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British Journal of Biomedical Science in 2015: what have we learned?

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ABSTRACT

In 2015, the *British Journal of Biomedical Science* published 47 reports on topics relating to the various disciplines within biomedical science. Of these, the majority were in infection science (15 in microbiology and two in virology) and blood science (seven in biochemistry, four in haematology, three in immunology and one in transplantation), with a smaller number in cellular sciences (four reports) and with one review across disciplines. The present report will summarise key aspects of these publications that are of greatest relevance to laboratory scientists.

KEYWORDS

Bacteriology; biochemistry; biomedical science; cellular pathology; clinical chemistry; cytopathology; haematology; histopathology; immunology; microbiology; transfusion science; virology

Introduction

The *British Journal of Biomedical Science* (BJBS) 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 practise of routine biomedical science in NHS hospitals, but can also embrace developing methods, cell and molecules, such as in tissue culture, pharmacology and molecular genetics. Although biomedical science includes many subdisciplines, for organisational reasons its practice in the UK is moving towards three broad groups: blood science (which includes the traditional subjects of biochemistry/clinical chemistry, haematology, immunology [with histocompatibility and immunogenetics] and transfusion science), cellular science (cytopathology and histopathology/cellular pathology) and infection science (bacteriology/microbiology and virology).[1] Allied disciplines include epidemiology, reproductive sciences and genetics and molecular sciences; the latter being relevant to all eight traditional subjects. The objective of this communication is to collate and summarise those papers published in BJBS in 2015 which, in the opinion of the Editors, report the most practical advances in biomedical science. These will be brought together in the three major stands of blood science, cellular science and infection science.

Blood science

Renal disease may be regarded as a 'cinderella' condition, often overlooked and underappreciated. Muhammad [2] drew our attention to this risk factor for cardiovascular disease,[3] particularly to the viewpoint that measures of renal function may be conducted, where appropriate, in the community in point-of-care testing (POCT). The importance of lipaemia (mostly related to chylomicrons), a possible source of error in many biochemistry methods, is considered by Cobbold and Crook [4]. Perhaps unsurprisingly, the triglyceride concentration correlated well with the index of lipaemia (correlation coefficient [r] = 0.61, probability of error [P] < 0.0001), whereas the correlation with cholesterol was inverse (r = –0.41) and was less strong (P = 0.0018). Sera from men and neonates were more likely to be lipaemic than those from women and adults. This theme of external factors influencing methodology was echoed by the report by Hasanato et al. [5] in their emphasis on an adverse effect of lipaemia, icterus (reflecting increased bilirubin) and haemolysis on the accurate measurement of ferritin, progesterone, thyroid stimulating hormone, vitamin B_{12} (all influenced by haemolysis and lipasemia), folic acid and β-human chorionic gonadotrophin (both influenced by lipaemia and icterus). The theme of laboratory methodology was also addressed by Woolley et al. [6], who compared two analysers measuring carbohydrate-deficient transferrin, and by Meess, who compared two methods for transfusing platelets.[7]

In a small case-control study of psoriasis, Chandra shekar and colleagues [8] brought together vitamin D, oxidative stress (marked by ischaemia-modified albumin, i.e. albumin that has been altered by the reactive oxygen species that are linked to ischaemia) and inflammation (marked by C-reactive protein [CRP]). Vitamin D was lower, but ischaemia-modified albumin and CRP were higher, in the cases compared to the controls.

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Table 1. Proposal to reduce red blood cell wastage.

Proposal	Detail
Reduce the stock of red cells	Reduce general stock by 25%, irradiated stock by 70% although clinical need may be compromised
Reduce the reservation period	Bring this down from 3–5 days to 24 h, although this may lead to more reissues and failure to supply in time
More reclaiming	Especially at weekends, but this requires more staff time However, one red cell pack saved pay for eight hours of biomedical scientist time
A traffic light system on blood stock refridgerator	Takes time to stock check and complete. Possible saving of a unit
Recycle flying squad earlier	Return blood to the laboratory sooner, although this may result in increased wastage of O RhD negative packs
Transfusion of group-compatible blood	Mixed-field reactions lead to increased cross-matching costs, and delay as cannot e-Issue
Montior expiry dates of received blood	Is blood supplied short-date, resulting in less time for use
Staff involvement	Education, display wastage figure, issue of blood not likely to be transfused (for example, close to expiry and issued late at night)

Source: Modified from Ref [16].

