What is clinical immunology?

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SUMMARY The clinical and laboratory details of 10 patients with predominantly immunological problems were circulated to selected physicians in different forms of hospital practice. In general, these physicians would prefer to select their own immunological tasks and could get these performed in their clinical pathology laboratories or regional immunology centres. Immunologists are seen predominantly as laboratory-based advisers rather than clinicians responsible for the care of such patients.

Immunology pervades the activities of most clinicians. This is scarcely surprising since so much human disease results from the failure to combat infectious agents or from allergic reactions to antigens in the form of drugs, chemicals, or simple flora and fauna. The importance of immunological mechanisms in the pathogenesis of disease is reflected in the context of prophylactic immunisation or the therapeutic manipulation of the immune response. These intellectual and practical considerations have provided the stimulus for establishing the new discipline of clinical immunology.

Traditionally clinical specialties have been organised according to the dictates of medical practice and, in general, physicians are classified according to their practical skills. Thus doctors with a penchant for investigating gastrointestinal complaints became recognised as gastroenterologists by their colleagues and learned to manipulate the instruments which transformed this specialty from one based on opinion to one based upon exact observation. Similarly, with the growth of medical science, diagnostic services were provided by laboratories with experience in the various branches of clinical pathology. Thus a logical system was devised whereby the patient's symptoms provide the first sign-post to the relevant clinical specialist and thereafter essential specimens are sent to the appropriate laboratory.

Advances in clinical sciences have complicated the operation of so simple a system. For example haematologists command a wide knowledge of clinical and laboratory practice. It is widely accepted

therefore that haematologists must have access to both beds and laboratory facilities so as to provide the best possible service for their patients. The dilemma facing immunologists is apparently similar to that of haematologists and they must find the best way in which increasing knowledge of immunological mechanisms in disease can be applied to the investigation and management of clinical problems. It is necessary, however, to make a firm distinction between academic immunology and immunology in clinical practice. The way in which T lymphocytes recognise antigens is a fundamental problem whose solution will have enormous therapeutic implications. This does not imply that a scientist investigating this problem should be integrated into institutions or teams dealing with clinical medicine. There may be circumstances in which the scientist investigating such fundamental problems is not only clinically qualified but also uses clinical material as the basis for much of his thinking and experimental work. This is not necessarily so and the situation is likely to arise only in academic centres.

There are two principal ways in which immunology affects clinical practice. The first arises when clinicians ask for immunological tests to manage a particular patient. Some immunological tests have now become so routine that the facilities to carry these out have long been provided. It is obviously essential that physicians should be able, for example, to order tests for detecting auto-antibodies and for measuring serum complement levels. However there are many other tests, such as assaying blood lymphocyte subpopulations, whose practical value has not yet been

firmly established. It is desirable for research purposes that in some centres provision be made for assessing the value of such immunological tests in adequate numbers of patients. However, hard pressed district general hospitals might reasonably take the line that, if only a relatively few such tests are indispensable for clinical management, these can readily be incorporated into the work of existing departments of clinical pathology and other tests referred to regional centres. Indeed the need for specialised regional immunological laboratories and their functions have been persuasively argued.^{1 2}

Secondly, immunological disturbances often produce major clinical problems whose solution demands specialised knowledge of immunology. Some hospitals, and particularly academic institutions, have created posts for clinical immunologists usually defined as physicians with specialised interests in a particular branch of clinical medicine and an active research programme, eg, rheumatology and renal medicine. Most hospitals could rightly retort that this is a luxury affordable only by research institutions and that the creation of a separate specialty of clinical immunology is artefactual. Over the years specialists in different branches of clinical medicine have accepted the need to incorporate many facets of basic biological sciences into their everyday practice. Immunology may count as an important one but other disciplines are at least as important and yet do not constantly lay claims to the establishment of a separate specialty. If modern clinical specialists can master immunology along with other basic sciences there is obviously less need for specialist immunologists with clinical responsibility. If difficulties arise concerning the interpretation of a modicum of immunological tests then the clinical pathologist with the most detailed interest in the immunological problem should hasten to the bedside in the manner of other clinical pathologists. Only in a few instances will the need to implement immunological techniques so dominate their clinical practice that clinicians will feel the need for a more formal association with immunologists.

Immunological methods have not been introduced into clinical practice in any systematic way. The manner in which immunological advances have been applied to clinical practice has been determined by the decisions of individual hospitals and clinicians. Thus the extent to which clinical immunology is a laboratory discipline, a clinical specialty in its own right, or a part of existing clinical specialties has been largely settled even while committees still debate these points. To obtain a complete picture of the solutions adopted throughout the United Kingdom would be a formidable task. The approach adopted in this survey was to ask a small number of

physicians to reveal how they handle immunological problems in their own practice. The results at least indicate what these physicians understand by the term clinical immunology.

