Draft
The role of the physician in laboratory medicine – an European perspective

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Introduction

An inevitable consequence of advances in medicine in the 20th century was the welcome development of physicians specialising in laboratory medicine (LM) or pathology.While the early pioneers were pluripotential in their approach embracing the breadth of LM, the pace of advance in tissue-based diagnosis and its immediately verifiable impact on disease management meant that histopathology (also known as morbid anatomy or cellular pathology) was the first laboratory-based specialty to carve out a distinct identity.Similarly, advances in diagnostics in other areas of LM and the need for particular expertise in distinct subject areas led to the emergence of laboratory-based physicians in haematology (including transfusion medicine), biochemistry (chemical pathology), microbiology and immunology.

Across Europe the pace of specialisation has varied with the practice of LM in its broadest sense, with the continuation of general pathology or polyvalent LM alongside the single specialties listed above. The development of a Section of Laboratory Medicine – Medical Biopathology within the European Union of Medical Specialist (UEMS) in 1962 in order to promote and harmonise high standards of training and practice across LM in the constituent countries of the European Union and its subsequent evolution has followed a similar vein. Although at its inception the section of LM acted as an umbrella body for all laboratory-based specialties, the presence of a critical mass of practitioners and the distinctive nature of practice in histopathology and microbiology led to the creation of individual sections for these specialties in 1988 and 2009 respectively.

Over the past few decades advances in medical laboratory technology have significantly influenced the role of physicians in many laboratory disciplines with the exception of histopathology. Despite advances in image analysis, the role of the histopathologist in the critical analysis of diseased tissue using a variety of conventional and molecular biological techniques, has to date, not been overtaken by technology.In contrast the automated analysis of blood and other fluids in biochemistry, haematology, microbiology and immunology laboratories using a variety of techniques is not dependent on direct physician involvement. What added value then, does a laboratory-based physician bring to practice in these disciplines? At a time of sustained financial pressure on health care systems and the drive to contain costs, it is timely to clarify the on-going importance of the contributions made by physicians in LM.

Influencing clinical outcomes

The integral importance of laboratory tests to the day to day practice of medicine is widely accepted. Although the assertion that test results influence approximately 70% of clinical decisions has recently been questioned[1], it is clear that a comprehensive laboratory medicine service is essential to deliver high quality evidence-based care. The difference that such laboratory tests make to clinical outcomes is beyond dispute but quantifying the effect of testing remains a challenging task. Although the importance of laboratory-related outcomes is now well recognised[2], difficulties in designing rigorous studies of the effects of laboratory tests on clinical outcomes has resulted in a limited evidence-base in contrast to the plethora of randomised controlled trials underpinning therapeutic interventions. Even more challenging is the

need to measure the added value of the contributions made by laboratory-based physicians (Table 1). As we increasingly move towards patient-centred health care systems, it could be argued that the only justification for laboratory-based physicians would be to ensure that they make a clear difference to patient outcomes. In this regard, the concept of laboratory-related patient outcomes is a welcome development. Three levels of laboratory-related patient outcomes have been defined (Table 2)[3].

Table 1 Responsibilities of a laboratory-based physician

- Direction of clinical laboratories
- Provision of appropriate test repertoire
- Clinical liaison and interpretation of results
- Attendance at multi-disciplinary meetings
- Quality assurance
- Assay development and validation
- Defining the role of emerging biomarkers for disease diagnosis, monitoring and treatment
- Clinical audit
- Demand management
- Hands on laboratory work (in some disciplines)

Table 2 Laboratory-related patient outcomes [3]

- Operational performance of a test – sensitivity, specificity
- Predictive value of the test using Bayes' theorem – probability of disease in a patient
- Probability of the test result influencing a change in health status resulting from a change in disease management

In addition to these measures, it is possible to use illustrative case histories to highlight the qualitative difference made by laboratory-based physicians in the various LM disciplines as shown by the examples below.

