management of this deficiency disease, suggesting the use of dichloroacetate as a treatment, principally because it may reduce the lactic acidosis, although there is often hyperammonaemia. A far more frequent disease is cystic fibrosis, most cases being caused by a deletion in *CFTR* at 7q31.2 leading to a loss of function of a membrane channel that regulates water and chloride levels. A consequence of this is that mucous secretions are more viscous, and may block ducts such as those of the pancreas, although a major primary clinical feature is pulmonary disease brought about by the increased viscosity of lung mucus. A consequence of this is an increased frequency of lung infections, often with bacteria of the *Pseudomonas* family, the most common being *aeruginosa*. Moore and colleagues collected samples from 100 patients with the condition, reporting the frequencies of other *Pseudomonas* species, the most common being *fluorescens* (*n*=38), *putida* (18) and *stutzeri* (6). Laboratory identification of the particular bacterium may help guide antibiotic therapy.



A major side effect of much cytotoxic and immunosuppressive therapy is leukopenia, resulting from the action of these drugs on the bone marrow. Although growth factors can help alleviate this leukopenia, it may also promote the development of myeloid-derived suppressor cells, which themselves may lead to a reduced generation of haemopoietic stem cells. Using a mouse model, Salem and colleagues produced a lysate of bone marrow cells, and used it, alongside cyclophosphamide, to enhance the number of such stem cells. The precise nature of the molecule(s) in the bone marrow lysate should help elucidate the exact mechanism(s) of this effect, leaving the path clear for studies in our own species. BMS

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