Design of the study

We selected 10 immunological problems encountered at this centre in the 12 months preceding the survey. An immunological problem was defined as a disease in which immunological mechanisms were the most important factors in the pathogenesis of the disease and where the control of these processes was the principal therapeutic problem. Detailed descriptions of the history, clinical findings, conventional investigations, and specialised investigations of these patients were sent to representative physicians but details of immunological investigations were mainly omitted. The recipients were general physicians or physicians with a specialist interest. Physicians practising in London and provincial teaching hospitals, and in metropolitan and provincial district hospitals, were asked to participate. A note of explanation accompanied the case histories:

'What is clinical immunology? The definition of clinical immunology and the function of clinical immunologists have been extensively discussed and analysed. At one extreme much of internal medicine has been regarded as applied immunology. At the other extreme immunology has been considered to be not a clinical discipline but rather one of the many basic sciences important to clinicians practising in a variety of clinical specialties. We therefore decided to ask knowledgeable, practising physicians to say how they would have handled selected clinical problems with a strong immunological flavour.'

The note emphasised three problems: (1) which immunological tests the physicians would consider important in the practical management of these patients; (2) whether these physicians would interpret the results of the relevant immunological tests themselves or would seek specialised immunological advice; (3) who would have performed these tests in their own hospital.

Case histories

The following case reports outline the information sent to the physicians and the questions posed, in abbreviated form.

CASE 1 is a 26-year-old single, bank clerk. At the age of 20 she was investigated for secondary amenorrhoea. Investigations revealed small, hypoplastic

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ovaries. There was normal pituitary function with increased gonadotrophin production while oestrogen excretion never exceeded 0.02 nmol/litre of urine. Chromosome analysis showed a normal female karyotype. The diagnosis was ovarian failure.

Hashimoto's thyroiditis was also diagnosed at the age of 20 but the patient was clinically euthyroid. Her protein bound iodine was raised at 829 nmol/l and thyroid microsomal auto-antibodies were detected but thyroid function tests were otherwise normal.

Two years later she developed polyarthritis in the hands, knees, and feet. The principal laboratory findings were Hb 11.7 g/dl, WBC $6.5 \times 10^9/l$ with a normal differential, and ESR 72 mm/h. Latex test 1:1280. Erosive changes were present radiologically.

At 26 years of age she was admitted with a two months' history of weight loss, thirst, and polyuria. Heavy glycosuria confirmed the diagnosis of acute diabetes mellitus which was rapidly controlled with soluble insulin.

Questions

- (1) What additional immunological tests do you regard as essential for this patient's management?
- (2) Do recent advances in basic or applied immunology help you to understand the theoretical and practical problems surrounding this girl's diseases?
- (3) Do you believe that a clinical immunologist could contribute to her management?

CASE 2, a 37-year-old housewife, gave a history of rash on the face and exposed surfaces of the limbs made worse by exposure to sunlight for 3 years and painful red lumps on the legs, diffuse pain and tenderness in the limbs, and lethargy for 1 year. She admitted to dyspnoea and chest discomfort on mild exertion. There was no past history of allergies and the patient was not currently receiving drug treatment.

She showed a fixed erythematous scaling eruption in the butterfly distribution of the face with telangiectasia and follicular plugging. There was generalised muscle tenderness more marked over the proximal muscles. Joint abnormalities, vasculitic lesions, hair loss, or lymphadenopathy were not present.

Investigations revealed Hb 11.5 g/dl with normochromic, normocytic red cells, WBC $3.7 \times 10^9/l$, of which $1924/\mu l$ were granulocytes and $1517/\mu l$ lymphocytes, and ESR 40 mm. There were no biochemical abnormalities and no urinary abnormalities. The chest x-ray was normal. Lung function tests showed a reduction in TLco of 13.8 ml/min/mmHg against a predicted 28.0. During a six-month period of observation she suffered two attacks of severe abdominal pain and two grand mal fits with a normal EEG.

Questions

- (1) What laboratory investigations would you need to diagnose the nature and extent of her 'systemic lupus erythematosus'?
- (2) Which ancillary tests do you use to evaluate the extent of any systemic involvement?

CASE 3 is an 18-year-old girl with severe bronchial asthma since the age of 3. She has mild sneezing bouts during the hay fever season and has noticed that house-cleaning and exposure to dogs exacerbate her asthma. She developed eczema in infancy but this cleared spontaneously. There is no obvious social stress and her attacks are not precipitated by obvious infection. There is no family history of allergic disorders. She is a fit-looking girl with scattered expiratory crepitations but no other respiratory or general abnormalities and a peak flow rate 340 l/min.