Integration of laboratory results in the clinical context – qualitative examples of laboratory-related patient outcomes

Immunology

Case history 1

A 4 month old Caucasian boy is hospitalised with acute undefined bacterial pneumonia.He is discharged from hospital 2 weeks later having apparently made a good recovery.His serum immunoglobulin (Igs) levels were reported to be satisfactory: IgG 3.0 g/l (Ref range 3.0 – 9.0),
IgA 0.1 g/l (0.15 – 0.7), IgM 0.3 g/l (0.4 – 1.6), Serum electrophoresis – not done, FBC – Hb 12.8,WBC 9.0 L – 2.0,N 5.9,Plt 256. Six weeks later he is re-admitted to another hospital with a further episode of pneumonia proven to be due to *Pneumocystis jiroveci* on this occasion.His repeat s Igs are as follows: IgG 2.7 g/l ,IgA 0.1 , IgM 0.1 , Serum electrophoresis – small monoclonal IgG band,

Lymphocyte surface marker analysis – T-B+NK-, Final diagnosis – Severe Combined Immunodeficiency (SCID)

Lessons from this case

- Clues to underlying diagnosis overlooked on first admission : Lymphopenia
- Failure to perform serum electrophoresis in a laboratory without clinical immunology input led to report of apparently 'normal'Ig profile ..Monoclonal bands are extremely rare in infancy and frequently signify underlying immunodeficiency[4].
- Delayed diagnosis due to failure to synthesize and correctly interpret data at first presentation.
- It is arguable that the significance of lymphopenia in a 4 month old infant with pneumonia and a borderline serum IgG that was likely to be largely maternal in origin was ignored because of the absence of clinical immunology expertise in the first hospital.

Case history 2

A previously well 28 yr old nurse presents to her general practitioner (GP) with a 6 month history of generalised arthralgia.The results of initial investigations are as follows:Rheumatoid factor 160 iu (ref range <40), Anti-nuclear antibody 1/160,CRP < 6 mg/l,Hb 12.0,WBC 6.4,Platelets 320,Na 142, K 3.8,Creatinine 120 (ref range 50 -145). On the strength of these results, a tentative diagnosis of rheumatoid arthritis is made by the GP.On rheumatological assessment , she is noted to have a purpuric rash on her legs but no clinical features to suggest RA. The results of further investigations are as follows: anti-DNA & ENA – negative,RF 225 iu (ref range < 40 units), Serum complement C3 1.2 g/l (ref range 0.6-1.8),C4 0.02 g/l (ref range 0.15 – 0.4), Serum IgG 8.4 (ref range 6 -13 g/l), IgA 1.0 (ref range 0.8 – 2.5 g/l),IgM 4.5 (ref range 0.4 – 2.0).Electrophoresis – Normal. The combination of a strongly positive RF and a low C4 leads to the possibility of mixed cryoglobulinaemia being raised in the laboratory report.Further investigations confirms the presence of a mixed cryoglobulin in serum accompanied by evidence of glomerular involvement (positive red cell casts in urine), leading to the unifying diagnosis of hepatitis C- associated mixed cryoglobulinaemic vasculitis.

Lessons from this case

- The correct diagnosis of mixed cryoglobulinaemic vasculitis associated with hepatitis C infection was a direct result of laboratory-generated clinical interpretative comments.

Biochemistry

Case history 3

A 51 year old woman with type 2 diabetes was being investigated by her GP for possible menopausal symptoms. The results of initial biochemical investigations are as follows: plasma luteinising hormone (LH)<0.1 IU/L(ref range >50), follicle stimulating hormone (FSH)0.6 (ref range > 50).The surprisingly low LH and FSH in a peri-menopausal woman prompted laboratory physicians to raise the possibility of pituitary disease. Further investigations instigated by the biochemistry laboratory revealed an elevated prolactin at 6.1 IU/L(ref range 0.09 – 0.52). The possibility of a macro-prolactin causing artefactual elevation of plasma prolactin was excluded by treatment of the specimen with polyethylene glycol.

Reassessment of the clinical history following the detection of elevated prolactin revealed chronic galactorrhoea which had previously been thought to be insignificant. Cranial imaging revealed the presence of a large pituitary tumour extending into the suprasellar area measuring 23 x 20 mm.Her vision was fortunately unaffected and imaging revealed no compression of the optic chiasm.

Lessons from this case

Correct interpretation of the significance of an unusually suppressed plasma FSH in a peri-menopausal female by a laboratory physician and instigation of additional tests revealed the underlying diagnosis of a pituitary tumour.

