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EDITORIAL

British Journal of Biomedical Science in 2018: what have we learned?

ABSTRACT

In 2018 the British Journal of Biomedical Science published one guideline (in reproductive science) and 40 research articles in the various disciplines the comprise biomedical science. The latter were 24 original articles and 16 'In Brief' short reports. Of these, 23 are of note to only one of the sub-disciplines (seven each to biochemists and microbiologists, six to cell pathologists, and one each to cytologists, immunologists and reproductive scientists). Reflecting the increasing complexity of laboratory science, thirteen papers crossed one boundary (three papers each relevant to biochemists and immunologists, and to haematologists and biochemists), whilst four papers were relevant to three or more disciplines. Indeed, biochemical techniques were used in 18 papers, microbiological techniques in 9, whilst histopathology was relevant to 11 papers. Notably, 20 papers used techniques in chromosome analysis and molecular genetics. The present report will summarise key aspects of these publications that are of greatest relevance to laboratory scientists.

KEYWORDS

Biomedical science; Cellular pathology; Clinical chemistry; Cytopathology; Haematology; Cellular pathology; Immunology; Microbiology; Transfusion science; Virology; Molecular genetics

Introduction

The *British Journal of Biomedical Science* is the leading international journal focusing on practice, research and education in all aspects of biomedical science as it applies to the diagnosis and clinical management of human disease. This generally focuses on the practice of routine biomedical/clinical science in NHS hospitals, but can also embrace developing methods, cell and molecules, such as in tissue culture, pharmacology and molecular genetics. The growing importance of the latter is demonstrated by the fact that of 40 data papers, 20 used techniques in RNA and/or DNA, a figure slightly lower than the rate in the 28 data papers (53.6%) published in 2017 compared to the 34 data papers (38.2%) published in 2016. In issue 1 of 2016, an article summarised work published during 2015 [1]. Similarly, issues 1 of 2017 and 2018 lead with an article summarising work published during those years [2,3]. The present communication aims to continue this process with a summary of those papers published during 2018, which report practical advances in biomedical science, classified by major discipline.

As in previous reports, the many disciplines that comprise biomedical science will be collected together into three broad categories that together make up the NHS's life sciences [4]. These are blood sciences (haematology, clinical chemistry [including toxicology], blood transfusion and transplantation, immunology), cellular sciences (histopathology, cytology) and infection sciences (microbiology, bacteriology, virology, mycology, parasitology). We will first look at the 23 papers that focus on a single discipline (9 in blood science, 7 in infection science and 7 in cell pathology) before moving to the 13 that cross two boundaries (7 in blood science, 6 in infection science) and the 4 that are multi-disciplinary. An immediate problem with this system of classification is that, by definition, it undermines the simple layout of the traditional disciplines: for example, the leading technique in the paper by Tong [5] et al. is molecular genetics in uterine sarcoma: it is placed in cellular science as it refers directly to organ disease, although no classical histology (stained H&E tissue sections, or even FISH) was performed. It could therefore be argued that this paper belongs in a separate section devoted only to molecular genetics.

Blood science

Liver disease is a continuing theme in the Journal [6–8]. Fibrosis markers are useful for the prediction of cirrhosis, but current clinical tools have limited accuracy for diagnosing significant fibrosis. Attallah et al. [9] hypothesised that collagen type IV, hyaluronic acid, platelet-derived growth factor (PDGF) and tissue inhibitor of metalloproteinase-1 (TIMP-1), together with other indirect fibrosis markers, would together construct a more sensitive and specific score capable of identifying fibrosis than existing scores. In multivariate analysis, age, AFP, PDGF, Collagen IV and TIMP-1 were all independent predictors of fibrosis and were brought together into a 'Fibro-Mark' score, which out-performed six other scores. This result may promote the adoption of these new molecules into routine clinical practice. Mousa et al. [10] measured biochemical indices in 200 pregnant women with non-alcoholic fatty liver disease (NAFLD) and 200 women free of this problem, finding increased glucose (P = 0.001), AST (P = 0.002), total cholesterol

(P = 0.001), triglycerides (P = 0.014) and uric acid (P = 0.001) in the former. These may be linked to the increased frequency of gestational diabetes, pre-eclampsia and hypertension in the NAFLD women, justifying increased laboratory monitoring.

Type 2 diabetes mellitus describes as a group of metabolic disorder characterised by prolonged elevated blood sugar levels, which further expose a person to risk of developing microvascular and macrovascular complications, and (unsurprisingly) is a frequency object of research [11,12]. Several environmental (obesity) and genetic factors (such as microRNAs) contribute to the multiple pathophysiological disturbances that are responsible for impaired glucose homeostasis in this disease. Amr and colleagues [13] hypothesised that plasma miR-126 and miR-210 are linked to coronary artery disease (CAD) in diabetes patients, recruiting 20 healthy volunteers and 100 patients with diabetes (54 patients without CAD and 46 patients with CAD). Plasma miR-126 and miR-210 (assessed by quantitative RT-PCR) were mean (SD) 0.38 (0.03) and 5.3 (0.56) in diabetes alone vs. 0.08 (0.03) and 21.44 (0.97) in diabetes with CAD, respectively (both $P < 0.0001$). The miRNAs significantly discriminated diabetes with and without CAD, with sensitivity 91.3% and specificity 100% for miR-126, and with sensitivity 93.5% and specificity 100% for miR-210. The authors conclude that these miRNAs may be biomarkers for diabetes and CAD. Rivzi et al. [14] also studied diabetes, comparing 200 patients with 200 controls, using PCR to determine the frequencies of SNPs in *KCNJ11* (coding for part of the ATP-sensitive potassium channel) and *SDF-1β* (coding for chemokine CXCL12). Their principle findings were that the A allele of SDF-*1β* was significantly (P = 0.006) protective against the risk of diabetes, and that SNPs in both *KCNJ11* and *SDF-1β* were significantly associated with diabetes. Abbas et al. [15] tested the hypothesis that SNPs in the gene for Toll-like receptor 4 (TLR4) are linked with nephropathy, hypertension and dyslipidemia in 370 diabetes cases (122 with nephropathy, 119 with hypertension and 129 with dyslipidemia) and 120 ethnicity matched healthy controls. Using PCR-RFLP, a significant difference in SNP rs5030717 was observed when the genotype frequencies of diabetic dyslipidemia cases compare with control (P = 0.001). Significant difference in SNP rs5030718 were found when the genotype frequencies of diabetic nephropathy cases (P = 0.03) and diabetic dyslipidemia cases (P = 0.001) were compared controls. They concluded that the *TLR4* SNP r5030717 is associated with the risk of dyslipidemia whereas SNP rs5030718 is linked with diabetic nephropathy and dyslipidemia.

