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British Journal of Biomedical Science in 2016. What have we learned?

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ABSTRACT

In 2016, the British Journal of Biomedical Science published 36 reports outlining specific advances in each of the various disciplines within biomedical science. These were one review, 25 original articles, 9 'In Brief' reports and one letter to the Editor. Of these, the majority were in blood science (5 in biochemistry, 7 in haematology and 2 in immunology) and infection science (8 in microbiology, 2 in virology) with a smaller number in cellular sciences (6 in cellular pathology and 2 in cytopathology). Three reports considered both biochemistry and immunology, while another reported an advance in the identification of chromosomal abnormalities. The present report will summarise key aspects of these publications that are of greatest relevance to laboratory scientists.

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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 National Health Service (NHS) hospitals but can also embrace developing methods, cell and molecules, such as in tissue culture, pharmacology and molecular genetics. Allied disciplines include epidemiology, reproductive sciences and genetics and molecular sciences; the latter being relevant to all eight traditional subjects. In issue 1 of 2016, the Journal published an article summarising work published during 2015 [1]. The present communication aims to continue this process with a summary of those papers published during 2016 which, in the opinion of the Editor, report the most practical advances in biomedical science, classified by major discipline.

Haematology

The Journal published eight articles of interest primarily to haematologists, the first being a review of methods for determining platelet function [2]. Gurney's comprehensive and authoritative synopsis of the many techniques for assessing this crucial participant in haemostasis is essential reading for all haematologists, especially those preparing for examinations. As acute allergic reactions (such as urticaria and anaphylaxis) can, in the extreme, be fatal, and call for admission to an acute medical bed, then the ability to detect those most in need of urgent care is highly sought-after. In this respect, Lippi et al. [3] showed that a combination of low haemoglobin and the increased red cell distribution width were independent predictors of which of those 120 presenting patients were one of the twelve who required hospital admission. Issue 3 was of particular interest to this discipline. Genetic analysis is an important part the work-up for a precise diagnosis of leukaemia. Although fluorescence *in situ* hybridisation is a rapid and sensitive technique for analysing genetic abnormalities, it cannot provide details of structural rearrangements. Karyotyping is necessary to determine the presence of changes such as translocations and inversions, and calls for leukaemic cells to be cultured with chemicals that induce the mitosis so that the finer details of chromosomes can be determined. Lin et al. [4] reported that a combination of a synthetic oligoribonucleotide and interleukin-2 is effective in improving the detection rate of chromosomal abnormalities in chronic lymphocytic leukaemia cells. With the ability to define deletions, inversions and trisomies, this finding could lead to changes in practice.

One of the more interesting and possibly important entrants into laboratory science in the last few years is microRNAs (miRNAs). We shall hear more of these short (18–25 nucleotides) non-coding ribonucleic acids that control gene expression after transcription [5,6] in this article and in the Journal in 2017. Fooladinezhad et al. [7] showed that miR-330-5p has a strong inhibitory effect on the expression of a specific surface marker for leukaemic

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stem cells *in vitro*, contributing to debate on the possible use of these molecules in therapy. The non-vitamin K antagonist oral anticoagulants (NOACs) are slowly but surely replacing warfarin and heparin as choice of anticoagulant in a number of defined situations, such as atrial fibrillation and orthopaedic surgery [8]. One advantage of these new therapeutics is that routine measurement is not required, but monitoring may be important in emergency settings, such as if overdosage is suspected. Zhang et al. [9] reported their validation of a method, using FXa activity, for detecting the effect of the NOAC rivaroxaban, suggesting that it could be used to evaluate risk of bleeding. The neutrophil-to-lymphocyte ratio (NLR: approximately 1.5 in health, greater in inflammatory disease) and platelet-to-lymphocyte ratio (PLR: approximately 100 in health, also higher in inflammatory disease) are indices easily and cheaply obtained from a full blood count and may be useful in a number of clinical situations [10,11]. Lee et al. [12] measured these ratios in patients presenting to hospital with pneumonia, finding that the NLR, but not the PLR or inflammation marker CRP was the preferred index for predicted those sufficiently ill to warrant entering an intensive care unit. The ease with which these ratios can be determined is a powerful factor in their adoption as routine clinical markers. Chukwuankwu et al. [13] tested the hypothesis that coinfection with malaria and HIV brings a greater weight of haematological pathology than either infection alone. Unsurprisingly, there were significant differences between the groups: those who were coinfected had the most adverse haematocrit, APTT, PT and platelet count, the latter three pointing to an increased risk of haemorrhage. This may lead to a change in clinical practice.