Case history 4

A 40-year old previously well man was brought to the Emergency Department by his friends. He had taken part in a martial arts competition on a hot day. He had been using a commercial sugary solution to keep himself hydrated, and had decided not to accompany his friends to a dinner at the end of the competition. They returned to find him semiconscious and wondered whether he might have had a seizure. The tests done in the ED showed a plasma sodium of 116 mmol/L, plasma osmolality of 242 mOsm/kg (reference range 290-300) and urine osmolality of 425 mOsm/kg, suggestive of dilutional hyponatraemia associated with the syndrome of inappropriate ADH secretion (SIADH).The rest of his metabolic profile, including renal function was normal. During an attempted lumbar puncture, he had a seizure, during which he vomited and inhaled. He was admitted to the ICU, and required antibiotic treatment for aspiration pneumonia .

In this case, hyponatraemia was associated with exercise and ingestion of glucose-containing fluid. It arises in individuals who activate ADH secretion on exercise but then do not switch it off when overhydrated. Hyponatraemia occurs with glucose containing fluids because as cells take up glucose under the influence of insulin and exercise, free water remains and causes dilutional hyponatraemia. ADH prevents the free water being excreted. Investigation includes measurement of plasma and urine sodium and osmolality, and reveals a picture characteristic of SIADH. Conservative management, with airway protection, and fluid restriction with addition of an ADH-receptor antagonist if necessary, is usually sufficient.

Lessons from this case

A physician in the biochemistry laboratory was directly responsible for the diagnosis of exercise and exogenous glucose-driven SIADH, which had initially been overlooked. This diagnosis enabled optimal management and thus obviated the need for outpatient neurological assessment and further investigation of his seizures.

Haematology

Case history 5

A 20 year old female with chronic renal failure undergoes unilateral renal transplantation with her mother as a donor. Peri-operative thrombo-prophylaxis was undertaken with unfractionated heparin. Following an uneventful operative procedure, however, multiple thromboses developed accompanied by a marked fall in platelet count from a pre-operative level of 220,000/mm^3 to 80,000/mm^3

During a post-operative multi-disciplinary meeting involving different specialties, the laboratory haematologist raised the possibility of the diagnosis of heparin-induced thrombocytopenia (HIT).On his recommendation,immediate substitution with alternative anti-thrombotic treatment (lepirudin) was commenced while laboratory investigations for confirmation of HIT were performed.

The diagnosis of HIT was confirmed by the demonstration of antibodies to heparin-platelet factor 4 complexes by ELISA.The dosage of anticoagulant therapy and further laboratory monitoring was undertaken by medical staff of the Haematology laboratory, who continued to supervise the patient's anti-coagulant therapy until the episode of HIT had resolved. Once the platelet count had normalised, the patient was commenced on oral warfarin.

Lessons from this case

- Failure to diagnose HIT by the transplant team.
- Consequent delay in stopping heparin.Indeed, it is likely that heparin would have been continued at a higher dose due to the mistaken assumption of inadequate anti-coagulation in the face of multiple thromboses.
- In addition to laboratory physicians being pivotal to the diagnosis of HIT, selection of alternative anti-coagulants and monitoring of treatment was also directed by the laboratory.

Case history 6

A 43 year old woman from Greece with a long history of lower abdominal discomfort was admitted via the emergency department with severe abdominal pain. Her routine blood tests were normal apart from a raised CRP and an MCV of 69fL. A contrast enhanced CT scan showed a splanchic vein thrombosis.
There was no family history of thrombotic disease and a thrombophilia screen including genetic testing for Factor V Leiden and prothrombin was negative.
The patient was started on Warfarin for six months and discharged. On review of her laboratory results including a low MCV with a normal haemoglobin, the laboratory haematologist raised the differential diagnosis of -/alpha alpha/alpha thalassaemia or iron deficient polycythemia rubra vera (PRV). She requested iron studies and a jak2 V617F mutation analysis which came back as positive confirming the diagnosis of iron deficient PRV. The patient was referred for upper and lower GI endoscopy. These showed a bleeding polyp which could be entirely removed. She was started on life-long Aspirin and advised never to receive iron replacement.