Questions

- (1) This girl has mild bronchial asthma; would you attempt to look for specific allergies?
- (2) How would you do this?
- (3) Who would do the relevant tests?
- (4) Do you think the results are of academic interest or of practical value?

CASE 4 is a 13-year-old schoolgirl with eczema of varying severity since birth. It now involves the entire body including the scalp. She had a severe attack of bronchial asthma 3 years ago but has no other allergic disorders. There is no family history of allergic disorders. She is not exposed to pets but believes that eggs worsen the condition. Topical and systemic steroids have produced little improvement. Examination reveals eczema affecting the entire skin but no systemic abnormalities. The laboratory findings are Hb 13.4 g/dl, WBC $7.8 \times 10^9/l$; eosinophils $1326/\mu l$, ESR 2 mm and no biochemical abnormalities. The urine is normal and the stools contain neither ova nor parasites. However the serum IgE is consistently over 50 000 IU/ml (normal range 0-200 IU/ml).

Questions

- (1) Would you look for specific allergies?
- (2) How would you go about this task in terms of clinical and laboratory assessment?
- (3) Who do you think should undertake these investigations?

CASE 5 is a 32-year-old research virologist who presented with a 12-year history of recurrent skin lesions of the lower limbs of progressive severity

diagnosed by several dermatologists as intermediate between mycosis fungoides and cutaneous vasculitis. Histology shows superficial changes consistent with mycosis fungoides and vasculitis in the deep dermis. The patient is occupationally exposed to several pathogenic viruses but his illness preceded this exposure. He is in excellent general health. Physical examination is normal apart from the rash and in particular there is no superficial lymphadenopathy and the liver and spleen are not palpable. Investigations showed Hb 17.2 g/dl, WBC $10.4 \times 10^9/l$ with a normal differential count, ESR 10 mm, no biochemical abnormalities and normal immunoglobulin concentrations.

The total body scan is reported to show unequivocal, massive enlargement of the paravertebral lymph nodes. The surgeon's opinion is that a biopsy of an enlarged lymph node will involve laparotomy and he is not convinced that the lymph nodes are involved by neoplastic disease.

Questions

- (1) How would you investigate the nature and cause of this patient's vasculitis?
- (2) Do you consider the lymphadenopathy clinically relevant?
- (3) Do you believe that assays of 'lymphocyte markers' or investigations of immune function would help to decide whether lymph node biopsy is unavoidable?
- (4) Who would undertake the relevant investigations in your hospital if you thought these were necessary?

CASE 6 is a 50-year-old lady with hypogammaglobulinaemia. At the age of 7 she is said to have had developed 'nephritis' of three years' duration. At the age of 23 she developed eczema followed by 'thyrotoxicosis' which was treated with thiouracil. Her first pregnancy at the age of 28 was marked by unexplained anaemia. At 32 years of age she suffered an attack of severe right-sided herpes zoster ophthalmicus leading to corneal abscesses and generalised varicella; secondary staphylococcal skin sepsis ensued. Her blood counts were Hb not less than 15.0 g/dl, WBC $8.29 \times 10^9/l$, granulocyte count $3.12 \times 10^9/l$, and platelet count $30.40 \times 10^9/l$.

The following year she suffered repeated superficial skin infections and repeated bruising. Steroids were started at this time. At 34 years of age her spleen was removed and this was grossly enlarged. It showed hyperplasia but no evidence of lymphoma or malignant infiltration.

Her platelet count improved and was maintained at between 300 and $450 \times 10^9/l$. Steroids were withdrawn over the next 12 months. She subsequently developed staphylococcal pneumonia and

staphylococcal septicaemia following a perianal abscess.

In 1974, at the age of 46, hypogammaglobulinaemia was first suspected and diagnosed. Regular treatment with gamma globulin injections and steroids was started but the latter were discontinued after two years. There is no family history of immunodeficiency.

Her current admission was precipitated by 6 months' cough and sputum, watery diarrhoea, and increasing tiredness. She was receiving no medication apart from γ -globulin injections.

On examination there were scattered small bruises on the legs; coarse crepitations were heard at both lung bases. Investigations revealed an Hb of 8.3 g/dl falling to 6.8 g/dl over 2 weeks observation with a macrocytosis of 120 fl and a reticulocyte count of 21.5%. The WBC was $13.2 \times 10^9/l$ with a normal differential, and the platelet count $230 \times 10^9/l$. The direct Coombs test was positive with broad spectrum, anti-IgG, anti-IgM, anti-IgA, and anti-C3d reagents.

