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EDITORIAL

British Journal of Biomedical Science in 2021. What have we learned?

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Introduction

The British Journal of Biomedical Science in its attempts to continue to make steps forward as a leading international journal, has seen a significant rise in its impact factor (IF) rating over the past year. The IF figure for 2019 was 2.712 and for 2020 it has risen to 3.829 (Figure 1). Within the category of medical laboratory technology, the journal is now ranked 6th out of 29. These data mark a significant improvement in the academic standing of the journal as compared to many of its direct rivals. The emphasis on focussing on practice, research and education in all aspects of biomedical science and its application to the study of human disease and treatment continues to remain its primary objective. As well as focusing on the scope and full range of scientific disciplines within pathology, the journal has also made significant steps to embrace the importance of molecular techniques and how these methodologies have increased our understanding of disease processes. There is also a significant attempt to keep pace with the changing scope of molecular techniques and how their constant evolution brings an ever increasing armoury of investigative tools that can be applied across a wide spectrum of pathological entities, constantly challenging traditional discipline-specific perspectives to research and development.

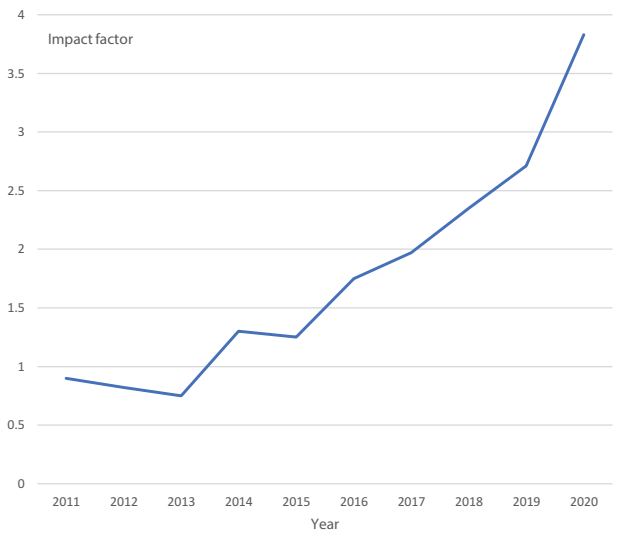

Figure 1. A reflective look at the BJBS impact factors over the past decade. Showing a steady rise over the past few years.

As seen throughout the articles published in 2021, volume 78 of the British Journal of Biomedical Science (BJBS) the molecular techniques discussed are often applied as an investigative tool to determine the clinical relevance of genes in an organism's genome employing genetic screens. It also emphasizes the increasingly important role this technology has across all the traditional biomedical science disciplines. This approach helps us to understand how molecular genetics can be used as a powerful methodology for linking mutations to genetic sequences, may aid the search for treatments and or possible cures for various genetic based abnormalities. Many conditions and illnesses still cause considerable misery and suffering. Better laboratory diagnostics are therefore needed to provide more accurate information and lead to improved patient care – the aim being to provide for a higher quality of life for individuals with these conditions. Moreover some of the molecules and approaches described in the journal, such as analysis of micro-RNAs and single nucleotide polymorphisms (SNPs) for a range of genes, may appear esoteric to many of us working in the laboratories, where more traditional methods hold sway. The important point here is to realize the pace of change in this area and also to recognize the importance of 'biomarker' studies as complementary to experimental studies on cell lines and animal based studies approach in the field, thus enabling a more synergistic approach to the study of disease mechanisms and pathological processes generally (Figure 2).

Molecular studies

Starting with Issue 1 in which one of the articles investigates liver cancer and the detection of mRNA levels of the Toll-like Receptor-7 (TLR-7) in peripheral blood mono-nuclear cells (PBMC) which have previously been shown to be a promising new marker for early

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Figure 2. A statue outside St. Thomas' Hospital main entrance, reflecting the unification of Guys and St. Thomas' NHS Trusts. The statue depicts the idea that in the modern era a combined molecular and an Immunohistochemical (IHC) biomarker expression on tissue sections approach to science is increasingly popular and links techniques.

detection of Hepatitis B associated cirrhosis and liver cell carcinoma. Mohamed et al [1] seek to extend this exploration and investigate the potential for TLR-7 in the early detection of Hepatitis C-associated cirrhosis and liver cell carcinoma and compare it to the utility of traditionally used and less selective detection of Alpha Fetoprotein (AFP) in serum.