The current gold-standard diagnostic laboratory test for prostate cancer, prostate specific antigen (PSA) is imperfect, being often raised in benign prostatic hyperplasia (BPH). Recent data suggests that serum relaxin-2 may be a new marker for different cancers. Xu et al. [11] investigated whether serum relaxin-2 is related to presence, progression and survival in 131 prostate cancer patients versus 66 with BPH and 48 healthy men. Relaxin-2 was median (interquartile range) 2.0 (0.2–3.7) ng/ml, 0.4 (0.3–0.7) ng/ml and 0.4 (0.2–0.6) ng/ml in cancer, BPH and healthy men respectively ($P < 0.01$). Patients with high relaxin-2 levels were more likely to have distant metastasis ($P < 0.01$) and had shorter outcome survival (P = 0.004) and disease-free survival (P = 0.003), suggesting that relaxin-2 could be a useful diagnostic and prognostic marker in prostate cancer. Polycystic ovary syndrome (PCOS) is a common disorder of reproductive age women, a key pathophysiology feature being matrix remodelling. Collagen is the chief component of extracellular matrix of ovaries and serves as a substrate for remodelling, a process regulated by prolidase, a cytosolic exopeptidase. Bhatnager et al. [17] recruited 400 subjects in a case control study, measuring serum prolidase by ELISA and the rs267606943 SNP of the prolidase gene by PCR-RFLP. They found prolidase levels to be markedly higher in the PCOS ($P < 0.001$), but no link with the SNP (P = 0.547). This effectively rules out a role for this SNP in the pathogenesis of PCOS.

Ulcerative colitis (UC) is a chronic disease that specifically affects the mucosa of the rectum and colon. Pathogenesis is not well defined, but it is possible that genetic and environmental factors result in an aberrant immune response to a subset of commensal enteric bacteria. Hosseinpour et al. [13] conducted a case-control study of 180 patients and 250 controls to evaluate variants in SNPs in genes for tumour suppressor protein p53 and miR-34b/c on the development of UC. They found that subjects with the p53 variant genotype (Pro/Pro) showed a significantly increased risk of UC relative to Arg/Arg carriers (Odds ratio 7.11, 95% CI 3.22–15.69; $P < 0.001$). The frequency of the miR-34b/c CC genotype was higher in the UC group than in the control group (OR = 5.5, 95% CI 2.44–12.38, $P < 0.001$). These data imply that the C allele-containing genotypes (CC and CT) brings a higher risk of developing UC, and so may be worthy of inclusion into the diagnostic process.

Tian and colleagues [14] evaluated the clinical value of serum anti-neutrophil cytoplasm autoantibodies (ANCA) directed against bactericidal/permeability-increasing protein (BPI) detection in chronic obstructive pulmonary disease (COPD) patients with pulmonary *Pseudomonas aeruginosa* colonisation. Serum BPI-ANCA was detected by ELISA in 59 BPI-ANCA(+) patients and 67 BPI-ANCA(–) patients. Lung function tests, the COPD assessment test and a 6-minute walking test (6MWT) were conducted on outset and at 6, 12 and 18 months follow-up. On outset, lung function was weaker in BPI-ANCA(+), who also had a greater disease duration and history of hospitalisation. After 12 months, all clinical indices were more adverse in the BPI-ANCA(+) group ($P < 0.05$), and at 18 months, this difference was more significant ($P < 0.01$). In serial analysis, all indices deteriorated in both groups ($P < 0.001$), but in the BPI-ANCA(+) group, lung function and distance walked in 6 min were reduced whilst the

number of hospital readmissions ($P = 0.02$) and hospitalisation days in acute exacerbation period ($P = 0.04$) were higher. Authors conclude that BPI-ANCA antibodies predict a poor prognosis for COPD patients with pulmonary *P.aeruginosa* colonisation, so may be used to help drive treatment and subsequent monitoring.

Although foetal trisomies of chromosomes 21, 18 and 13 can be detected in maternal blood, the presence of maternal chromosomes is confounding and lead to incomplete sensitivity and specificity. He et al. [20] reported an improvement of the method for detecting foetal DNA with a size-selective agarose gel electrophoresis step, validating their new method in 114 clinical cases, demonstrating improved a positive predictive value for these aneuploidies.