The severity of the skin disease correlated very strongly with CRP ($r = 0.89$, $P < 0.0001$) and ischaemia-modified albumin ($r = 0.71$, $P < 0.0001$), but inversely with vitamin D ($r = –0.71$, $P < 0.0001$), and, unsurprisingly, CRP and ischaemia-modified albumin correlated significantly ($r = 0.44$, $P < 0.0001$). Although this small observational study was unable to propose causal mechanisms (such as that low vitamin D is a key metabolic player in the pathogenesis of psoriasis), the authors nonetheless speculated that vitamin D supplementation might reduce systemic inflammation and oxidative stress and so help in delaying the pathogenesis of co-morbidities associated with this disease. The considerable weight of misunderstanding of the value of vitamin D supplements was clarified in November 2014 by the UK's National Institute for Health and Care Excellence guideline.[9] Oxidative stress is also a feature of many other conditions,[10] and its effect may be assessed by a total antioxidant score.[11] Researching into diabetes in women, Okuonghae and colleagues [12] reported a significant inverse relationship between random blood glucose and a total antioxidant score ($r = –0.26$, $P = 0.015$) and between blood glucose and a key antioxidant enzyme, glutathione reductase ($r = –0.40$, $P < 0.001$), but that the relationship between glycated haemoglobin and total antioxidant score was not significant ($r = –0.17$, $P = 0.119$). This report reinforces the importance of the oxidant/antioxidant balance in diabetes and so, by association, in other diseases.

Thyroid pathology is relatively common, said to be present in 1% of the population. A leading contribution of the laboratory in this condition is in determining levels of the two thyroid hormones (T3, T4) and their key regulator, thyroid stimulating hormone (TSH). While knowledge of all three provides the practitioner with a fuller picture of thyroid physiology and (perhaps) pathology, there is debate as to the practical value of taking this approach and whether or not measurement of T3 is in itself valuable.[13] The contribution of Livingston et al. [14] to this debate is to support the position that T3 measurement does not add anything to the interpretation of thyroid hormone levels in subjects with hypothyroidism on levothyroxine replacement therapy. Unnecessary testing could be avoided if this were more widely appreciated. In addition, over-replacement, with its attendant risks, would be more readily recognised and not wrongly excluded on the basis of a falsely reassuring normal T3 result. Creatine kinase (CK) is a key enzyme in the metabolic pathway for deriving energy (in the form of ATP) from substrates such as glucose. Increased levels of this enzyme are found in the blood following damage to muscle cells, perhaps the most important being after myocardial infarction, but there is less emphasis on low levels. Cobbold and colleagues [15] reported a year's audit of this enzyme, finding 329 cases with a low level. Although their laboratory reference range was 26–180 IU/L, they chose a cut-off result of <20 IU/L to be more confident in recording only truly low levels. Their data found that although low-serum CK activity is rare it is usually found in critically ill patients, such as those on intensive care units, that it is more common in females and the elderly, that it is associated with long hospital stay and hospital mortality, and that it is associated with sepsis, organ failure and cancer. Interestingly, one result was from the coronary care unit, where, by definition, there would be heart disease and so high levels would be expected. The most frequent diagnosis of those with a low CK was sepsis (including pneumonia) at 37.9%, followed by renal failure (17% of patients), respiratory failure (10.6%) and carcinoma (7.6%). The authors concluded that understanding the reasons for reduced-serum CK activity may allow this enzyme to be used as a marker to indicate poor prognosis or as a possible warning sign to initiate emergency treatment in certain patient groups.

Red blood cells are a very valuable resource, and every care must be taken to ensure each pack is used correctly. Smith et al. [16] highlighted eight measures of direct value to blood transfusion units by which red cell wastage may be reduced (Table 1). A major problem with stenosis of the mitral valve is that it is a very likely cause of potentially fatal thrombotic stroke, and accordingly hypercoagulability is an important pathophysiology. Murugesan et al. [17] tested the hypothesis that the presence of a clot within the left atrium (the fragmentation of which could run up the carotid artery and so cause a stroke) is associated with platelet

aggregability, fibrinogen, homocysteine, vitamin B_{12} and folate. Our colleagues found that raised fibrinogen, lowered homocysteine-vitamin determinants and lowered mitral valve area were associated independently with presence of a clot within the left atrium, and concluded that an increase in procoagulant mechanisms contributes to increased risk of thrombosis. These data support the use of anticoagulants in this particular disorder.