The bone marrow aspirate showed increased cellularity with erythroid hyperplasia, normal granulopoiesis, plentiful megakaryocytes, and no excess of lymphocytes. The serum immunoglobulin concentrations were IgG 1.9 g/l, IgA 0.1 g/l, and IgM 0.3 g/l. There were no other biochemical abnormalities and there was no evidence of malabsorption. Chest x-ray, sputum culture, MSU blood cultures, and stool cultures produced no evidence of significant infection.

Questions

- (1) What further investigations do you think appropriate for elucidating the nature of her hypogammaglobulinaemia and haemolytic anaemia?
- (2) Who do you think should manage this patient's problems in the short and long term assuming that gamma globulin would be made available for whoever undertook this responsibility?
- (3) If you accepted this responsibility yourself, how would you manage her haemolytic anaemia and her immunodeficiency?

CASE 7 is a 21-year-old woman who developed tenosynovitis 18 months ago. The arthritis spread over the next 12 months and has been progressively disabling.

In the past 6 months she has suffered sore throats, recurrent mouth ulcers, intermittent fever, and worsening lethargy. She has also noted recurrent pleuritic pain and dyspnoea on exertion. She has lost 10 kg weight in the past 2 months. She has received various non-steroidal anti-inflammatory drugs, short courses of gold, and penicillamine.

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She was pale, underweight, and febrile (39°C) with generalised firm lymphadenopathy. There was minimal symmetrical soft tissue swelling of small joints in the hands and feet.

There was no rash or vasculitic lesions. Systemic examination was normal save that fine inspiratory crackles were heard at both lung bases.

Investigations revealed a normochromic, normocytic anaemia, Hb 8.2 g/dl, WBC $4.5 \times 10^9/l$, with granulocytes $2621/\mu l$ and lymphocytes $1428/\mu l$, platelets $295 \times 10^9/l$ and ESR 131 mm. The blood urea was 8.1 mmol/l, electrolytes normal, albumin 25 g/l, total globulin 38 g/l, and serum iron 6 $\mu mol/l$.

No other biochemical abnormalities were noted. Renal disease was indicated by 10×10^6 leucocytes and 160×10^6 RBC/l urine, 5.1 g proteinuria/24 h and a reduced GFR 55 ml/min. Creatinine clearance was normal and the urine was sterile. The direct Coombs test was negative. The serum IgG concentration was raised at 21.1 g/l but other immunoglobulin concentrations were normal. Total haemolytic complement was reduced at 1 in 2, as was the C3, 24 mg/100 ml and C4, 4 mg/100 ml. Antinuclear antibody was detected at a titre of 1/1280; precipitating antibodies to DNA and ENA and C1q binding material were readily detectable.

The chest x-ray showed minor left lower lobe consolidation, and lung function tests showed severely impaired lung capacity, flow rate, and gas exchange.

Questions

We would all accept that this girl is suffering from systemic lupus erythematosus.

- (1) Who should look after her, a rheumatologist, nephrologist, general physician, other specialist, or a combination of specialists?
- (2) If there was a 'clinical immunologist' on the staff of your hospital would you rely on him or her for advice, for total management, or would you dispense with their services?
- (3) How would you treat this patient (given that all possibilities were open to you including plasmapheresis)?
- (4) If you were solely responsible for her management, which laboratory tests would you regard as essential for controlling her disease activity and her drug treatment?
- (5) Which department in your hospital would undertake these tests?

CASE 8 is a 60-year-old man presenting with a nephrotic syndrome. Three months beforehand he suffered a severe attack of 'influenza' with a productive cough. Thereafter he became progressively more lethargic. For the past month he has noticed swelling of the lower limbs. He has not received any medica-

tion in the year preceding admission and there is no history of allergies. There is a family history of ichthyosis.

The patient was euthyroid, with congenital ichthyosis and oedema of the lower limbs as far as the mid-abdomen. There were no cardiovascular or respiratory tract abnormalities. BP 140/80 mmHg. There was obvious ascites, but the liver and spleen were not palpable and there were no abnormal masses. Investigations showed Hb 13.6 g/dl, WBC $6.3 \times 10^9/l$, platelets $575 \times 10^9/l$, ESR 106 mm/h, blood urea 1.9 mmol/l, serum creatinine 115 mmol/l, albumin 15.0 g/l, globulin 26.0 g/l. Liver function tests, thyroid function tests, and immunoglobulins were normal. The IVP showed poor contrast but was otherwise normal. Proteinuria consistently exceeded 5.0 g/24 h and was non-selective. The renal biopsy showed some mesangial thickening but no other abnormalities by light microscopy. Chest x-ray, ECG, and lung function tests were unremarkable. There was no significant increase in anti-viral antibody titres or anti-streptolysin O titre. The VDRL and WR were negative. The clinical diagnosis was 'minimal change nephrotic syndrome'.