Following on from this, Faghih et al [2], investigate the expression of OX40 genetic variants in patients with breast cancer. Recently, it has been proposed that OX40 plays an essential role in anti-tumour immunity, as defects in the OX40 signalling pathway are associated with progression in head and neck cancer.

Also in the field of breast cancer research in Issue 2 of the journal Riah et al [3] investigate the over expression of long non-coding RNA MCM3AP-AS1 in breast cancer tissues and its potential role in carcinogenesis. After using cDNA synthesis and Quantitative Real-Time PCR techniques, it was found that the lncRNA MCM3AP-AS1 may be a novel breast cancer lncRNA with high expression levels in breast cancer patients' tissue. In another study, Haghi et al [4] investigate haplotypes of the 3′-UTR region of the HLA-G gene to see if they are linked to breast cancer. Using peripheral blood DNA from 100 patients affected by breast cancer and 100 controls and employing PCR sequenced for genotyping of 25 HLA-G 3′-UTR regions, it was concluded that certain variants in the 3-UTR, and their combination as a haplotype, of the HLA-G gene are linked to breast cancer.

Continuing in Issue 1 In a study on fertility Tajalli et al [5] investigate the role of the maternal hTERT rs2736100 genotype on the success or failure of IVF and embryo transfer in infertile women. It has previously been shown that a SNP of the human telomerase transcriptase (hTERT), named rs2736100 (A allele) is associated with lower hTERT mRNA expression and shortened telomere length in gastric cancer tissue and cell lines. When all else fails, couples frequently turn to assisted reproductive technology, such as in vitro fertilization (IVF), to help with conception. Unfortunately, approximately 75% of IVF treatments are unsuccessful. Multiple factors are considered to contribute to IVF outcome to include; maternal age, embryo quality, endometrial receptivity and more recently genetic factors. However, the exact mechanisms surrounding IVF and embryo transfer outcome are still largely unknown. One hypothesis centres on the proliferative activity of the ovarian granulosa cells and the efficiency of human telomerase. Basically, telomerase acts as a reverse transcriptase in the elongation of telomeres to protect them from degradation and it has been shown that the decreasing telomerase activity in the granulosa cells leads to increased rate of apoptosis and number of atretic ovarian follicles, with suggestions that short telomeres in the oocytes contribute to anomalous fertilization of gametes and abnormal cleavage of embryos.

A study investigating predicting which women are more likely to be affected by gestational diabetes during pregnancy as an attempt to manage the condition

more effectively Abdeltawab et al [6] investigate the potential for circulating micro RNA-223 and angiopoietin-like protein 8 to fulfill this role.

On the theme of dietary issues a molecular study in Chinese adults for blood lipid levels by Mo et al [7] investigated polymorphisms in the SLCO1B1 gene and showed that individuals with specific genotypes have decreased ability to metabolize drugs, such as statins, leading to increased risk of rhabdomyolosis and myopathy. In the cohort of individuals enrolled, 2.7% of patients were identified as having the high-risk genotype that could potentially result in adverse reactions to statins.

In Issue 2, Maruei-Milan et al [8] investigating thyroid disease studiedg long non-coding ANRIL RNAs in papillary thyroid cancer and discovered that certain ANRIL single nucleotide polymorphisms (SNPs) play a significant part is disease onset and progression. Certain haplotypes of ANRIL SNPs are associated with papillary thyroid cancer. ANRIL rs1333048 and rs4977574 variants were associated with larger and smaller tumour sizes, respectively.rs10757274 and rs1333040 variants might lead to lower III–IVcancer stages. These SNPs may be important in the diagnosis of this form of thyroid cancer.