Cellular sciences

Histo(pathology) and cytology are no longer only about staining cells and tissues with dyes: as we have seen [6,11,13–15], micro-RNA (miRNAs) are slowly insinuating their way into all disciplines of biomedical sciences. Tong and colleagues [5] recruited 101 patients with uterine sarcoma and 54 healthy subjects, measuring serum miR-152, miR-205, miR-222, miR-24, miR-150 and sirtuin-1 by qRT-PCR. They found that miR-152, miR-24 and sirtuin-1 were lower and miR-205, miR-222 and miR-150 were higher in the sarcoma patients, and that all miRNAs were linked with stage of the sarcoma. Furthermore, patients had better survival rates with high-level miR-152 and miR-24, with a 5-year overall survival of 21.8% and 67.5%, respectively. They conclude that altered miRNA species in uterine sarcoma are linked to disease stage. Will these miRNAs one day enter routine practice?

Oxidative stress may be linked to the initiation and progression of breast cancer, and may be countered by selenoproteins, many of which have been shown to have redox functions, acting as antioxidants. Mohammaddoust et al. [21] probed the association of SNPs in *SEPP1* and *SEP15* with the risk of breast cancer in 150 cases and 200 cancer-free controls using PCR-RFLP and allele-specific PCR (AS-PCR). The AA genotype (Thr/Thr) for *SEPP1* and AA genotype for *SEP15* were linked to a higher risk of breast cancer (OR = 3.89; 95% CI, 2.02–7.49; $P < 0.0001$ and OR = 2.82; 95% CI, 1.04–7.62; $p = 0.04$, respectively). In addition, the *SEPP1* A allele was linked with higher breast cancer risk, pointing to the possible use of these SNPs in routine screening. Mashayekhi et al. [22] also investigated breast cancer, looking at miR-27a, mir-196a2 and miR-146a in 353 cases and 353 controls. The principle finding was that the CC genotype of *miR-146a* (rs2910164) was seen in 45 (12.7%) patients with breast cancer and 18 (5.1%) controls (OR 4.09 [95% CI 2.19–7.67] $P < 0.001$) whilst the minor allele G of *miR-27a* was associated with a decreased risk of breast cancer (OR 0.24 [95% CI 0.14–0.42] $P < 0.001$) suggesting that these variants contribute to breast cancer and so may also, one day, be used in a routine setting.

p21 is a protein involved in regulating the cell cycle, and genetic variants are linked with various diseases. To clarify whether polymorphisms in p21 were associated with meningioma, Mashayakhi et al. [23] also conducted a case-control study of *p21* C98A and C70T SNPs in 225 meningioma patients and 320 healthy control subjects. Although both SNPs were linked to the tumour, presence of the A allele in *p21* C98A brought an increased risk of the disease compared to the T allele in *p21* C70T, with an odds ratio of 2.38 (95% CI 1.58–3.57) ($P < 0.001$). Toxicology is an important aspect of our work [24]. Certain forms of chemoradiotherapy generate toxic reactive oxygen species, which may be suppressed by antioxidant enzymes such as glutathione S-transferase (GST). Genetic polymorphisms of *GST* may predict treatment outcomes and can be used as genetic marker to screen patients before treatment. Abbas and colleagues [25] hypothesised an effect of *GST* SNPs on toxicities in 227 women with cervical cancer receiving cisplatin based chemoradiotherapy. Severe gastrointestinal and haematological toxicities were present in 22 (9.4%) and 16 (7.0%), respectively. In single locus analysis, *GSTP1* AG and GG were linked to the greatest risk of severe gastrointestinal toxicity (OR 3.12, $P = 0.035$ and OR 6.99, $P = 0.01$, respectively). In gene–gene interaction analysis, *GSTM1*null-*GSTP1* GG brought a 4.2-fold higher risk of severe gastrointestinal toxicity ($P = 0.014$). *GSTT1* null-*GSTP1* AG reached statistical significance with a 3.9-fold higher risk of high-grade gastrointestinal toxicity ($P = 0.038$). There findings may lead to new clinical initiatives to identify those women at increased risk of these side effects.

There is considerable evidence of miRNA involvement in many malignancies, such as oesophageal and gastric [26,27]. Mirnoori et al. [28] hypothesised altered expressions of *pri-miR-124–1* rs531564 and transcription factor *STAT3* rs1053023 SNP in 250 patients with gastric cancer and 310 healthy individuals. They found a difference in the distribution of the rs531564 genotype: G allele carriers had a reduced gastric cancer risk (OR = 0.62; 95% CI = 0.49–0.80, $P = 0.0002$) whilst the minor allele of rs1053023 was linked with higher risk (OR = 2.29; 95% CI = 1.79–2.93, $P < 0.0001$). This strong link between *pri-miR-124–1* rs531564 and *STAT3* rs1053023 and gastric cancer may be pathogenic, yet more evidence that these markers may become routine.

The thyroid is another organ of interest to laboratory scientists [29,30]. Yang et al. [31] hypothesised that miR-146b measurement in a fine-needle aspiration biopsy (FNAB) will distinguish papillary thyroid cancer (PTC) in 246 patients from benign thyroid masses in 90 controls. miR-146b expression was

higher in PTCs ($P = 0.0013$); high miR146b expression levels were linked to cancer stage ($P = 0.018$), lymph node metastasis ($P = 0.04$) and distant metastasis ($P = 0.002$). The accuracy of FNAB for PTCs was 80.5%, the sensitivity and specificity were 76.9% and 86.4% with a positive predictive value of 85.3%, and a negative predictive value of 94.6%. The accuracy of miR-146b for PTCs was 90.6%. The AUC of miR-146b was 0.87 (cutoff value 45.6, sensitivity 92.1%, specificity 82.3%), and a positive predictive value of 93.3%, and a negative predictive value of 96.2%. These data suggest that miR-146b may be used to improve the diagnostic accuracy of FNA biopsy and to distinguish PTCs from benign thyroid masses.