Clinical chemistry

Few of us would consider there to be a strong physiological or pathological link between the prostate and the thyroid/parathyroid. The precise cellular basis of benign prostatic hyperplasia (BPH) is unclear, but endocrine processes are not believed to be implicated. It was therefore interesting to learn from Eldhose et al. [14] that men with BPH have higher T3 and T4, and lower TSH, than healthy men. Unsurprisingly, prostate-specific antigen correlated strongly with the size of the prostate ($r = 0.53$, $p < 0.001$), but TSH and T3 levels correlated inversely (r = -0.43, 0.005)/positively (r = 0.34, p = 0.031, respectively) with prostate size. It is tempting to suggest, from this data, that the thyroid influences prostate size, were it not for the well-known fact that correlation does not always imply causation. The Journal has a long history of publishing research into vitamin D [15–18], and this continues with the report from Parra et al. [19], who compared the performance of two different methods for measuring serum levels of this micronutrient. Although there was good overall concordance, one method found levels to be 6.5% higher than the other. This has implication for reference ranges and underlines the issue that (ideally) each laboratory should provide its own reference range for the method it uses.

Despite its high prevalence, the pathophysiology of osteoporosis remains largely unknown, and the laboratory has little to offer in diagnosis or management. This may change should the work of Chen et al. [20] be confirmed and extended. The chemokine CXCL1 (also known as fractalkine) seems likely to have a role in osteoclast biology [21], the contribution of Chen and colleagues being that they report increased serum levels of this marker in post-menopausal women with osteoporosis compared to age-matched women free of osteoporosis. They also reported significant correlations between this molecule and bone density (e.g. $r = -0.39$, $p = 0.004$) and a disability score (e.g. $r = 0.38$, $p = 0.005$), thus linking the laboratory with physiological status and a clinical index, although sensitivity and specificity data are needed from a large cohort of patients to help determine clinical value. Due to the variety and non-specific nature of presenting signs and symptoms, the diagnosis of multiple sclerosis (MS) is hampered by lack of specific markers. Hassan and colleagues [22] used a proteomic approach with two-dimensional electrophoresis and MALDI-TOF/TOF mass spectroscopy to probe cerebro-spinal fluid from MS patients and controls. Four proteins (alpha-1-antichymotrypsin, prostaglandin-H2 D-isomerase, desmoplankin and hornerin) where present in significantly higher levels in the MS patients, suggesting these may be used as potential CSF markers of this disease.

Zhang et al. [23] showed that serum copper levels in children aged 0–14 years varying according to the season (by up to 8% higher in the Spring), a finding that may have implications for reference ranges. Chronic kidney disease (CKD) is a growing problem and brings an increased risk of cardiovascular disease [24]. The best renal function tests are undoubtedly urea and creatinine, the latter generating an estimated glomerular filtration rate (eGFR). Moolchandani and colleagues [25] studied 188 patients, and with very strong correlation ($r = 0.92$, $p < 0.001$) between the eGFR and total bilirubin to suggest that the latter may be an alternative test of renal function, should the gold standards be unavailable.

Immunology

The healthy response to a microbe includes proliferation of protective circulating leukocytes. Mahmoudi et al. [26] studied the response of peripheral blood mononuclear cells to co-culture with extracts of *Streptomyces calvus*. Unsurprisingly, cell proliferation was marked, but in addition, our colleagues noted an increased expression of genes coding for pro-inflammatory IL-2 and IFN-γ, and a reduction in the expression of the gene for the immunosuppressive cytokine IL-10. The authors conclude that

one of more of these extracts could have immunomodulator properties, perhaps in stimulating the immune response in immunodeficiency. Psoriasis is a relatively common autoimune disease characterised by leukocyte infiltration into the skin. In a well-powered study of 189 cases and an equal number of controls, Priyadarssinia et al. [27] provide data in support of the hypothesis that changes in certain T lymphocyte subsets (Th1/Th17) have a role in the pathogenesis of this disease, as indicated by a link with disease severity (e.g. $r < 0.75$, $p < 0.001$). If widely confirmed elsewhere, the assessment of these lymphocyte populations by fluoresence flow cytometry could enter routine practice.