Moving on to autoimmune states in Issue 2 Abdelaleem et al [9] investigate Behçet's disease, which is a chronic relapsing and remitting autoimmune multisystem inflammatory disease characterized by oral aphthae, genital ulcers, skin lesions, gastrointestinal involvement, arthritis, vascular lesions and neurological manifestations. Using Behcet's disease current activity index (BDCAI) to assess patients'disease activity status. MiR146a(rs57095329) was genotyped in all participants using RT-PCR and results in patients analyzed according to clinical features. It was concluded that the miR-146a (rs57095329) is associated with Behçet's disease and certain genotypes and alleles with oral ulcers, and with ocular and neurological manfestations. Keeping on the theme of auto immunity this time in the study of rheumatoid arthritis (RA) Hu et al [10] on a study of serological markers in the diagnosis of (RA), explored the clinical value of collagen triple helix repeat containing-1 (CTHRC1) and 14-3-3η protein, compared to routine markers, in the diagnosis of RA. The authors concluded that CTHRC1 and 14-3-3η are promising serological indicators of RA, and when combined with anti-CCP, anti-MCV and ESR, can improve the diagnosis of this disease.

Three reports were published in Issue 2 in the biomedical science in brief category. Firstly Aminmalek's et al [11], concerning epidermal growth factor +61A/G (rs4444903) promoter polymorphism and serum levels and whether they are linked to idiopathic male infertility. Studying SNP's in blood samples it was indicated that a link existed between the EGF + 61A/G (rs4444903) SNP and its serum concentration with idiopathic male infertility. The second report by McIlroy et al [12] looked at the antibiotic susceptibility of infectious pathogen Pseudomonas aeruginosa and its interplay when grown in the presence of Candida culture. The study demonstrated the novel interplay involving antibiotic susceptibility, between an established respiratory bacterial pathogen and hitherto, what was regarded as commensal yeast organisms. This interplay may be exploited therapeutically in the clinical management of cystic fibrosis airway disease, as well as helping to further develop our understanding of complex ecological interactions.

Finally in Issue 2, Siahpoosh et al [13] discussed KISS1R polymorphism rs587777844 (Tyr313His) and its link to female infertility. The results of this study demonstrated the important role of this gene in female reproductive function. The results of the study were consistent with previous findings and indicated the rs587777844 to be functional SNPs of KISS1R gene that might be linked to infertility. It was revealed that the presence of the C allele could be a risk factor for infertility among women.

Continuing in Issue 3, a study of β-thalassaemia investigated the role of the Homeobox (Hox) genes in this group of disorders as data from zebrafish suggest these have an important role in normal haematopoiesis (Reference). β-thalassaemia is a spectrum of hereditary blood disorders characterized by defects in the synthesis of the β chains of haemoglobin. The severity of symptoms is related to the extent of absent production of β-globin chain (these range from severe to asymptomatic). The genotypic variability of β-globin synthesis is designated as β(+) for decreased production and β(0) for absent production. The phenotypic variability is designated as either minor, intermediate, or major. β-thalassaemia minor is heterozygosity with one unaffected beta-globin gene and one affected, either β(+) or β(0). Homozygosity or compound heterozygosity with β(+) or β(0) causes intermediate and major. The molecular defects in β-thalassaemia result in absent or reduced β-chain production. Alpha chain synthesis is unaffected, and hence there is an imbalanced globin chain production leading to an excess of α chains. In the absence of their partners, they are unstable, and they precipitate in the red cell precursors, giving a rise to large intracellular inclusions, which interfere with red cell maturation. The Hox genes are heavily involved in embryo segmentation with two members *HoxA9* and *HoxA5* expressed in red cell progenitors. Badr et al [14] showed an increase in *HoxA9* in β-thalassaemia patients that was related to disease severity. The authors hypothesise this could be due to increased self-replication of the haematopoetic stem cells. They found no changes in *HoxA5* suggesting this gene has no role in this process. The authors acknowledge it as a case control study and that there may be misdiagnoses or bias as well as the effects of

transfusion. However, *HoxA* gene analysis shows promise in the identification of patients with thalassaemia and in differentiating between its two subtypes of major and intermediate thalassaemia.

Focusing on colorectal cancer in Issue 3, Atef et al [15] investigated the role of the epidermal growth factor receptor family in the pathogenesis of the disease as one of its downstream effectors (STAT3) has a role in multiple cancer types. A further variable in this area are the roles of micro RNA (miRNA) and long non-coding RNAs (lncRNAs), and these two variables may interact to provide a further mechanism for gene regulation. The authors hypothesised alterations in the EGFR-AS1/miR-133b/EGFR/STAT3 axis in colorectal cancer, and examined in tissue biopsies: Phosphorylated-EGFR, STAT3, Survivin and Capsase 3 were determined by ELISA and EGFR-AS1 (the lncRNA) and miR-133b by PCR. They found increased EGFR-AS1 and EGFR overexpression were linked to both tumour grade and metastasis, with a negative correlation between EGFR-AS1 and miR-133b, with low expression of miR-133b associated with the overexpression of EGFR and p-STAT3 levels. Finally, they showed low EGFR-AS1 expression was associated with a higher survival rate and may be a potential biomarker for early diagnosis and survival prediction.