Infection sciences

The emergence of resistance against antimicrobial agents has led to the search for more efficient agents and new techniques for treatment of various microbial infections [32]. Nehra et al. [33] set out to determine the antibacterial and antifungal activity of bare and chitosan coated Fe_3O_4 nanoparticles (NPs) against five organisms, *Escherichia coli* (*E. coli*), *Bacillus subtilis* (*B. subtilis*), *Candida albicans* (*C. albicans*), *Aspergillus niger* (*A. niger*) and *Fusarium solani* (*F. solani*). The antimicrobial property of NPs was tested by agar well diffusion and analysed by measuring the diameter of the inhibition zone. Mean diameter of inhibition zone of synthesised chitosan coated Fe_3O_4 NPs was in the range 14.5 to 18.5 mm. The effect of chitosan coated iron oxide nanoparticles was *F. solani/A. niger* < *C. albicans* < *E. coli/B. subtilis* ($P < 0.001$). The authors conclude that nanoparticles are effective antimicrobial agents and so may be developed as a microbial resistant coating for biomedical devices. As many clinical laboratories convert between Stokes, Clinical and Laboratory Standards Institute (CLSI) and European Committee for Antimicrobial Susceptibility Testing (EUCAST) methods, the problem of comparing differently derived sets of antimicrobial susceptibility testing (AST) data with each other arises, owing to a scarcity of knowledge of inter-method comparability. O'Halloran et al. [34] set out to determine the comparability of CLSI, EUCAST and Stokes AST methods for determining susceptibility of uropathogenic *E. coli* to several antibiotics in 100 urine *E. coli* isolates that were obtained from patients attending GP surgeries. For EUCAST and CLSI, the Kirby-Bauer disc diffusion method was used and results interpreted using the agreement for ciprofloxacin. For the Stokes method, direct susceptibility testing was performed on the urine samples. The lowest levels of agreement were for amoxicillin-clavulanate (60%) and ciprofloxacin (89%) between the three AST methods, when using 2017 interpretive guidelines for CLSI and EUCAST. A comparison of EUCAST and CLSI without Stokes showed 82% agreement for amoxicillin-clavulanate and 94% agreement for ciprofloxacin. Their data indicate that discrepancies generated through using different AST methods and different interpretive guidelines may result in confusion and inaccuracy when prescribing treatment for urinary tract infection.

Uropathogenic *E. coli* (UPEC) are a predominant cause of community acquired and nosocomial urinary tract infections (UTIs). Salehzadeh et al. [35] studied the association of several virulence determinant genes (VFG) and bacterial phylogeny in 100 UPEC isolates from patients with community acquired UTI. Most isolates belonged to the phylogenetic groups B2 (52%) and D (28%) whilst 14 and 6 isolates belonged to groups A and B1, respectively. The highest prevalence of VFGs was recorded for *traT* (92%) and *fimH* (86%). Amongst virulence factors, a positive association was observed for *fimH, sfa-S, foc/G* and *chuA* with phylogenetic group B2. In addition, *hlyA* and *PAI* were significantly more prevalent amongst the strains associated to the groups D and A, respectively. Most isolates were resistant to piperacillin (91%), cefixime (80%), ciprofloxacin (76%) and cephalothin (76%), whilst only 12 isolates were imipenem resistant. The authors conclude that a higher prevalence of VFGs and drug resistance amongst phylogenetic groups B2 and D results in higher bacterial infectivity, development of infection and therapeutic failure.

As *Streptococcus pneumoniae* is the most frequent cause of bacterial pneumonia of people of all ages, as well as an important cause of meningitis and otitis media, the ability to genotype suspect organisms will aid both diagnosis and treatment. Moore and colleagues [36] examined the complete 16S-23S rRNA region in 78 *S pneumoniae* isolates through PCR amplification and sequencing to determine the degree of sequence heterogeneity within this internal transcribed spacer (ISR) region. Twenty-five 16S 23S genotypes (Genotype A – Genotype Y) were identified amongst the 78 isolates, dominated by genotypes A and B, with 28 and 20 members, respectively, accounting for 61.5% of the total pneumococci examined, with the remaining isolates clustered into 19 genotypes (Genotypes G-Y) containing only one member. This study showed that this ITS region in community-acquired isolates of pneumococci is variable and not totally conserved. These colleagues of ours from Belfast added to the literature [37] on the difficulty in separating the culture of *Pseudomonas aeruginosa* from pan-resistant *Burkholderia cenocepacia* isolates. This they achieved with the development of a new form of agarose which supports the growth of *P. aeruginosa* but not *B. cenocepacia*.

Helicobacter pylori is an important and common pathogen [27,38]. Yakoob and colleagues [39] studied the link between this organism and common protozoal parasites in 161 patients with abdominal discomfort and chronic diarrhoea compared to 114 age and sex matched controls. Stool samples were examined by microscopy and DNA extracted for PCR with

specific primers for *H. pylori* and protozoal parasites *Blastocystis* sp., *Entamoeba* sp. (*Entamoeba histolytica, Entamoeba dispar* and *Entamoeba moshkovskii)* and *Giardia duodenalis* (*G. duodenalis*). Patients with diarrhoea were more likely to be infected with *Blastocystis* sp. ($P < 0.001$), *E. histolytica* ($P = 0.027$) and *E. moshkovskii* ($P = 0.003$). There was no difference in the frequency of *H. pylori* ($P = 0.528$), *G. duodenalis* ($P = 0.697$) or *E. dispar* ($P = 0.425$). Thirty-three patients and 27 controls had *H. pylori* infection. Of these, 22 patients and 6 controls were infected with *Blastocystis* sp. ($P = 0.001$), 6 patients and no controls with *E. histolytica* ($P = 0.02$), and 7 patients and 9 controls with *E. dispar* ($P = 0.292$). The authors conclude that diarrhoea is linked to infection with *Blastocystis* and *Entamoeba* sp., whilst in *H. pylori* infection, diarrhoea is linked to *Blastocystis* sp. and *E. histolytica* infection. These associations may be linked pathogenically.