Immunology and clinical chemistry

These disciplines come together in a number of reports. The active metabolite of vitamin D, calcitriol, is generally measured by biochemists, while cytokines, such as IL-1 and TGF-β, are most often the preserve of immunologists. Gonzalez et al. [28] married these two, showing that the micronutrient decreased the expression of certain inflammatory cytokine genes in endothelial cells *in vitro*. This finding adds to the debate as to the purpose of the vitamin D receptor on endothelial cells [29], suggesting that the micronutrient help maintain vascular health [30]. The clinical chemistry laboratory monitors the pathological response of the myocardium to a heart attack by measuring the MB isoform of creatine kinase (i.e. CK-MB) and a product of a damaged cardiomyocyte:troponin-T. Liu et al. [31] measured not the gene expression of TGF-β (as above), but the molecule itself in over 100 patients who suffered an acute myocardial infarction (AMI) and 100 healthy controls. Although the mean level of TGF-β was 7.3 times higher in the AMI group, levels of troponin-T were 10.3 times higher. However, troponin-T was no different in the AMI patients with an S-T elevation MI (STEMI) compared to those with a non-S-T elevation MI (NSTEMI), whilst TGF-β was significantly higher (by 21%, $p = 0.019$) in those who suffered a STEMI. Furthermore, levels of TGF-β peaked far earlier (3–6 h) than did troponin-T (12–24 h). The authors conclude that TGF-β could be a novel marker of AMI in general and STEMI in specific and so could conceivably enter routine practice, especially in accident and emergency. The cardiology theme was continued with the work of Santas-Alvarez et al. [32], who examined the dynamics of endothelial progenitor cell (EPC) levels in patients undergoing stent placement within a coronary artery. Levels of these cells (as defined by fluorescence flow cytometry and surface markers CD45, CD34, KDR and CD133), whose function is to replace effete and dead endothelial cells in the coronary circulation, correlated with the extent of the disease in the affected arteries. Levels of EPCs were unrelated to biochemistry markers of inflammation (CRP), renal function (cystatin C, GFR), hyperglycaemia (glucose, HbA1c, advanced glycation end products) or myocardial damage (CK, CK-MB, troponin).

Microbiology

Helicobacter pylori continues to be the subject of considerable research in this Journal and elsewhere [33–36]. The contribution of Mamishi et al. [37] was to demonstrate that mother-to-child transmission of the organism is the main route of intrafamilial infection and that molecular genetic fingerprinting can be used confirm it is present. Mamishi et al. [37] also used molecular genetics (a multiplex PCR), but to determine the presence of this organism in gastric biopsies from 230 patients. The PCR found *H. pylori* in 138 patients, far more than standard microbiological culture ($n = 22$), a rapid urease test ($n = 39$) and histology ($n = 29$). It follows that the latter three methods carry a high burden of false-negative results, leading to many possible mis-diagnoses, a finding that may also lead to a change in practice.

Antibiotic resistance continues to be a major international problem in clinical microbiology, as reflected by the high frequency of scientific research into this topic [38–45]. Although group B *Streptococcus* species are widely believed to be sensitive to penicillin, a screening method for the possibility of reduced sensitivity (i.e., resistance) has been developed [46]. Cooper and colleagues [47] examined 200 isolates and failed to find any that were susceptible, leading to the conclusion that a more robust screening method is necessary. *Candida albicans* is one of the leading mycotic pathogens and causes a common mucosal infection, with the greatest prevalence in women aged 20–30. The development of resistance to a common antifungal, fluconazole, has led to investigation into the role of certain genes, such *ERG11* [48]. Khajeh et al. [49] reported that a plant extract reduces the mRNA expression of two genes, CDR1 and CDR2, overexpression of which are reputed to promote resistance. This promising result lends support to the view that plant products represent a new opportunity to counter antibiotic resistance [50]. Last year, Pitt et al. [51] presented data that an extract of mucus from a snail has antimicrobial activity, a finding confirmed and extended by Bortolotti et al. [52] in three common bacteria and *Candida albicans*. They also provided safety data in that their mucus extract had no critical effect on a transformed human T lymphocyte cell line *in vitro*.