Looking at a rare genetic disease and assessing polymorphisms Yuan et al [16] studied the xeroderma pigmentosum group G (XPG) gene in glioma (the most common childhood malignancy after leukaemia). The main role of XPG protein is in the removal of damaged DNA, so increased activity may be a risk, as tumours with higher DNA repair ability are more likely to metastasise and invade. They examined a number of polymorphisms in this gene in 171 patients with a glioma against 228 age and sex match controls. They selected cases in young children (aged 24 to 96 months) as there appear to be differences between gliomas in children and adults. They found patients carrying 5 of the risk genotypes has a significantly increased risk compared to those with 0 to 4 of the risk genotypes, and this was pronounced in the subgroups of >60 months age, males, astrocytic tumours and low grade clinical stage. In addition, they note that one of the SNPs effects other genes surrounding it which may have bearing on the development of these disorders.

In Issue 3, we read a comprehensive study regarding the early SARS-CoV-2 antibody assays in mild and asymptomatic subjects Cramer et al [17] which highlights the difficulties in rapid development of assays for a rapidly emerging clinical need. Definitive diagnosis of the disease depends on PCR, which will only identify current illness or viral carriage and is affected by a number of factors including viral load, time of sampling and how thoroughly the sample is collected from the nasopharynx. A number of serological assays were rapidly released onto the market, which were targeted to a number of the antigenic proteins associated with the virus. The speed at which these assays were brought to market meant that these were not calibrated against any international standards, so results were qualitative. In addition, there was variation in the antibody type detected (IgG or IgM) and the target epitope used in the assay. The methods were often tested against sera obtained from patients with severe infection and high antibody levels and these were often used to set the cut-offs defined by the manufacturer. The authors highlight the efforts of the WHO to produce a reference standard which is now available (details on the WHO website).

There were also two biomedical science in brief papers in Issue 3. The first Abdi et al [18] on gastric cancer. Gastric cancer has a number of risk factors, and the study of Abdi et al examined the importance of lncRNAs in the pathogenesis of this disease. Two such molecules, HOX transcript antisense RNA (HOTAIR) which functions as a molecular scaffold whose overexpression causes invasiveness of cancer cell lines *in vitro* and triggers tumour growth and metastasis *in vivo* and Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), which has been shown to be overexpressed in gastric cancer, but its mechanism of action is unknown. Interactions between single nucleotide polymorphisms (SNPs) are known to exert large effects on certain disease processes, so the authors examined potential links between SNPs in both genes and using bioinformatics showed decreased binding to microRNAs. This study emphasises the need to place genetic studies into clinical context and to consider the interaction with other molecules in the increasingly complex systems involved in the control of gene expression and protein translation.

Also in this issue, Albonaim et al [19] examined the effects of polymorphisms in the opioid receptor kappa type 1 (OPRK1) which has a role in nicotine dependence. This receptor affects the activity of brain reward systems to the beta-endorphins and enkephalins so has a proposed role in addiction. The authors noted significant differences in the SNPs tested and propose that opioid receptor antagonists may assist in reducing the negative impact of nicotine withdrawal. However, the literature is confusing, with many confounding factors (for example addiction to other substances) and in this study a small sample size and a limited number of SNPs studied. This area is of importance given the adverse effects of nicotine which can cause an increase in blood pressure, heart rate, flow of blood to the heart and a narrowing of the arteries. Nicotine may also contribute to the hardening of the arterial walls, which in turn, may lead to a heart attack (and other) addictions on health in general.

In Issue 4, Ghasemian et al [20] investigate whether single nucleotide polymorphisms (SNPs) in *DACT1* are associated with an increased risk of colorectal cancer.