Extended spectrum beta lactamase [ESBL] producers and ESBL associated cephalosporin resistance amongst *Acinetobacter baumannii* is emerging in recent years. Smiline et al. [40] contributed to this field by analysing the molecular characterisation of ESBL producers of *A. baumannii* in 73 isolates from 100 patients with severe UTI. Preliminary screening for ESBL's was by the Kirby Bauer disc diffusion method with ceftazidime, cefotaxime and ceftriaxone discs. Phenotypic confirmation was performed with clavulanate based tests viz., DDST and CDT methods. Plasmid DNA was extracted and PCR performed: *blaTEM* was present in 57.7% of isolates, *blaSHV* in 6.8%, but none of the strains showed the presence of *blaCTX- M*. Both *blaTEM* and *blaSHV* was present in 3 isolates. These data point to the value of determining the presence of *blaTEM* with regards to antibotic resistance.

Dual-discipline

Histologists are interested in the presence of disease in tissues, immunologists in molecules recognised by certain lymphocytes, such as major histocompatibility complex class I-related chain A (MICA, a soluble form of which, sMICA, can be found in serum). Zhao and colleagues [41] tested the hypothesis of a link between sMICA and clinicopathological features from 196 histologically proven gastric cancer cases and 120 controls, and in determining prognosis after a minimum of 5 years follow up. Gastric cancer patients had significantly higher sMICA levels (mean (SD) 255 (69) versus 17 (4): $P < 0.001$). A sMICA level cutoff value of 92 ng/mL provided the best discrimination between cases and controls with a ROC/AUC of 0.83 (95% CI 0.75–0.89: $P < 0.001$). Patients with a high serum sMICA > 92 ng/ml showed a significantly worse prognosis than patients with a low serum sMICA ($P = 0.008$), giving a hazard ratio of 1.87 (95% CI 0.93–4.84) $P = 0.028$). The authors conclude that sMICA is a promising marker for the presence, clinical severity and survival outcome in gastric cancer, possibly the first lab test to offer these clinical features. Liu et al. [42] also measured sMICA, but in a cohort of 136 cases of prostate cancer. The principle finding was that sMICA was linked to clinical stage of the cancer. Univariate analysis of all patients demonstrated that extent of disease on bone scanning ($P = 0.003$), sMICA ($P = 0.001$) and prostate specific antigen ($P = 0.004$) were all linked with a significantly lower survival rate. However, in multivariate analysis, only extent of disease ($P = 0.0025$) and sMICA ($P = 0.027$) were significant, further emphasing the value of this novel serum marker. A third report of sMICA was made by Xing et al. [43] in 106 cases of non-small cell lung cancer, 76 with nonmalignant disorders and 76 healthy controls. sMICA was significantly higher in lung cancer patients [median 359 (IQR 29–3676) pg/ml] compared with non-cancer controls [36 (9–105) pg/ml] ($P < 0.001$). sMICA was also raised in lymph node metastases and a higher disease stage, and predicted those with a shortened survival (p = 0.028). These three preliminary reports, in different malignancies, suggest sMICA may have role as a routine marker of certain malignancies.

We have already noted that Abbas et al. [15] looked at SNPs in *TLR4* in diabetes. As the receptor itself is found on macrophages and dendritic cells, and recognises bacterial, viral and fungal structure, both virologists and immunologists will have an interest. El-Bendary et al. [44] hypothesised that SNPs in *TLR3, TLR7* and *TLR8* (which all recognise viruses) influence susceptibility to hepatitis C virus infections in 1800 subjects chronically infected, 108 who have spontaneously cleared their infection, and 1460 non-infected family members. In a thorough study of 7 SNPs, they found differences in subjects whose hepatitis C infection persisted and those whose infection had been resolved, presumably by the body's own immune system. It follows that (unsurprisingly), variations in *TLR*s influence immune responses.

Henoch–Schönlein purpura (HSP) is an inflammatory small-vessel vasculitis, the leading pathophysiology being IgA and complement component 3 leading to nephritis (hence HSPN). In a case-control study of 105 HSP patients, 120 HSPN patients and 192 healthy controls, Zhu et al. [45] tested the hypothesis of a link between the red cell distribution width (RDW) and HSP and HSPN. The RDW values were significantly higher in the HSPN group than the HSP group and controls ($P < 0.001$), and significant correlations were found between RDW and ESR ($P = 0.001$). A combination of the markers in a receiver-operator characteristic (ROC) curve showed 80% sensitivity and 85% specificity in the HSP patients, with 86% sensitivity and 94% specificity in the HSPN patients. A multivariate regression analysis

revealed that RDW (OR 1.69, 95% CI 1.16–2.48, $P = 0.007$) was an independent predictor of HSPN, pointing to a value in diagnosis and management of this disease.