One of the problems in prolonged surgery is of ischaemia (when the tissues are denied oxygen) and subsequent reperfusion (with restoration of oxygen-rich blood flow). There is evidence that this ischaemia/reperfusion is inflammatory and may be related to organ damage such as renal and pulmonary problems. Sayed et al. [18] tested the hypothesis that different types of anaesthetic (propofol and isoflurane) have an effect on this surgical inflammaory response. Twenty-four hours after surgery, patients randomised to propofol had significantly lower levels of inflammatory markers CRP, interleukin (IL)-6 and IL-8 (all $P < 0.001$) than patients randomised to isoflurane. They interpret their data as that the use of propofol is associated with a less adverse inflammatory profile than is isofluorane. To some extent this study supports the view of many others, such as Farhan and colleagues [19], in that IL-6 may be worthy of being assessed as a routine marker, as is CRP.

Pentraxin-3 is an acute-phase reactant that can be used as a marker to assess the severity in a number of inflammatory and other diseases, such as of the liver.[20] Nandeesha and colleagues [21] assessed pentraxin-3 and tumour necrosis factor-*α* (TNF*α*, a marker of inflammation) in 47 patients with alcoholic cirrhosis and their association with disease severity, compared to 32 controls. Serum pentraxin-3 and TNF*α* were significantly increased in alcoholic cirrhosis patients compared to controls. Pentraxin-3 had a significant positive correlation with TNF*α* ($r = 0.30$, $P = 0.039$), and two different scores of disease activity (Child-Pugh score ($r = 0.394$, $P = 0.006$) and MELD score ($r = 0.291$, $P = 0.047$)). They concluded that elevated pentraxin-3 is associated with severity of alcoholic cirrhosis, adding weight to those papers we have already discussed,[18,19] and which support the proposition that this molecule may (like IL-6) be worthy of being added to a routine profile.

The theme of cytokines was continued by Indhumathi et al. [22], who investigated polymorphisms in *TNFAIP3* and *TNIP1*, two genes involved in the signalling of TNF*α*. Their study of 360 patients with the skin disease psoriasis and 360 controls free of this disease suggested that the single nucleotide polymorphisms rs610604 and rs17728338 of *TNFAIP3* and *TNIP1*, respectively, were associated with psoriasis both at allelic and genotypic levels. They further suggested that these polymorphisms confer increased risk of psoriasis and may play a vital role in its pathogenesis. Moore [23] discussed the use of stem cells in the treatment of amyotrophic lateral sclerosis, a progressive neurodegenerative disease.

Cellular science

A useful tool in the field of Mohs micrographic surgery is immunocytochemistry.[24] Orchard and colleagues have an established expertise in this area,[25] and extended this with an evaluation of staining for pan-cytokeratins in basal cell carcinoma,[26] finding that AE1/AE3 is the most consistent marker. The same group also reported the development of new and accurate measurement devices (TruSlice and TruSlice Digital) for use in histological dissection.[27] As pancreatic cancer is the fifth leading cause of cancer-related death in industrial Western countries, with <5% survival after five years, it is the object of considerable research, such as into the role of nuclear transcription factors, some of which are interestingly named Snail, Twist and Slug [28]. Wang et al. [29] extended our knowledge of Snail by reporting that its mRNA expression in pancreatic cancer cells obtained by fine-needle aspiration is strongly linked to lymph node metastases and so may be useful in predicting outcome Mendes et al. [30] reviewed the biology of lung cancer, focusing on immunological aspects and radiotherapy.

Infection science

The dominant issue in this section is of baceterial and fungal resistance to existing antibiotics, as ably reviewed by Kenny and colleagues [31], who highlighted the view that plant products may be a source of new (ideally effective) agents. In the search for new antibiotics, Moore et al. [32] pointed out that 31% of UK-licensed antibiotics were used exclusively in veterinary medicine, and reviewed the proposition that some of these agents may also be effective in our own species. The same group also reported [33] that *Pseudomonas aeruginosa* displays an altered phenotype *in vitro* when grown in the presence of mannitol, a finding that could have important clinical repercussions for diagnosis and management. This is particularly relevant in those conditions, such as cystic fibrosis, where inhaled mannitol is an effective antimucolytic agent for those with lung complications. There may be other novel sources of new antibiotics. Pitt et al. reported another new potential source of antimicrobial agents, that being the mucus from the snail *Helix aspersa*. [34] Our colleagues showed that substances with a relative molecular mass of 30–100 kDa have a strong effect against several *P. aerogniosa* strains and a weak effect against *Staphylococcus aureus*. The detailed identification of these agents will be eagerly awaited.