The implication being, this may affect the tumour suppressor function of *DACT 1*, and therefore allow for aberrant Wnt/Beta-catenin signalling.s conducted in a specific population with small numbers in a defined geographical area, so require repeating in other populations. Again in Issue 4, we read about chronic obstructive pulmonary disease (COPD), which is now a leading cause of death world-wide. In the vast majority of cases, it is caused by smoking and therefore preventable by tobacco cessation. The effects of COPD are not reversible. Asthma is an allergic reaction that results in obstruction of the airways by airway wall thickening and increased mucous secretion. Unlike COPD the effects are reversible and the exact cause of the condition is unknown. Both COPD and asthma can exhibit similar clinical signs and symptoms. However, it would be reasonable to assume that patients with these symptoms who are young or who have never smoked are unlikely to be suffering from COPD. Sahu et al [21] investigate the utility of SNPs in genes for 'A disintegrin and metalloproteinase 33' (ADAM33) and Aquaporins (AQPs) to discriminate between COPD and Asthma.

Summary of the molecular genetic papers

The summary of the molecular-based papers in Issues 1–4 have demonstrated its wide spread appeal in the study of disease and in particular disease pathogenesis. However, although molecular genetics has greatly increased the understanding of diseases in which there is a single gene defect for example single-gene testing is often used when there is already a known gene mutation in a family. For example, testing for *BRCA* mutations only looks for changes in *BRCA1* and *BRCA2* genes. It becomes harder to elucidate in cases where there are a multitude of gene defects, for example EGFR-targeted therapies don't work particularly well when there are also BRAF or KRAS mutations present. However, the use of multi-gene panel testing (MGPT) with next-generation sequencing (NGS) for the diagnosis of hereditary cancer predisposition has increased significantly over recent years Undeniably, however discovering the gene responsible and its function will help determine the pathogenesis of the disease and may also provide guidance on targeted treatment-gene therapy [22]. Following the completion of the human genome project, we are slowly discovering the secrets of disease and more significantly the associated gene mutations or defects that trigger them thus increasing the continued importance of studying these gene-based approaches and determining their findings in disease. It should also be mentioned that disease processes are often caused by multifactorial events not all governed by genetic defects for example cancer may result from the combined influence of many genetic factors acting in concert with environmental insults (e.g. ultraviolet radiation, cigarette smoke, and viruses). It is also the case that the use of biomarker assay data can provide information on detecting cancer in different stages of initiation, development and progression to assist and guide the treatment regimens and allow more elaborate patient-tailored approach to disease management. Recent advances have developed non-invasive, sensitive and specific biomarkers which enable the detection of cancers at early stages of disease progression.

Biomarkers

An effective way to evaluate protein expression in disease tissue is to use immunocytochemistry, we learnt more about this in Issue 1. Immunohistochemistry is commonly used in the vast majority of clinical cellular pathology laboratories throughout the world, predominantly in tests to determine tumour cell lineage. However, Zhang et al [23] show us how the technique can be used to intricately map out a range of proteins simultaneously using fluorescent labels and confocal microscopy. The authors define the fine structure of the human retina using five panels of antibodies, each panel comprising three different markers that are applied simultaneously to tissue sections of human retina. The value of being able to map out proteins simultaneously in structures using this type of approach is only now starting to be fully appreciated. Visualisation of proteins that are mapped out in this way will no doubt greatly enhance our understanding of the relationship between cells in both health and disease. Continuing in the area of cellular pathology in issue two Gabriel et al [24] looked at technical evaluation of different haematoxylin stain subtypes for the optimal microscopic interpretation of cutaneous malignancy in Mohs frozen section histological procedure. It was determined that Carazzi's haematoxylin was the most optimal staining dye for the identification of basal cell carcinoma (BCC) tumours for use as part of the Mohs micrographic surgery procedure.

Revisiting colorectal cancer in Issue 4, we again see the importance of biomarker assays. Globally, colorectal cancer is one of the most common malignancies. Whilst survival from this disease is excellent if detected early, it is frequently only discovered at a later stage, which results in significant mortality. Consequently, the value of developing more efficient markers for early detection and for its molecular classification to allow prediction of response to targeted therapies. Presumably for convenience, colon cancer historically is grouped with rectal cancer (colorectal cancer) even though these days surgical treatment is different for the two conditions. Moreover, the rectum and colon derive from different embryology, the epithelia is different and the structures serve different functions. In the future, no doubt molecular classification of these

two diseases will allow for more accurate treatment. Lie et al [25] looked at the efficiency of some well-known tumour markers (CEA, AFP, CA125 II) and some lesser known ones (CA19-9, CA72-4) in differentiating between colon cancer and rectal cancer. Only CA125 II was found to be useful in this respect.