Two papers in ovarian cancer crossed discipline boundaries. CA125 has poor sensitivity and low specificity for detecting early ovarian cancer, and serum ferritin is elevated in many malignancies. Zhao et al. [46] evaluated the performance of ferritin alone and in combination with CA125 as a diagnostic tool in 124 cases of epithelial ovarian cancer compared with 50 women with other gynaecological problems and 50 healthy women. Serum ferritin and CA125 were higher in ovarian cancer compared to both control groups (both $P < 0.001$), and two lab markers failed to correlate significantly. Both ferritin and CA125 discriminated ovarian cancer from healthy controls, but ferritin showed better diagnostic accuracy than CA125 ($P = 0.048$). Ferritin was superior to CA125 in discrimination early cancer ($P = 0.002$), but in advanced stages, CA125 was superior ($P = 0.026$). As combination of ferritin and CA125 marginally increases the diagnostic accuracy to discriminate ovarian cancer, the authors conclude that serum ferritin could serve as a biomarker to complement the standard CA125 test.

As the metastasis-related S100 calcium binding protein A4 (S100A4) could be released from tumour cells, Lv et al. [47] investigated its clinical significance in 160 women with ovarian cancer, 52 patients with benign ovarian neoplasms and 52 age-matched healthy women. Serum S100A4 was significantly higher in the cancer patients than in both control groups ($P < 0.01$) and correlated with disease stage ($P = 0.001$), lymph node metastasis ($P < 0.001$), ascites volume ($P = 0.018$), recurrence ($p = 0.037$) and chemotherapy response ($P = 0.046$). High serum S100A4 brought significantly shorter disease-free survival and overall survival time ($P < 0.05$). In a multivariate analysis along with clinical prognostic parameters, serum S100A4 was an independent adverse prognostic variable for disease-free survival and overall survival, suggesting it may be a clinically useful indicator for diagnostic and prognostic evaluation in ovarian cancer.

Cancer was also the subject of the paper from Attallah et al. [48]. Although established markers such as CEA and CA19-9 are important for diagnosing early stages of colon cancer, they are not ideal. Developing promising markers include cytokeratin 1 (CK1) and mucin-1 (MUC1), but the combined value of each of these markers is unclear. Our colleagues evaluated a combined laboratory-based score of these four markers in the diagnosis of colon cancer in 200 patients who had undergone colonoscopic examination and standard histology of biopsy and excised tissue (150 colon cancer, 50 benign growths) and 35 healthy subjects. Serum levels of all markers were increased in the order colon cancer > benign disease > healthy controls ($P < 0.001$). In multivariate analysis, CA19.9 ($P = 0.025$), CK1 ($P < 0.001$) and MUC1 ($P = 0.009$) were significant independent predictors of cancer. Together, these gave a score that provided superior discrimination, sensitivity and specificity for colon cancer versus benign growth, and for tumour stage, lymph node invasion and distant organ metastases than each individual marker. They conclude that their colon score derived from serum CEA, CA19-9, CK1 and MUC1 is a potentially valuable non-invasive index that could be used for detection and screening early stage colon cancer patients.

Two papers employed both haematology and clinical chemistry tests. The first-line treatment option for intermediate stage hepatocellular carcinoma is transarterial chemoembolization (TACE). Certain blood indices, such as routine LFTs, alpha-feto protein (AFP) and full blood count are prognostic biomarkers in certain diseases. Elalfy et al. [49] hypothesised roles for certain blood indices, and the clinical model for end-stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores of disease severity, as prognostic predictors for early recurrence of hepatocellular carcinoma after TACE in a cohort of 147 patients. Sensitivity and specificity of the indices for hepatocellular carcinoma recurrence 36 months after TACE were estimated by ROC curve. In multivariate regression analysis, only male sex, AFP, the lymphocyte count, the monocyte/granulocyte to lymphocyte ratio (MGLR) and the MELD score significantly ($P \leq 0.01$) predicted recurrence, but only the MGLR and MELD score AUCs were sufficiently robust. The authors conclude that high MGLR and MELD scores are linked to hepatocellular carcinoma after TACE, and could be used as novel, simple, non-invasive prognostic tests.

Noninvasive liver fibrosis evaluation is an important issue in chronic hepatitis B infection and may be assessed using transient elastography (Fibroscan) or with blood markers, such as the FIB-4 score (a composite of age, AST/platelet ratio and ALT). Lee et al. [50] compared the value of Fibroscan with that of a panel of routine serum markers in 278 chronic hepatitis B patients who underwent Fibroscan and HBV DNA testing. Fibroscan assessments were made, and blood taken for the gamma-glutamyl transferase (GGT) to platelet ratio (GPR), platelet count, AST, ALT, international normalised ratio (INR), total cholesterol, trigylcerides, bilirubin, mean platelet volume (MPV), AST to platelet ratio index (APRI) and neutrophil to lymphocyte ratio. Numerous markers were higher, and platelet and cholesterol were lower in severe liver fibrosis than in mild liver fibrosis. Elevated GPR (OR 95% CI 9.1 [1.66–50.0] $P = 0.011$) and FIB-4 (2.3 [1.2–4.2], $P = 0.01$) were linked to greater risk of liver fibrosis. The AUCs were 0.84 for GPR at a cut-off of 0.299 and 0.82 for FIB-4 at cut-off 1.57. They conclude that FIB-4 and GPR may be useful blood markers for evaluating the severity of liver fibrosis in chronic hepatitis B patients.

Hypercoagulability is a leading factor in diabetes and cardiovascular disease, and retinal vessel responses to flickering light are an important tool for assessing ocular function. Heitmar et al. [51] merged these two areas, hypothesising a significant relationship between systemic markers of haemostasis and retinal vessel function. Intra-ocular pressure and retinal microcirculation function were measured in 116 patients with diabetes and/or cardiovascular disease using arterial and venous retinal vessel responses to flickering light. Haemostasis was evaluated by platelet microparticles, soluble P selectin, and five functional markers of fibrin clot formation and lysis, hyperglycaemia by HbA1c. They found that intra-ocular pressure was linked to the rates of clot formation ($P = 0.006$) and clot dissolution ($P = 0.013$) whilst other abnormalities were linked to HbA1c ($P = 0.017$), but no measures of platelet activity were linked to ocular and retinal blood vessel indices. These associations may have pathophysiological significance.

