useful tests on the basis of general availability and diagnostic discrimination are serum T3, T4, TSH, and technetium thyroid scanning. In a prospective study on 55 patients with suspected hyperthyroidism serum T3 was raised in all 46 toxic patients, T4 was raised in 83%, T3:uptake ratio raised in 78%, and two-stage (uptake $\times$ T4) FTI raised in 76%. A variety of kits measure T4 followed by a single stage or 'sequential FTI' which correlates well with free T4 concentration. However, in a trial on 100 patients the two-stage FTI was slightly superior to both the Ames Thyrolute sequential FTI or T4 alone (Howorth *et al*, 1975). Eight of 17 patients with solitary autonomous 'hot' nodules, as defined by scanning, were toxic with raised T3; five had a normal T4. Nine were euthyroid with normal T3 and T4. Patients receiving carbimazole for hyperthyroidism had normal or slightly low T4 and elevated T3 and TSH when euthyroid and very low T4, normal T3, and markedly elevated TSH when clinically hypothyroid. Euthyroid patients after therapy usually had normal T4 and TSH with minimally raised T3. Relapse occurred in 13 of 22 patients followed up for one year after carbimazole therapy. T3 measurements gave the earliest warning of relapse but T4 was adequate for routine follow-up since relapse was preceded by an elevated T4 (8 cases) or accompanied by it (3 cases). Biochemical hyperthyroidism preceded clinically apparent relapse for 12 weeks on average.

Red cell zinc and the zinc-metalloenzymes are promising tests of the peripheral metabolic effect of thyroid hormone. Red cell zinc and carbonic anhydrase B level fall in hyperthyroidism but a marked elevation in glyceraldehyde - 3 - phosphate dehydrogenase activity, which catalyzes the formation of 1:3 diphosphoglycerate, has been reported (Pangaro *et al*, 1974). 2:3 Diphosphoglycerate, an important regulator of oxygen delivery to the tissues, is formed from 1:3 diphosphoglycerate and is elevated in hyperthyroidism (Miller *et al*, 1970).

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- Models of immune complex diseases and the role of antibody affinity**
- M. W. STEWARD (*Immunology Division, The Mathilda and Terence Kennedy Institute of Rheumatology, London*) Several experimental models of human immune complex disease are currently being studied and can be classified into three main types: (a) those in which non-replicating antigens, such as serum proteins, are injected into animals to induce either an acute or chronic disease; (b) those in which the injection of replicating antigens, ie, viruses, are used to induce immune complex disease in susceptible hosts; and (c) spontaneously occurring immune complex diseases of animals. The extent to which the study of these models has contributed to the understanding of the immunopathology of immune complex disease will be discussed. Discussion will also focus on the factors which affect the formation and clearance or deposition of immune complexes with particular reference to the role of antibody affinity in these processes.
- Systemic lupus erythematosus and rheumatoid arthritis**
- G. R. V. HUGHES (*Department of Rheumatology, Royal Postgraduate Medical School, Hammersmith*) In both RA and SLE evidence for immune complex mechanisms is abundant. In RA, they are principally detectable within the synovial space and adjacent cartilage (measurement of synovial fluid complement levels is one of the few useful early diagnostic tests in RA), while in SLE circulating complexes as well as tissue-bound deposits are more frequent.
- However, despite the strong evidence obtained from immunofluorescence and elution studies, a number of questions remain unanswered. In RA, the factors concerned — genetic, antibody, affinity, chemical mediators, and rheumatoid factor—which result in the marked localization of complexes are not clearly defined.
- In SLE, despite the strong evidence for DNA—anti-DNA complex involvement, the relative roles of other complexes such as denatured DNA—anti-d-DNA, lymphocytotoxins—'shed' lymphocyte antigen, RNA—anti-RNA virus-antivirus etc, as well as the reasons for varying disease

patterns (eg, CNS or renal lupus) are unclear.

Recently, detailed serial studies were carried out over a four-year period in this unit on 38 patients with SLE. As well as the usual markers of disease activity including DNA-binding and haemolytic complement CH_{50} determinations, evidence for circulating complexes was regularly sought by electron microscopy, Clq precipitation, anticomplementary activity, and DNAase digestion of serum.

Clq precipitins were detectable in 22 out of 56 SLE patients and correlated poorly with disease activity. Anticomplementary activity was detected in 44 of 150 sera from 19 patients. Positive results correlated well with disease activity but were not confined to patients with renal disease.

DNAase digestion, suggested as a method for the detection of DNA—antibody DNA complexes, was significantly positive in only one patient, a child with aggressive renal lupus, in whom low MW complexes were detected. This technique may depend on antibody affinity and has major drawbacks.

The factors currently known to affect disease pattern and activity in SLE and RA are discussed.

Hepatitis B, immune complexes, and the pathogenesis of polyarteritis nodosa

A. J. ZUCKERMAN (*Department of Virology, School of Hygiene and Tropical Medicine, London*) Early studies have suggested that hepatitis B antigen immune complexes may play an aetiological role in the pathogenesis of some cases of polyarteritis nodosa. In collaboration with Trepo, Prince, and Bird (Trepo *et al*, 1977), Zuckerman, (1975) sera from 55 patients with histologically confirmed polyarteritis nodosa were tested for hepatitis B surface antigen and surface antibody by sensitive techniques. The surface antigen was detected by radioimmunoassay in 54.5% of the patients and there was an approximately equal distribution of subtypes av and ay . Surface antibody was found by passive haemagglutination in 28% of the patients. Overall, 69% of the patients had either antigen or antibody in their serum and 11% had had both.