Biomarkers in diabetic kidney disease (DKD) was also looked at in Issue 4. DKD is on the increase in many parts of the World due to the ever-increasing numbers of people with type 2 Diabetes. DKD is has been described as the result of a complex interaction of metabolic, inflammatory and haemodynamic changes, with the involvement of energy pathway related metabolites. It is characterized by increased urinary albumin excretion and a reduced glomerular filtration rate (eGFR). Early detection of DKD can help prevent subsequent kidney damages in a large proportion of the cases. As DKD is the result of a metabolic disease state it seems plausible that early detection of the events leading to DKD should be possible utilizing metabolomic profiles generated from advanced mass spectrophotometry. Abdelsattar et al [26] explore this possibility and show that acylcarnitines are stronger predictors of the albumin and creatinine ratio (ACR) than HbA1c and therefore of value in diagnosing early cases of DKD.

In patients with heart failure, ventricular tachyarrhythmias can be fatal. The clinical assessment of left ventricular ejection fraction (LVEF) is the main stay of predicting this event. Consequently, identification of cardiac biomarkers that could improve risk stratification would be very useful. C-terminal proendothelin-1 (CT-proET-1), mid regional pro-atrial natriuretic peptide (MR-proANP) and mid regional pro-adrenomedullin (MR-proADM) are released in a response to increased cardiovascular stress, pressure and volume overload, increased wall tension and endothelial shear stress. In Issue 4, Burger et al [27] investigate the utility of these markers for improving risk stratification in patients with heart failure.

Rheumatoid arthritis (RA) is characterized by an autoimmune response, resulting in chronic inflammation and destruction of the synovial membrane. It is an insidious disease, lacking specific clinical signs and symptoms and therefore frequently not diagnosed at an early stage. Rheumatoid factor (RF) and more recently anti-cyclic citrulline polypeptide (anti-CCP) and anti-mutant citrulline vimentin (anti-MCV) are the most commonly used serum markers to aid in the diagnosis. However, additional markers with greater sensitivity and specificity, would be useful. Sirtuin-1 is a deacetylase, responsible for deacetylating a range of proteins to include histone, non-histones and it is also involved in regulating cell energy metabolism, inflammation and oxidative stress. In addition, there is evidence from *in vitro* and animal studies that sirtuin-1 is involved in immune regulation. Again in Issue 4, Li et al [28] compare the value of measuring sirtuin-1 levels, anti-CCP and anti-MCV in cases of RA. The authors find sirtuin-1 to be elevated in RA and to have great specificity than the other markers tested.

Case histories

There were a wide assortment of case reports presented throughout the journal in all issues starting with Issue 1, Ekbatani et al [29], in their series of three case studies of children, describe how the infants presented initially with gastro-intestinal symptoms and only on subsequent chest X-ray and PCR testing for SARS-CoV-2 were found to have the typical lung opacities associated with the virus and a positive result, respectively. Consequently, if children with gastrointestinal symptoms present at hospital, the possibility of an underlying SARSCoV-2 infection should not be overlooked. In Issue 2, we saw the application of next generation sequencing (NGS), Galliguez et al [30] using (NGS) metagenomics to identify Prevotella pleuritidis in a diabetic adolescent with large parapneumonic effusion and negative growth of pleural fluid culture. The report described a 12-year-old diabetic boy with a right-sided parapneumonic effusion and pneumonia who failed initial empirical antibiotics. Prevotella pleuritidis was identified from the pleural fluid using next-generation sequencing-based clinical metagenomics with cultures of pleural fluid and blood resulting negative. The patient responded well to intravenous meropenem followed by oral metronidazole. In Issue 3, we saw a case study on congenital analbuminaemia, which is a rare autosomal recessive disorder, characterized by the near-complete absence, or very low levels, of serum albumin. However, this is difficult to diagnose using traditional methods of albumin measurement as levels can be decreased in disease and routine methods are not capable of accurately determining very low levels in serum. Diagnosis therefore has to be made by mutation analysis of the albumin gene. Caridi et al [31] describe a novel mutation in the gene detected in an adult. The proband was heterozygous for the mutation and showed near normal albumin levels (as occurs in other cases involving mutation of this gene). The authors suggest that the majority of the defects in the gene arise from spontaneous mutations, with the possibility of hypermutable regions of the gene.