Condyloma acuminatum (CA) is a common, viral, sexually transmitted disease worldwide, and is linked to human papillomavirus (HPV, as is cervical cancer). Zhong et al. [52] developed a loop-mediated isothermal amplification (LAMP) method to detect HPV in 294 cervical smears, of which 152 were positive for one of the HPV genotypes (defined by PCR using specific primers), whilst 142 were HPV-negative, and compared it with the Luminex method. Tissues from 40 patients with a pathological diagnosis of CA were paraffin-embedded and analysed by LAMP and Luminex. The kappa value between the two methods varied between 0.68 and 0.98 for different HPV genotypes. Of the 142 HPV-negative samples determined by the Luminex assay, HPV-6 was detected in eight and HPV-11 in one by LAMP. Amongst the 40 CA samples, the results of LAMP and Luminex were in agreement in 38 (95%). These data indicate that the LAMP assay is superior to the Luminex method in terms of sensitivity and specificity, and is therefore a useful, quick and accurate method for the clinical diagnosis of HPV subtypes.

Clarithromycin and metronidazole resistance of *H. pylori* is increasing worldwide and has resulted in a loss in the effectiveness of therapeutic regimens, such as for gastric cancer. Pourakbari et al. [53] combine microbiology and histopathology by evaluating common mutations of resistance genes to clarithromycin (A2143G, A2142G and A2142C) and metronidazole (*rdxA* and *frxA*) in *H. pylori* strains in 110 formalin-fixed, paraffin-embedded gastric biopsies. After DNA extraction, *UreC* (for urease C) PCR was performed for analysis of A2143G and A2142G mutations. One hundred cases of *H. pylori* (91%) were detected by PCR, and of these, 34 were clarithromycin-resistant. Of these, 17, 10 and 7 had *A2143G*, A2142G, A2142C, respectively. Resistance rate to metronidazole was 60%. In sequencing *rdxA* and *frxA* in the mutated strains, missense mutations were most frequent (60 and 57%, respectively), and there were differences in frameshift and nonsense mutations ($P < 0.001$). Resistance rate to clarithromycin was high and the highest percentage of mutation was of A2143G. The paper is of interest as PCR-RFLP was used directly with formalin-fixed gastric biopsies, thus avoiding the requirement for time-consuming culture-based methods. The isolates that developed resistance were mainly associated with mutations of both *rdxA* and *frxA* genes.

Multi-disciplinary

Spontaneous bacterial peritonitis (SBP) is diagnosed by ≥ 250 polymorphonuclear neutrophils (PMN)/mm^3 in the ascites and the absence of surgically treatable cause of intra-abdominal infection. Blood neutrophil lymphocytic ratio (NLR) is an inexpensive and simple test for inflammation, whilst C-reactive protein (CRP) is an inflammatory marker used for the diagnosis and follow-up of many diseases and morbidities. Mousa et al. [54] evaluated the clinical utility of combined blood NLR and CRP as a non-invasive test in 180 cirrhotic patients with ascites (126 with and 54 without blood-culture proven SBP). Both NLR and CRP values were significantly higher in SBP ($P < 0.001$). For SBP diagnosis, a blood NLR of > 2.89 had a sensitivity 80.3% and specificity 88.9%. CRP > 11.3 mg/dL had a sensitivity 88.9% and specificity 92.6%. In logistic regression analysis, combined blood NLR and CRP had a sensitivity 95.1% and specificity 96.3% at the same cutoff values. Combined NLR and CRP could be used as a novel, simple, low-cost, non-invasive test for SBP diagnosis.

A SNP in the interleukin 28B (IL28B) gene may alter the trajectory of hepatitis C virus (HCV) chronic infection. Several studies have sought to determine a link between *IL28B rs12979860* SNP and the development of HCV-related hepatocellular carcinoma (HCC), but with variable results, and consensus is awaited. Attallah et al. [55] hypothesised that *IL28B rs12979860* is linked to hepatocellular carcinoma (HCC) in HCV type 4 infection in 300 patients with HCV-related fibrosis (n = 100), cirrhosis (n = 100) and HCC (n = 100). In *rs12979860* TT genotype carriers, the proportions of moderate/severe fibrosis, advanced cirrhosis and HCC (50%, 84% and 60.2%, respectively) were higher ($P < 0.05$) than in CC/CT carriers (4.3%, 46% and 23%, respectively). The SNP was linked significantly ($P < 0.05$) with cirrhosis progression and HCC advanced stages, whilst the percentage of large tumours increased in TT carriers (81.8% *vs* 52.6% in CC/CT, $P = 0.028$). Thus, as the IL-28B *rs12979860* TT is more prevalent in advanced fibrosis, cirrhosis and

HCC stages, and is linked with poor outcomes (such as HCC), it may become part of the routine work-up of HCV-infected patients.