Circulating immune complexes were found by electron microscopy in eight out of 27 patients, but no correlation was found between clinical and laboratory indicators of activity of polyarteritis and detection of circulating immune complexes.

Seroconversion or the presence of anti-

body alone was associated with a better prognosis. The observation that the titre of antigen may fall during exacerbation of the illness and that clinical improvement may coincide with disappearance of antigen and appearance of antibody is compatible with the hypothesis of an immune complex mechanism for the pathogenesis of polyarteritis nodosa. Such a mechanism is also suggested by analogy with much of the symptomatology, including arthralgia, myalgia, urticaria, and glomerulonephritis, and the characteristic features of human or experimental serum sickness.

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Mechanisms of immune complex induced nephritis

J. G. P. Sissons (*Department of Medicine, Royal Postgraduate Medical School, Hammersmith*) The particular susceptibility of the kidney to involvement by circulating immune complexes (IC) results, at least in part, from its anatomical structure with high intracapillary pressure and blood flow; reduction of renal blood flow reduces IC deposition. However, the recent claim for a specific receptor for C3b in the human glomerulus suggests another potential mechanism of IC localization. Local release of vasoactive amines from platelets (Gelfand *et al*, 1975), brought about by the release of a platelet activating factor from basophils, increases glomerular basement membrane permeability and is one determinant of IC localization in experimental nephritis.

The mediation of allergic glomerular injury has been studied mainly in experimental acute IC nephritis and nephrotoxic serum nephritis. In the acute IC model, glomerular injury can occur independently of C and polymorphonuclear leucocytes (PMN) (Henson and Cochrane, 1971). In the chronic IC model defibrination or massive heparinization prevents crescent formation (Thomson *et al*, 1975) but the role of C and PMN have not been assessed. However, in the nephrotoxic serum model PMN-mediated damage can occur independently of C⁴, possibly because PMN have an Fc receptor.

The size and rate of deposition of IC

appear to determine the histological pattern of nephritis in experimental models, and morphological variations in human nephritis may occur on a similar basis.

It has been postulated that relative immunodeficiency may predispose to the development of spontaneous IC disease (Alpers *et al*, 1972; Peters and Lachmann, 1974). There is no direct evidence for this in human nephritis, except perhaps in rare patients with genetic C deficiencies. In the majority of patients with isolated nephritis of presumed IC aetiology definite antigens and circulating IC can still not be identified, making more logical approaches to therapy difficult.

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Enzyme defects in mucopolysaccharidoses

I. C. BARNES AND C. A. PENNOCK (*Department of Chemical Pathology, Bristol Royal Infirmary, Bristol*) The mucopolysaccharidoses are a group of inherited connective tissue disorders in which excessive cellular accumulation and urinary excretion of glycosaminoglycans (GAG) occur. They are now recognized as disorders of GAG degradation affecting metabolism of heparan sulphate, dermatan sulphate, and keratan sulphate. In the past three years all of the enzymes which are either absent or show diminished activity have been identified. Types I H (Hurler) and I S (Scheie) are deficient in α -L-iduronidase; type II (Hunter) in dermatan sulphate sulphatase; type III (Sanfilippo) subtype a in heparan sulphamidase, and subtype b

in N - acetyl - α - D - glucosaminidase; type IV (Morquio) in N-acetyl-hexosamine - 6 - sulphate sulphatase, type VI (Maroteaux-Lamy) in N - acetylgalactosamine-4-sulphate sulphatase, and type VII in β -glucuronidase.

The importance of these recent discoveries is that definitive diagnosis may be achieved, antenatal diagnosis is now available, and enzyme replacement therapy is possible. However, a number of practical difficulties may be encountered when the enzymes are assayed, especially on cultured amniotic fluid cells or cultured fibroblasts. Most of the enzymes require a natural substrate which may be difficult to purify, or a suitable artificial substrate which may be difficult to synthesize.

Advantages of the 'blind simulated clinical' specimen in quality control in microbiology

W. A. BLACK AND SUE DORSE (*Department of Microbiology, University Hospital, Ontario, Canada*) The use of recognizable 'specimens' either in the form of lyophilized cultures or simulated clinical specimens is suitable for measuring the best performance of a laboratory in bacterial identification and antibiotic sensitivity testing. It may also be the only technique which is feasible when the participating laboratories are spread over a large geographic area. However, the test conditions are abnormal, and this method of control gives little indication to the laboratory director of the real quality of work in his laboratory.

Our regional programme compared data retrieved from 'blind, simulated clinical' specimens and lyophilized specimens using the same organisms in each specimen type. Six surveys were carried out over two years with an average of six simulated 'specimens' per survey, usually two 'urines', two 'faeces', and two 'pus swabs'. These specimens were introduced surreptitiously into the 17-20 participating laboratories. To arrange this properly involved about 1000 miles of travel per survey. Major quantitative and qualitative differences in performance with simulated and lyophilized test specimens were noted. In particular, whereas the putative origin of the specimen did not affect performance with the lyophilized specimens, it played a major role in performance with the simulated specimens, showing for the latter deteriorating performance in the order faeces > pus > urine. Bacterial identification was noticeably better with lyophilized specimens where this depen-