Finally in Issue 4, we read about a case study by Zhan et al [32] of a young female patient with bone marrow failure syndrome −4 (BMFS-4), a very rare autosomal recessive genetic disease characterized by early-onset anaemia, leucopenia, B-cell loss and thrombocytopenia. In addition, some patients develop facial deformities, bone abnormalities and growth retardation. Mutations in the *MYSM1* gene, which codes for a deubiquitination enzyme have been linked to BMFS.

Methods

Papers based on methodology rather than pure and applied science have great value. Obesity is a major public health problem in developed and developing countries of the world and is associated with a range of chronic conditions to include; cardiovascular disease, type-2 diabetes and cancer. Two surgical procedures that are used for the treatment of morbidly obese patients who have failed to respond to conservative treatment are laporoscopic gastric bypass and laporoscopic sleeve gastrectomy. In Issue 1 Yan et al [33] compared the efficiency of these two procedures in treating obese patients with type-2 diabetes.

In Issue 3, Mousa et al [34] investigated the speed of treatment for acute oesophageal variceal haemorrhage. The international guidelines are not consistent and appear not to be based on scientific data but on 'expert opinion'. This study compared treatment within 12 h of admission to that within 24 h of admission. It was noted that early treatment was associated with a shorter hospital stay, a greater fall in ammonia level and improved encephalopathy grade. This study was in patients with viral-related cirrhosis, so differences may be seen in patients with oesophageal varices due to other factors.

Whilst on the subject of liver pathology in Issue 2 Omar et al [35] introduce a simple, non-invasive model based on routine parameters for predicting hepatitis C virus-related hepatocellular carcinoma, termed the HCC-Mark. Employing logistic regression analyses and receiver operating characteristic (ROC) curves to develop and validate the HCC-Mark model comprising AFP, high-sensitivity C-reactive protein, albumin and platelet count. They discovered that HCC-Mark is an accurate and validated model for the detection of hepatocellular cancer and certain of its clinical features.

Review papers

The final section of publications included three review papers. In Issue 1, Farsimadan and Motamedifar [36] reviewed the evidence to implicate a range of viral infections in infertility to include, human immunodeficiency virus, human papilloma virus, Herpes simplex −1 and 2, human herpes virus 6 and 8, cytomegalovirus and hepatitis B.

In Issue 3, we had a review by Naughton et al [37] On infectious mononucleosis (glandular fever) and the challenges in its diagnosis. Correct and early diagnosis of the disease is important to avoid the unnecessary administration of antibiotics and reduce the need for other investigations as some cases can present with splenomegaly, hepatomegaly or even suggest haematological disorders. The review starts with a description of the disease and its causative pathogen, Epstein Barr virus (EBV). EBV infection is very common with 95% of the entire world's population being infected at some stage in their life. The main route of transmission appears to be via saliva, though blood transfusions and transplantation are clinically important routes. EBV is able to force B cells into becoming 'memory' cells and can thus persist and only display a limited number of the viral proteins, thus avoiding detection by the host immune system. Typically, in immunocompetent individuals, the virus is able to remain in the host for life. The review then considers the laboratory tests available for the diagnosis of the infection. EBV is able to cause the presence of heterophile (non-specific) antibodies which are the basis of the older Paul Bunnell test and the more sensitive Monospot test. Whilst this test is very useful in diagnosis as the antibodies may not be present at high levels in active disease, or be present at high levels after the acute phase, thus leading to misdiagnosis. The authors then go on to describe more specific tests for the virus. Finally, the authors highlight the lack of a standard international diagnostic algorithm for the disease, particularly given its long history. Finally in Issue 4, Pattison et al [38] reviewed the complexities involved in producing effective fungal vaccines and in particular to *Aspergillus* antigens.

Many invasive fungal infections are notoriously difficult to treat and are an ever-present danger for those with a compromised immune system. The importance of fungal infections has recently been highlighted by the occurrence of mucormycosis (black fungus) in patients with COVID-19. One approach to addressing fungal infection is to prevent their occurrence in the first place by the development of fungal vaccines.

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