The relationship between hepatitis B virus (HBV) infection, leptin and insulin resistance remains unclear. Mousa et al. [56] hypothesised links between serum leptin and insulin resistance in non-diabetic patients with chronic viral hepatitis B infection and their relation to liver fibrosis in 190 untreated patients with chronic HBV infection and 72 healthy controls. Serum leptin, fasting glucose, insulin, liver function tests (LFTs), C-peptide and homeostasis model assessment-IR (HOMA-IR) were measured/calculated by standard techniques: leptin, C-peptide (both $P < 0.001$), HOMA-IR ($P = 0.021$) and several LFTs were increased in patients with chronic HBV-infection. In multivariate regression analysis, both HOMA-IR ($P = 0.003$) and leptin ($P = 0.002$) were significant independent predictors of HBV infection. There were significant positive correlations ($P < 0.01$) between leptin and HOMA-IR ($r = 0.81$), between serum leptin and METAVIR activity ($r = 0.95$), and between HOMA-IR and BMI ($r = 0.75$), fasting glucose ($r = 0.005$), and fasting insulin ($r = 0.81$). Several LFTs, glucose and insulin correlated modestly ($r = 0.61$ to 0.69, $P < 0.05$) with leptin, and leptin may be related to the rate of fibrosis progression in nondiabetic patients with chronic HBV infection. The authors conclude that follow-up by serial measurement of serum leptin and HOMA-IR in non-diabetic HBV-infected patients may be used as a non-invasive marker of early liver fibrosis.

Summary

Table 1 summaries certain aspects of the papers published in 2018. The organs most reported on were the liver (n = 8), kidney, bowel, stomach, ovary (all n = 3), breast, lung and prostate (all n = 2). The most commonly

Table 1. Summary of 2018 papers.

Ref.	Science	Organ	Type of disease	Pathogens
[5]	miR-152, miR-24	Uterus	Sarcoma	DNA mutation
[33]	Anti-microbial effect of nanoparticles	Not applicable	Infections	*E. coli, B. subtilus, F. solani, C. albicans, A. niger*
[9]	AFP, PDGF, collagen IV, TIMP-1, and others	Liver	Fibrosis	Hepatitis C virus
[34]	CLSI, EUCAST, Stokes anti-microbial profiles	Not applicable	Infections	*E. coli*
[45]	ESR, red cell distribution width, immunoglobulins	Kidney	Auto-immune	Autoantigen
[21]	*SEPP1* and *SEP 15*	Breast	Carcinoma	DNA mutation
[35]	Genes linked to *E. coli* virulence	Kidney	Infections	DNA mutation
[31]	miR-146b	Thyroid	Papillary cancer	DNA mutation
[18]	*P53* and miR-34b/c	Colon	Autoimmune	Autoantigen
[43]	sMICA	Lung	Carcinoma	DNA mutation
[38]	*H. pylori* genes	Stomach	Infection	*H. pylori*
[46]	CA125, ferritin	Ovary	Cancer	DNA mutation
[54]	Neutrophil/lymphocyte ratio, CRP, LFTs	Liver	Infection	Various microbes
[22]	miR-27a, miR-196a, miR-146a	Breast	Cancer	DNA mutation
[13]	miR-126, miR-210	Heart	Atherosclerosis, diabetes	Thrombosis, hyperglycaemia
[47]	S100A4 (metastatin)	Ovary	Cancer	DNA mutation
[23]	*p21*	Brain	Meningioma	DNA mutation
[36]	16S-23s RNA region	Not applicable	Infection	*S. pneumoniae*
[42]	sMICA, PSA	Prostate	Cancer	DNA mutation
[37]	Bacterial identification	Not applicable	Infection	*P. aeruginosa, B. cenocepacia*
[39]	Genes in *H. pylori* and parasites	Bowel	Infection	DNA mutation
[52]	Genes in HPV	Anus and genitals	Infection	DNA mutation
[51]	Haemostasis	The eye	Atherosclerosis, diabetes	Thrombosis, Hyperglycaemia
[48]	CEA, CA19-9, cytokeratin-1, mucin-1	Colon	Cancer	DNA mutation
[50]	LFTs, platelets	Liver	Fibrosis	Hepatitis B virus
[21]	Detection of foetal DNA	Not applicable	Chromosome trisomy	DNA mutation
[14]	SNPs in *KCNJ11* and *SDF-1β*	Not applicable	Diabetes	DNA mutation
[16]	Serum relaxin-2, PSA	Prostate	Cancer	DNA mutation
[17]	Serum prolidase and SNP in *prolidase*	Ovary	Polycystia	Endocrine
[55]	SNP in *IL28B*	Liver	Infection	Hepatitis C virus
[15]	SNPs in *TLR4*	Kidney, Arteries	Diabetes	DNA mutation
[25]	SNPs in *GST*	Cervix	Cancer	DNA mutation
[44]	SNPs in *TLR3, TLR7, TLR8*	Liver	Infection	Hepatitis C virus
[28]	Pri-miR-124–1 and STAT3	Stomach	Cancer	DNA mutation
[49]	Monocyte/granulocyte to lymphocyte ratio	Liver	Cancer	DNA mutation
[56]	Leptin, HOMA	Liver	Fibrosis	Hepatitis B infection
[10]	LFTs, lipids, uric acid	Liver in pregnancy	Gestational diabetes, pre-eclampsia	Fat
[40]	Genes encoding β-lactamases	Not applicable	Infection	*A. baumannii*
[41]	sMICA	Stomach	Cancer	DNA mutation
[19]	Anti-neutrophil cytoplasmic antibodies	Lung	Infection	*P. aeruginosa*

described disease processes were cancer (n = 15), infections (n = 13) and atherosclerosis and its risk factors (n = 5). The leading causes of these diseases were DNA mutations (n = 21), bacteria (n = 8 and viruses (n = 6). In common with previous annual summaries, this commentary is the object of a journal-based learning event for continuing professional development.

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A Blann
Institute of Biomedical Science, London, UK.
andrewblann@ibms.org