Questions

- (1) What contribution has 'clinical immunology' to make to elucidating the cause and deciding the management of this patient's disease?
- (2) If you decided that complement studies, for example, were necessary and that the renal biopsy should also be examined by immunofluorescence and electron microscopy, who would undertake these investigations and interpret the results?

CASE 9 is a 48-year-old female white physician born in Portugal, with Raynaud's phenomenon since age 42. Two years later she developed epigastric pain while working in Rio de Janeiro, and over the next two years the symptoms worsened with progressive dysphagia. For the last year of this period she suffered recurrent chest infections.

At the age of 46 hiatus hernia repair was attempted. Forty-eight hours postoperatively she developed pulmonary embolism of both lungs. She was treated with anticoagulants and improved clinically. However in the next four weeks the dyspnoea returned; the heart size increased radiologically with a pericardial effusion. Her dyspnoea continued and her PO_2 did not rise above 60 mmHg while breathing room air. Right heart catheterisation revealed pulmonary arterial hypertension but no evidence of pericardial tamponade or constriction. On admission one month later to Northwick Park Hospital there was no change in her condition. The patient was naturally dark-skinned with areas of hyper- and

hypo-pigmentation. Striae and maculopapular lesions suggested lichen sclerosus et atrophicus or morphea to the dermatologist.

There was congestive cardiac failure with pulmonary hypertension. Haematological investigations were normal and there were no biochemical abnormalities of note. Serum immunoglobulin concentrations were normal. There were no renal abnormalities. Scales from the skin lesions on the fingers grew epidermophyton floccosum. Skin biopsy showed lichen sclerosus et atrophicus. Lung function tests showed a severe diffusion defect.

Questions

The two most important diagnoses considered during this admission were systemic sclerosis and thromboembolic disease with pulmonary hypertension. She has been seen by general physicians, rheumatologists, and dermatologists. Do you think that a 'clinical immunologist' would help to clarify the problem and what would you expect of this person?

CASE 10 is a 70-year-old retired carpenter. His illness began at the age of 58 as a mixed motor and sensory neuropathy of all four limbs. There have been no systemic symptoms of note. There is no past medical or family history of significance. He has worked exclusively in the house-building industry and has had no obvious exposure to toxins or heavy metals. He had received no regular drug treatment before the start of this illness and denies taking any unauthorised medication. He smoked heavily up to 1974 (120 cigarettes daily) but has drunk alcohol sparingly.

All abnormalities were confined to the central nervous system. There was no intellectual deterioration and the cranial nerves were intact. There was symmetrical weakness and wasting of the muscles in both the upper and lower limbs, more marked distally. There was sensory impairment affecting all modalities in the same distribution as the motor changes. The clinical diagnosis was a chronic demyelinating polyneuropathy. Investigations showed Hb 16.2 g/dl with normal red cell indices, WBC $9 \times 10^9/l$, with a normal differential, ESR 27 mm and total serum globulin 33 g/l, IgG 7.4 g/l, IgA 1.9 g/l, IgM 7.2 g/l.

Other biochemical tests, serum B_{12} and folate concentrations were normal. The WR and VDRL were negative in the blood and CSF; no excessive porphyrinuria was detected. Bone x-rays and scans were normal, and a computerised body scan showed no evidence of a neoplasm. The only CSF abnormality was an increase of protein (1.75 g/l). An EMG showed severely impaired conduction in the

right median and right ulnar nerves, and a sural nerve biopsy revealed severe demyelinating changes without inflammatory reaction or infiltration.

Questions

The only clue to the aetiology of this polyneuropathy is the high serum IgM concentration.

- (1) Is this clue worth pursuing?
- (2) Who should do the pursuing?
- (3) Are such results of practical importance?
- (4) Do you recognise a sub-specialty termed 'neuro-immunology'? If you knew of a 'neuroimmunologist' would you seek his/her advice?

Results

The results of enquiry are summarised in Table 1 and the outcome of the clinical problems in Table 2. The results allow some provisional conclusions to be drawn. All 5 physicians had clear ideas about which investigations they thought necessary from their own knowledge and experience. In some instances their appraisal of current immunological practice would lead to firm action. Thus all 5 physicians were prepared to search for specific allergens in patient 3 with bronchial asthma, and only one of the five was not prepared to embark on a similar exercise in patient 4 with intractable eczema. All the respondents had personal preferences for certain tests when investigating patients with inflammatory connective tissue diseases rather than adopting the complete gamut of available tests. This was reflected by differing predilections for complement determination, measurement of circulating immune complexes, or various autoantibody assays in patient 2 with suspected systemic lupus erythematosus. Similarly there was no blanket request for immunological tests to monitor the progress of patient 7 with obvious systemic lupus erythematosus. It was also evident that the physicians had adopted an informed but cautious attitude towards other tests. There was little enthusiasm for assaying blood lymphocyte populations in patient 5 with a suspected lymphoma, or autoantibodies in patient 9 in whom the clinical arguments in favour of diagnosing systemic sclerosis or thromboembolic disease were finely balanced.