Lessons from this case:

- Splanchnic vein thrombosis is a recognized complication of myeloproliferative diseases such as PRV. Iron-deficient PRV can be easily overlooked, as was the case here, as the only hint might be a low MCV in the presence of a normal haemoglobin.
- In this case of a woman originating from the Mediterranean, the obvious explanation would have been a mild alpha thalassaemia trait. Without the input from the haematologist, the diagnosis of PRV would have been missed and the patient left untreated after completion of six months warfarin therapy.
- Importantly, the patient might have been started on iron replacement, which can lead to a rapid increase in haemoglobin levels and precipitation of thrombotic events in PRV patients. The diagnosis of iron deficiency also led to further GI investigations and the removal of the underlying cause, in this case a polyp.

Microbiology

Case history 7

Matthews et al[5] present the case of a 73 year man with a history of progressive right-sided facial and periorbital swelling, right-sided nasal blockage, serous nasal discharge, and visual blurring. The patient was immunocompromised following treatment for prostatic carcinoma, and at the time of presentation had a disseminated vesicular rash. Based on clinical and radiological findings, a diagnosis of necrotizing maxillary and ethmoid sinusitis with periorbital cellulitis and conjunctivitis was made, together with disseminated varicella-zoster virus infection. After surgical debridement, a microbiological diagnosis of acute necrotizing sinusitis caused by *Staphylococcus lugdunensis* was made. No other organisms, including fungi, were grown from the operative samples, and histology was negative for fungal elements. The patient made a good recovery after six weeks of appropriate therapy.

Staphylococcus lugdunensis is a coagulase-negative *Staphylococcus* that is a normal commensal of human skin. Coagulase negative Staphylococci are commonly isolated from clinical samples, and are usually disregarded as being non-pathogenic or contaminants unless found in association with a prosthetic device or endocarditis, and repeatedly isolated. *Staphylococcus lugdunensis* is now well recognised as a significant pathogen that can cause invasive disease similar to *Staphylococcus aureus*, and can also (as in this case) initially be mis-identified as a *Staphylococcus aureus* . Clinically it is usually associated with infections such as endocarditis following interventions in the groin eg vasectomy or cardiac catheterisation via the femoral artery.

Lessons from this case
In the laboratory it is not cost-effective to identify all coagulase negative Staphylococci to species level, especially from non-blood culture isolates. The role of the laboratory-based physician in this case was to instigate appropriate further investigations to correctly identify *Staphylococcus lugdunensis*, liaise with the clinical team to clarify its role as a significant pathogen in the clinical context described and ensure that appropriate treatment was instituted

Case history 8
A 19 year old man presented to his general practitioner with a 3 month history of unilateral cervical lymphadenopathy, general malaise, night sweats and weight loss. On examination the GP was concerned to find mild hepatosplenomegaly, and given the duration of the history performed some routine investigations, including EBV and CMV serology. He planned to refer him for urgent Haematological assessment, concerned about possible lymphoma. The EBV and CMV serology results were not consistent with recent infection. Given the clinical history, the laboratory physician arranged additional tests for *Toxoplasma*; the results were consistent with recent *Toxoplasma* infection (*Toxoplasma* IgM and IgG strongly reactive). The patient went on to make a full recovery over the next three months with no further intervention.

Lessons from this case
In this case recognition of the possibility by a laboratory-based physician and subsequent confirmation of Toxoplasma infection led to the avoidance of outpatient assessment and lymph node biopsy.

Toxoplasma infection is estimated to cause 3-7 percent of clinically significant lymphadenopathy [6] and is commonly confirmed by serology following lymph node biopsy with suggestive histology in such cases.

Discussion

As the above case histories illustrate, the interpretation of laboratory results in the clinical context by an expert laboratory-based physician makes a significant difference to clinical outcomes for individual patients [7].Laboratory-based physicians with discipline-specific specialist expertise are well placed to provide

expert clinical interpretation by virtue of comprehensive training in both clinical and laboratory aspects of diseases in their respective specialties.In some countries of the EU such as the UK this extends to laboratory-based physicians undertaking training in general internal medicine followed by specialty training in the relevant LM specialty (Immunology, Biochemistry, Haematology, Microbiology) thus providing the requisite competencies for combined laboratory and clinical practice as consultants.