Not all strains of common bacteria have the same degree of virulence – some are markedly more toxic than others. This can be demonstrated by their effects on various cell types *in vitro*. Champion et al. [53], building on their previous work [54], presented a model for assessing the virulence of *Pseudomonas aeruginosa* via its effect on the amoeba *Dictyostelium*, finding that bacteria isolated from patients with cystic fibrosis (CF) are significantly less cytotoxic than bacteria from other sources, such as

Table 1. Data on accuracy and reproducibility.

Tissue type	Number of specimen	Precision (%)	Accuracy (%)	Tissue type	Number of specimen	Precision (%)	Accuracy (%)
Skin	30	95	100	Spleen	2	85	75
Gall bladder	3	70	75	Liver	4	90	95
Lipoma	7	60	60	Decalcified bone	2	80	80
Uterus	25	100	80	Stomach	9	85	90
Kidney	13	80	90	Small bowel	2	70	75
Lung	5	60	60	Colon	27	95	90
Breast	32	70	75	Rectum	28	85	90
Cervix	17	95	98	Appendix	1	85	85
Sailvary gland	6	85	90	Fallopian tube	8	90	90
Ovary	9	67	65	Local excision	15	80	90
Lymph node	12	75	75	Sentinel lymph nodes	8	75	70
Prostate	2	85	85				

Source: Ref. [67].

from urine and the hospital environment. Atkinson and Tristram [55] also focussed on CF, but upon infections with *Haemophilus influenzae*. One of the drivers of their study was a report of an increased frequency of antibiotic resistance by this organism in CF patients [56]. However, Atkinson and Tristram failed to find evidence of resistance compared to non-CF isolates, a result that could be explained by changes in practice (the original report being some 13 years old) and clinical differences in how samples were obtained. This underlines the need for advice on antibiotic resistance to be evidence based, applicable to region and contemporary.

Nakajima, Moore and colleagues have long been at the forefront into the use of molecular genetics in microbiology research [57], especially in the study of *Campylobacter* species [58–60]. In issue 2, they reported, using complex and powerful techniques, the presence of genes coding for catalase and catalase like proteins that, according to the authors, may provide the organism with a method for protecting itself from toxic oxygen stress [61].

Virology

Of course, prevention is better than cure, but it can go wrong. Mamishi et al. [62] used PCR to detect mumps viral RNA in the CSF of children presenting with aseptic meningitis within six weeks of a measles–mumps–rubella vaccination. Over the 7 years from 2006–2012, an average of 13,618 children were admitted to hospital each year, of whom an average of 18 were subsequently diagnosed with aseptic meningitis (a frequency of 13 per 10,000). Of these, the mumps viral sequence was found in 49 (39%), giving a mean annual incidence of mumps-viral vaccine-associated aseptic meningitis of some 5/10,000. The authors acknowledge the weakness that they have no comparative data on children not vaccinated, but nonetheless contend that the vaccine is a causative agent for aseptic meningitis. Although real-time PCR for the presence of influenza is the gold standard, it (as yet) cannot be used easily in the field. Ryu et al. [63] compared rapid diagnostic tests for influenza (Sofia, Veritor and Bioline) in 314 symptomatic subjects of whom 192 were proven by PCR to carry the virus. All the methods showed 100% specificity, but the Sofia (77.8%) and Veritor (73.4%) produced consistently better mean sensitivities than the Bioline method (61%).

Cell pathology

Lung cancer is the most common cause of cancer-related death worldwide, while in the United Kingdom, combined cancer of the trachea, bronchus and lung was linked to most (21.1%) cases of malignant cancer deaths [64]. Diagnosis and staging may be supported by computed tomography (CT) of the chest (e.g. for detecting nodules and the size of presumed tumours) and by the presence of the Ki-67 proliferation index of excised tissue defined by standard histopathological methods. Chen et al. [65] used both methods in a study of 116 patients with lung adenocarcinoma, finding that adding CT data to the Ki-67 index provided higher specificity for predicting the differentiation and lymph node metastatic state of this cancer.