Their informed attitude towards immunological tests was reflected in firm ideas about clinical responsibility. There was a strong preference for leaving such responsibility in the hands of traditionally trained specialists. Thus no one was prepared to delegate the care of patient 1 with multiple endocrine problems to a clinical immunologist whatever that person's claims to understand the abstrusities of genetic susceptibility to these diseases. Similarly no one believed that a clinical immunologist was more

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Table 1 Summary of replies to questionnaire

Questions	1 London Teaching Hospital	2 Provincial Teaching Hospital	3 Scottish Teaching Hospital	4 Provincial District Hospital (A)	5 Provincial District Hospital (B)
Case 1 (endocrine)					
(1) essential immunological tests	none	antibody and cell-mediated immune reactions to endocrine autoantigens	none	autoantibodies	autoantibodies
(2) immunology's contribution	theoretical only	theoretical and practical helpful but ancillary	theoretical only	theoretical only	none
(3) clinical immunologist relevant?	no		no	no	no
Case 2 (SLE)					
(1) essential immunological tests	autoantibodies complement, immunoglobulins	complement autoantibodies, immune complexes	anti-nuclear antibodies	autoantibodies, complement, immunoglobulins	autoantibodies, complement
(2) systemic screen	skin biopsy	skin, lung biopsy	skin biopsy	skin and renal biopsies. O ₂ brain scan	possible renal, lung or muscle biopsy
Case 3 (bronchial asthma)					
(1) search for allergens	yes	yes	yes	yes	yes
(2) methods	history; prick tests	history; prick tests provocation tests	skin tests	IgE, prick tests; RASTs	skin tests
(3) responsibility for tests	technician	chest physician	respiratory unit technician	IgE: biochemical lab. prick tests: clinic nurse. RASTs: regional immunology laboratory	chest physician
(4) practical value	yes	yes	yes	yes	yes
Case 4 (eczema)					
(1) search for allergies	yes	no	yes	yes	yes
(2) methodology	diary card, prick tests exclusion diet	doubtful relevance	take advice from immunology laboratory	RAST tests for food allergens, exclusion diet	prick tests; RASTs exclusion diet
(3) responsibility for tests	physician	dermatologist	immunology laboratory	commercial laboratory for RAST tests	physician
Case 5 (vasculitis)					
(1) investigations	blood lymphocyte populations	immune complexes	biopsy of lymph node	autoantibodies	drug history
(2) significance of lymphadenopathy	yes	yes	await histology	dubious	yes
(3) lymphocyte analysis helpful?	possibly	yes	no	no	doubtful value
(4) responsibility for tests	oncologist and oncology laboratory	regional immunology laboratory	lymph node to histopathology	regional immunology laboratory	regional immunology laboratory
Case 6 (immunodeficiency)					
(1) investigations	lymphocyte populations, red cell survival	drug history, exclude thymoma	uncertain	autoantibodies, lymphocyte populations, complement, small bowel studies	lymphangiogram; autoantibodies, lymphocyte populations
(2) clinical responsibility	any competent clinician	clinical haematologist	clinical haematologist	clinical haematologist	general physician
(3) treatment	γ-globulin-antibiotics	γ-globulin; antibiotics, steroids	uncertain	γ-globulin, steroids	γ-globulin, steroids
Case 7 (SLE)					
(1) clinical responsibility	physician with help of nephrologist	nephrologist	any one of those specialists with advice from others	one physician	general physician
(2) role of clinical immunologist	irrelevant	advisory	advisory	advisory	advisory; possibly for overall responsibility
(3) treatment	steroids, azathioprine-anti-coagulants?	steroids—possibly cytotoxics and plasmaphoresis renal function; complement; DNA-bindings	steroids and azathioprine	steroids, cytotoxics—possibly plasmaphoresis	steroids, plasmaphoresis
(4) essential tests	blood count, ESR	immune complexes biochemistry; regional immunology laboratories	ANA; DNA-binding antibody	Ig, complement, ANA, DNA-binding antibody, ESR, acute phase proteins	DNA-binding antibody complement
(5) laboratory responsibility	clinical pathology		immunopathology laboratory	biochemistry and regional immunology laboratories	regional immunology laboratory

(contd)

Table 1 (contd)