The pressure for expert advice on test selection and interpretation of results is likely to grow as primary care physicians are called upon to provide care to patients with increasingly complex problems[8].Additionally, the drive to reduce medical error (from misinterpretation of test results) and contain costs are powerful reminders of the need for informed clinical interpretation of test results. Inappropriate test selection leading to further testing can not only exact a severe financial cost but also lead to exposure to unnecessary irradiation due to inappropriate imaging, as exemplified by the uncritical use of tumour markers[9] . Equally, inappropriate clinical decisions may be made in patients as a result of errorneous test results generated by interference by heterophilic antibodies in many routine immunoassays[10,11,12]. An example of the serious adverse consequences of misinterpretation of spuriously elevated serum human chorionic gonadotrophin (HCG) levels is the needless treatment of young women for 'occult' trophoblastic disease with chemotherapy and surgery[13]. Conversely, false-negative results may also have adverse clinical consequences due to inappropriate or delayed treatment as exemplified by erroneous thyroglobulin measurements due to interference by anti-thyroglobulin antibodies in patients with thyroid carcinoma[14]. In the current climate of economic austerity, it is essential that hospitals and commissioners of laboratory medicine services guard against the temptation that a results-only laboratory service would be adequate on the assumption that the requesting clinician is fully capable of interpreting any laboratory test. Although routine blood results such as blood counts,renal and hepatic function which fall in to the reference range will require little or no interpretation, the fallacy and clinical risks surrounding such a proposition are amply illustrated by the afore-mentioned case histories.

Audit designed to improve clinical outcomes is an essential function of a diagnostic laboratory. Physicians play a key role in designing and leading clinical audit projects to ensure appropriate test selection, minimise unnecessary testing[15] and validate gating policies for test utilisation.These initiatives form the basis for evidence-based demand management and enable clinical audit to be a powerful tool in improving patient management. For example, the use of a gating policy to ensure testing for anti-neutrophil cytoplasmic antibodies (ANCA) was restricted to patients with a high pre-test probability of ANCA-associated vasculitis[16] minimises the occurrence of false-positive ANCA and consequently, reduces the risk of AAV and instigation of inappropriate immunosuppressive treatment.

The concept of multi-disciplinary team meetings to devise optimal treatment and management plans for individual patients was originally devised for patients with solid organ cancer. Laboratory physicians, in this case histopathologists play a vital role not only in making an accurate diagnosis, but also in molecular typing to

enable selection of targeted treatment as exemplified by the use of Trastuzumab to treat breast cancers over-expressing the epidermal growth factor receptor. Similarly, in haematological malignancies, haematologists have integrated specialist knowledge of cancer with laboratory expertise in developing molecular diagnosis to enable targeted treatment with other therapeutic monoclonal antibodies and small molecule tyrosine kinase inhibitors.

In focusing on the role of physicians in the laboratory it is important not to overlook the vital role played by scientists in laboratory medicine. Although traditionally many scientists have concentrated on the detailed technical and operational aspects of laboratory medicine, many scientists have successfully undertaken leadership roles within LM, including the directorship of diagnostic laboratories, thus precluding the absolute need for a medical degree in fulfilling the responsibilities outlined in Table 1. However, a physician with a medical degree complemented by a solid grounding in general internal medicine and further sub-specialty training is better equipped to integrate and interpret laboratory results in the context of complex or unusual clinical case histories. Thus, whilst acknowledging the particular skills of scientists and physicians, it is important to emphasise the complementary roles fulfilled by these individuals in running clinically responsive diagnostic laboratory services.

The past two decades has seen traditional boundaries between individual LM disciplines being blurred by the ability to assay on a single platform an ever-increasing range of analytes, previously considered to be discipline-specific in biochemistry, haematology, immunology and microbiology. This has led to the emergence of blood science laboratories (core automated laboratories) enabling rapid-throughput of large numbers of samples. Whilst welcoming such technological advances it is essential not to overlook the importance of expert interpretation of test results emanating from these centralised facilities.Irrespective of the wide variations in the practice of LM across Europe, it is our hope that this paper has highlighted the crucial importance of continuing active physician involvement in clinical diagnostic laboratories.

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All patient case histories are anonymised or hypothetical.

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