Last year, Orchard and colleagues [66] presented limited data on a new and accurate method for use in histological dissection. They followed up this initial work with a multicentre study [67] of the TruSlice and TruSlice Digital devices where 267 fixed tissues samples from 23 types of tissue were examined (Table 1). Overall, the mean score for precision was 81%, while the accuracy score was 82%, although this varied with type of tissue. Accuracy and precision were strongly correlated ($r_p = 0.83$, $p < 0.001$). The authors concluded that the TruSlice Digital devices offer an assured precision and accuracy performance which is reproducible across an assortment of tissue types. The use of a micrometre to set tissue slice thickness is innovative and should comply with laboratory accreditation requirements, alleviating concerns of how to tackle issues such as the 'measurement of uncertainty' at the grossing bench.

miRNAs

As mentioned earlier [7], miRNAs are a relatively recent development in laboratory science, as indicated by three papers in issue 4 of the Journal. Sun et al. [68], used a quantitative RT-PCR method to show low levels of miR-124 in 126 patients with pancreatic cancer (mean/SD 0.14/0.05 units) compared to 28 with pancreatitis (0.91/0.08 units) and 47 healthy controls (0.14/0.05 units). They supplemented this by showing that the lowest levels predicted not only the extent of disease but also four-year outcome survival. This powerful data strongly supports the view that miR-124 should become a routine marker in pancreatic cancer. Ren et al. [69] investigated the role of miR-21 in osteosarcoma, comparing expression by TaqMan RT-PCR in 84 pairs of cancerous and non-cancerous tissue. In contrast to the work of Sun et al. [68] in the serum in pancreatic disease, Ren et al. [69] found markedly increased expression in tumour tissues (mean/SD 7.88/1.04 units) compared to normal bone tissue (1.12/0.37 units, $p < 0.001$). The highest levels predicted the most adverse outcome, both overall survival and disease-free survival. Similarly, this powerful data also strongly support the view that miR-21 should become a routine marker in osteosarcoma. In contast to these studies, Yadegari et al. [70] failed to find, against expectation, that a polymorphism in miRNA-146a is linked to gastric cancer. One possible problem with negative results is a fear of a false negative, possibly due to small numbers. However, this particular study has good power, with 120 cases of cancer and 120 controls, leading to the likelihood that the result is genuine.

Cytopathology

Lymph nodes are important in a number of diseases such as lymphoma, in chronic infective diseases (such as tuberculosis) and in cancer. Although it may not always be appropriate to remove a diseased lymph node surgically, contents (and so a diagnosis) can be determined by aspiration followed by microscopy, hence fine-needle aspiration cytology (FNAC). In 2015, Wang et al. [71] reported using this method to detect levels of the mRNA of a transcription factor (Snail) in pancreatic cancer. In issue 1 this year, Zhou et al. [72] reported the result of FNAC examination of 2136 lymph nodes from 1362 patients with lymphadenopathy. The most common findings were metastatic tumours (present in 53.6% (far more prevalent in males [675 from 1178] than in females [470 from 958, chi-squared $p < 0.001$]), chronic non-specific lymphadenitis (15.2%) tuberculous lymphadenitis (8.7%) and reactive lymphadenitis (7.5%). Naturally, this distribution reflects the local population in China and so may not be applicable elsewhere. A problem with FNAC is its hit-and-miss nature: should the needle probe part of the tissue where disease is absent, a false negative is likely. Li et al. [73] reported an improvement in the sensitivity, specificity, accuracy and negative predictive value of combining FNAC with the measurement of thyroglobulin in the washout of the biopsy for the detection of thyroid cancer. With improved false-positive and false-negative rates, this finding could lead to a change in practice.

Chromosome analysis

Few of us are unaware that advances in technology constantly demands we re-assess our methods and work patterns. In this respect, the widespread adoption of molecular genetics has lead to the development of entire sections whose work crosses the traditional disciplines of laboratory science. Where once methods, such as karyotyping, were the preserve of the research laboratory, these are now entering mainstream pathology. The determination of chromosome abnormalities in reproductive science is such as an example. Zhu et al. [74] used standard chromosome analysis in addition to SNP arrays to examine in 80 placental villi and foetal tissues from miscarried or aborted foetuses, finding abnormalities in 42. The most common abnormalties were trisomy, monosomy, translocations, duplications and deletions, while triploidy 69, XXX and tetraploidy 92, XXXY were also found.

Note

This commentary is the object of a journal-based-learning event for continuing professional development.

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