Questions	1 London Teaching Hospital	2 Provincial Teaching Hospital	3 Scottish Teaching Hospital	4 Provincial District Hospital (A)	5 Provincial District Hospital (B)
Case 8 (nephrotic syndrome)					
(1) immunological contribution	autoantibodies; immunofluorescence studies of biopsy	complement, immunofluorescence studies of biopsy	complement, immunofluorescence studies of biopsy	general physician requests complement, immunofluorescence studies of biopsy	complement, immune complexes, immunofluorescence studies of biopsy
(2) laboratory responsibility	histopathology	nephrologist; immunopathologist	immunopathology laboratory	hospital and regional immunology laboratories	renal immunopathologist
Case 9 (scleroderma?)					
(1) immunological contribution	autoantibodies, inc. latex, ENA	autoantibodies, immunofluorescence studies of skin biopsy	none	characterise any anti-nuclear antibodies, immunofluorescence studies of skin biopsy	autoantibodies, complement
Case 10 (polyneuropathy)					
(1) high IgM	yes—exclude macroglobulinaemia	yes	yes	possibly	yes
(2) clinical responsibility	physician or neurologist	neurologist and clinical immunologist	immunopathologist	physician or clinical haematologist	renal immunology laboratory
(3) practical importance	yes as guide to treatment	yes as guide to treatment	imponderable	yes, to characterise primary disease	yes
(4) contribution of neuroimmunology	doesn't exist	doesn't exist, alas	immunologically informed neurologist	doesn't exist, alas	doesn't exist, alas

Table 2 Outcome of clinical problems described in questionnaire

Case 1:	<i>Hashimoto's thyroiditis, secondary amenorrhoea, rheumatoid arthritis and diabetes mellitus</i> Apart from documenting the presence of organ-specific auto-antibodies, we have thrown no fresh light on this girl's disease.
Case 2:	<i>Rash, painful limbs, and tiredness</i> The serum showed no haemolytic complement activity but a normal C 3 concentration. The suspicion of C 2 deficiency was confirmed by Dr David Brown (New Addenbrooke's Hospital, Cambridge). She has atypical connective tissue disease associated with C 2 deficiency; her C 2 deficiency is not familial.
Case 3:	<i>Bronchial asthma</i> The patient is highly sensitive to house-dust mite (established by Dr Tom Platts-Mills) and is responding to allergen-exclusion.
Case 4:	<i>Eczema</i> This girl is highly sensitive to house-dust mite and other allergens (established by Dr Tom Platts-Mills) and is responding to allergen-exclusion.
Case 5:	<i>Cutaneous vasculitis</i> Circulating immune complexes were detected but neither auto-antibodies nor abnormal proteins were present and the complement system was normal. Blood lymphocyte populations were normal judged by markers and in vitro function and no monoclonal lymphocyte population was detected. No enlarged lymph nodes were found at laparotomy.
Case 6:	<i>Immunodeficiency</i> The patient has adult, late-onset hypogammaglobulinaemia. No gastrointestinal lesion or infection was found to account for her diarrhoea. She responded to treatment with antibiotics, steroids and maintenance injections of γ -globulin.
Case 7:	<i>Systemic lupus erythematosus</i> Treatment with high dose steroids, azathioprine, and anti-lymphocyte globulin has induced a remission.
Case 8:	<i>Nephrotic syndrome</i> No immunological abnormalities were found in the blood. The renal biopsy showed immune complex deposits in the glomeruli by immunofluorescence and electron-microscopy. Three months later the first radiological evidence appeared of carcinoma of the bronchus and this diagnosis has been confirmed histologically.
Case 9:	<i>Cardiopulmonary disease</i> Circulating immune complexes, rheumatoid factor and precipitating serum antibodies to extractable nuclear antigens were detected in high titre and these changes were associated with a marked reduction in circulating T lymphocytes. These abnormalities are consistent with systemic sclerosis but we do not consider them diagnostic.
Case 10:	<i>Polyneuropathy</i> The patient has a kappa paraprotein which is weakly auto-reactive with myelin. He is being treated with plasmaphoresis and cytotoxic drugs but so far without apparent benefit.

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qualified than a physician or a clinical haematologist to look after case 6 with immunodeficiency. There was a similar reluctance to accept that a clinical immunologist should undertake the management of patients with systemic lupus erythematosus, undeniably the queen of immunological disturbances. Attitudes towards the care of case 10 with polyneuropathy were also conservative; three of the five physicians felt that a competent neurologist should be able to master any additional complexities immunology might add to that already formidably intellectual discipline.