Perhaps the prime example of the dangers of antibiotic resistance is that of methicillin-resistant *S. aureus* (MRSA), a problem of over 30 years' duration,[35] and which has been a common topic in this journal.[36,37] Interestingly, methicillin-resistant *Staphylococcus* species are also an issue in veterinary practice.[38] Despite this problem, although MRSA continues to be a global problem, and can be acquired in the community,[39] there are

advances. Aguadero and colleagues provided an update on different methods (pulsed-field gel electrophoresis, the DiversiLab system and *spa* typing) for genotyping this organism.[40] Other biomedical scientists from around the world shared their bacteriological research into other organisms, including group B *Streptococcus* species and *Helicobacter pylori*.[41,42] The latter micro-organism is a major problem worldwide, and so generates much research interest.[43–45] Yakoob et al. [42] showed an association between the virulence marker 'induced by contact with epithelium A' (iceA) alleles (type 1 and type 2) and clinical features, reporting that the type 2 was dominant and associated with chronic active inflammation, gastric ulcer and carcinoma. This result has clear diagnostic and management implications. Mohammadi et al. [46] emphasised the problems of multidrug resistance of *Enterococcus* species, focusing on resistance to vancomycin brought about by *vanA* and *vanB*, although over 80% of cultured *Enterococcus faecalis* were also resistance to erythromycin, ampicillin and ciprofloxacin.

AmpC β-lactmase is an enzyme commonly produced at low levels by *Escherichia coli*. The clinical problem arises when increased levels are produced, as this confers resistance to cephalosporin and penicillin.[47] Lewis and colleagues [48] studied 50 pathogenoic strains o*f E. coli*, finding AmpC β-lactamase resistance in 92%. They found that a link to resistance was a mutation in the promotor region of the gene, and this caused enzyme hyperproduction. The most common mutation was a T→A transition at position –32, which increased enzyme production 46-fold. Carbapenemases are a form of β-lactmase, and the presence of these enzymes is a further cause of resistance to β-lactam antibiotics, and consequently their accurate and rapid identification is highly sought-after. Boran and colleagues evaluated screening methods, with the aim of developing an algorithm that would be of practical use in the laboratory.[49] They concluded that the rapid CARB screen method and the CheckMDR Carba method, when used in combination, will yield results with 97.3% sensitivity and 99.6% specificity, and that the introduction of the proposed algorithm would lead to an improved turnaround time of four days from isolation to carbapenemase detection.

As reviewed by O'Connor and colleagues [50], although tuberculosis continues to be a further worldwide problem,[51] the laboratory is at the forefront of our understanding of this organism and how it can be defeated.[52–54] At a broader level, Connel et al. [55] demonstrated the value of the supraregional reference laboratory in ensuring the correct identification of defined organsisms. Finally, microbiology encompasses mycology, a leading pathogen in this class being *Candida albicans*, which has the potential to cause various morbid conditions, such as vaginitis, and severe infections may contribute to mortality.[56] It has even been hypothesised that this organism may be a cause of diabetes.[57] Teymuri et al. investigated the molecular mechanisms involved in fluconazole (the leading antibiotic) resistance in *C. albicans* clinical isolates.[58] The enzyme lanosterol 14*α*-demethylase, the target of fluconazole, is an essential component in the synthesis of ergosterol, and production is encoded by a gene designated as *ERG11*. The over-expression of *ERG11* results in production of a large amount of lanosterol 14*α*-demethylase and continuous synthesis of ergosterol, which enables *Candida* to resist fluconazole. Our colleagues found that *ERG11* in five fluconazole-resistant *C. albicans* isolates was upregulated approximately fivefold relative to a control strain, and recommended that the surveillance of antifungal resistance patterns and investigation of other mechanisms of azole resistance in all *Candida* spp. isolates be promoted.

Kabir and colleagues published two reports of interest to virologists. In the first,[59] they described a reverse-transcriptase method for enriching DNA generation from bacteriophage RNA using a DNA polymerase from *Bacillus stearothermophilus* (hence RT-Bst). They subsequently [60] clinically validated this method to detect viral sequences in nasopharangeal samples, comparing it with a multiplex one-step RT-PCR and with routine laboratory detection. Their principal findings were that when using RT-Bst PCR, 28% of samples yielded a viral pathogen compared to 20% with RT-PCR and 12% using routine diagnostic tests. Furthermore, RT-Bst PCR was shown to have particular utility in the detection of respiratory syncytial virus (RSV) RNA, as this was present in 20% of the samples studied compared to 8% when using RT-PCR. For one patient, RT-Bst PCR was able to detect RSV five days earlier than conventional hospital diagnostic testing. They concluded that RT-Bst and RT-Bst PCR can be used as alternative approaches to reverse transcription and one-step RT-PCR, respectively, for sequence-independent amplification of RNA virus sequences, and a larger scale analysis of this new diagnostic approach is warranted.

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