Finally these physicians would be able to get these tests carried out although the practical arrangements would be different in each hospital. The majority of the tests considered necessary in patients 3 and 4 with disorders of immediate hypersensitivity would be carried out by the physicians themselves and the remainder in their clinical pathology laboratories. However in many hospitals radioallergosorbent tests (RASTs) are sent to commercial laboratories. The immunological tests in patient 5 with vasculitis, patient 7 with systemic lupus erythematosus, patient 8 with the nephrotic syndrome, and patient 10 with a polyneuropathy, would be widely distributed among existing laboratories of clinical pathology and laboratories more specifically devoted to immunology. It is noteworthy that the tests undertaken by immunological laboratories are almost exclusively serological procedures involving the detection of autoantibodies, complement measurement, and the handling of biopsies, rather than the less well established procedures involving lymphocyte function. Indeed the one specific request that blood lymphocyte populations should be investigated in patient 5 with vasculitis is the responsibility of the department of oncology in the hospital concerned.

Nevertheless all five physicians welcomed the establishment of specialised laboratories of immunology and immunopathology and would seek the advice that the consultant staff at such laboratories could give with more complicated problems. Recourse to this kind of assistance was reflected particularly in those problems which are less commonly encountered in recognised clinical specialties. Thus three of the five would use the services of their regional immunology laboratory in investigating the problems of patient 5 with vasculitis. There would be a similar dependence on the opinion of a specialist immunopathologist in interpreting the renal biopsy in patient 8 with the nephrotic syndrome, and indeed immunofluorescence studies were considered an essential part of evaluating such biopsies. Although there was less unanimity of opinion with respect to the more unfamiliar problems of patient 6 with immunodeficiency complicated by haemolytic anaemia, all

but one of the clinicians would seek the advice of a neuroimmunopathologist in investigating patient 10 with polyneuropathy if such a specialist were available.

Discussion

This study suggests that physicians accept the responsibility for mastering those aspects of immunology which are relevant to their clinical interests. Their insight into such immunopathological mechanisms as immediate hypersensitivity reactions and immune complex deposition means that they do not depend on immunologists for managing diseases such as chronic eczema, bronchial asthma, and systemic lupus erythematosus. Moreover they express precise preferences for immunological tests rather than simply reiterating a list of all the possible tests that have been advocated. Indeed immunologists may wryly conclude that the many symposia and textbooks devoted to teaching immunology to clinicians have been too successful.

There are few situations in which physicians see the need for transferring clinical responsibility to immunologists in the way that particular patients come under the care of recognised medical specialists. There are complicated problems of the kind included in this questionnaire for whose solution immunologists' opinions are welcomed. Almost invariably these relate to the choice of relevant tests, the interpretation of the results, and their practical application. Immunologists are seen to act in an advisory capacity, and their specialised contribution is concerned primarily with directing the laboratory investigations.

All the hospitals concerned have made provision for carrying out a limited number of essential immunological tests. These are predominantly serological or involve the analysis of biopsy material. There was little indication that clinicians see the need for those tests of lymphocyte function which loom so largely in the thoughts of academic immunologists when they consider clinical problems. There is obviously much local variation in the way specific tests are allocated to different laboratories: complement levels, for example, are measured by the biochemistry laboratory in some hospitals and by the regional immunopathology centre in others. However it is likely that most immunological tests are performed in regional immunology centres.

This survey therefore leaves the strong impression that clinicians regard immunology as a form of clinical practice based on the laboratory and its consultant staff. This is supported by the most recent analysis³ which lists immunopathology as a recognised specialty: there are 35 consultants in this

specialty constituting nearly 3% of the 1259 specialists in the different branches of general and clinical pathology. Moreover immunopathology is now a recognised subject for the membership examination of the Royal College of Pathologists. Conversely clinical immunology is not listed as a medical specialty in the 1980 report, and the Royal College of Physicians has only this year⁴ announced its intention of laying down a training programme in clinical immunology as part of specialist training in general medicine.

There are obvious clinical advantages if physicians are familiar with those immunological advances which affect their own specialty. Similarly it is more economical and convenient if existing departments of clinical pathology incorporate standard immunological techniques in their working programmes. On the other hand our ability to analyse and control immunopathological events will only improve if specialised immunopathology laboratories are largely responsible for immunological tests. Such laboratories are in a better position to test and exploit improved techniques in collaboration with research laboratories. The diagnosis of C2 deficiency in patient 2 illustrates this point.

As methods for immunological intervention become more sophisticated it is also conceivable that their application to medicine will need the services of clinicians exclusively engaged in this task. This will certainly be the case in academic centres, for example, in the context of regulating undesirable immune reactions with appropriate antisera to antigens on abnormal B lymphocyte populations or to

the idiotypes these cells express. At present however clinical practice is almost exclusively organised in terms of diagnosing and treating patients attending traditional specialist clinics. Patients with allergy attributable to disorders of immediate hypersensitivity are perhaps the only group whose clinical problems can be defined almost entirely in immunological terms. Unhappily allergy is a subject which fails to appear in the list of clinical specialties recognised by the Department of Health and Social Security.

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