the same patient were consistent when repeated. In comparison with the macrophages in Hodgkin's disease, those in sarcoma showed significantly more multinucleated forms and the maximum number of nuclei seen in a single cell was higher. In a single patient with lymphosarcoma, macrophage mitosis was noted, but has not been found in any other patient even when colcemid has been applied locally.

These changes may suggest a disordered cellular response.

**Serum Creatine Phosphokinase Changes in Psychotic Illness**

G. OWEN, R. GOSLING, AND R. J. KERRY (Northern General Hospital, Sheffield)

Increased serum creatine phosphokinase (CPK) levels have been reported in acutely psychotic patients. This study examined the proportion of psychotic and non-psychotic patients showing raised serum CPK activity. This occurred in about half of the patients with psychotic illnesses but was absent in the non-psychotic patients. Raised serum CPK was significantly associated with second order factor score patterns on the Inpatient Multiphasic Psychiatric Scale (IMPS) suggesting that mania and paranoid schizophrenia were more involved with this enzyme change than depression and non-paranoid schizophrnesia.

Raised serum CPK suggests that psychotic illness may be present. If a patient is found to have an increased level of CPK, in the absence of organic illness, further psychiatric investigation is required. Increased CPK activity may precede the clinical manifestations of the psychotic illness by a few days. This has been seen in the symptom-free outpatients with a raised CPK who have been admitted to hospital a few days later with acute psychotic illness. Creatine phosphokinase estimation would appear to be a worthwhile screening procedure for both inpatients and outpatients. Patients with raised CPK need continued psychiatric supervision.

**The Incidence of Syphilis in Thailand**

P. SONGHAPRASERT, B. RUNGPIRANGSI, AND S. PHANSOMBOON (Siriraj Hospital, Bangkok, Thailand)

Serological investigations for syphilis, carried out on specimens collected as a routine from Bangkok hospital outpatients, gave positive results in 7.1% of cases. This suggests the high incidence of syphilis of 7100 per 100000 population.

**Management of Cases of Myelomatosis**

E. WILSHAW (Royal Marsden Hospital, London)

The malignant proliferation of plasma cells exposes a patient to certain hazards which must be dealt with adequately if he is to benefit from any remission achieved by chemotherapy.

**Bone Lesions**

Solitary filling defects are best treated with large doses of radiotherapy with a view to cure. Large osteolytic areas in limbs should be supported by pinning since recalcification of myelomatosis lesions is very rare. Paraplegia must be treated early, preferably by laminectomy followed by radiotherapy. Hypercalcemia is treated with prednisone and neutral phosphate together with alkylating agents. Patients should be mobilized as soon as possible.

**Paraprotein Production**

Hyperviscosity can be alleviated temporarily by plasmapheresis while giving time for the alkylating agents to reduce the mass of myeloma. Amyloid deposition is irreversible but the carpul tunnel syndrome can be relieved by surgical excision of the retinaculum.

**Bone Marrow Function**

The ability to make normal numbers of erythrocytes, leucocytes, and platelets can be restored by alkylating agents provided that the treatment is given persistently. Rises in haemoglobin may be seen only when treatment has been given for a year.

**Factors of Prognostic Significance in Myelomatosis**

R. PETO (Radcliffe Infirmary, Oxford)

In 1964 the MRC initiated a clinical trial which compared two protocols for the treatment of myelomatosis. Nearly 300 patients were notified by 1968, and by 1971 all these patients had been at risk for at least three years. Because the protocols proved therapeutically identical, this series was ideal for assessing the influence on subsequent prognosis of the initial condition of a myelomatosis patient. Features such as hypercalcemia, which are corrected by the MRC protocol, do not appear in this series to influence prognosis. Conversely, renal failure is irrelevant to the neoplastic disease but, being irreversible by the MRC protocols, dominates prognosis so strongly that a patient presenting with a blood urea above 80 mg/100 ml is likely to be dead within two months, whereas one presenting with a blood urea below 40 mg/100 ml is likely to live over three years. To study the actual myeloma we therefore need to find what, given the effect of renal failure on prognosis, is the effect on prognosis of the various biochemical, histological, haematological, and radiological measurements made in the MRC trial as the patients were notified. We found to our surprise that although many measurements were abnormal, few of these abnormalities mattered. None of the radiological, histological, haematological (other than anaemia), or biochemical (other than hypoalbuminaemia) measurements mattered at all (except insofar as they correlated with renal failure), and the series is so large that this is quite a definite conclusion. We do not really know why anaemia matters. Perhaps it is a measure of marrow displacement, but then why do low platelet or neutrophil counts not matter at all? We have still less idea why hypoalbuminaemia matters. In experimental animals, some tumours can concentrate labelled albumin in them and cause hypoalbuminaemia, so perhaps the more active myelomas catabolise circulating albumin.

**The Clinical Significance of Bence Jones Proteinuria**

H. MCLAUGHLIN (Westminster Hospital Medical School, London)

Bence Jones protein is monoclonal light chain, found in the urine because of its low molecular weight (22 000). Monoclonality is demonstrated by cellulose acetate electrophoresis of concentrated urine in parallel with serum. Immunoelectrophoresis will identify the type of L chain involved. Free light chain will react with its corresponding antiserum across 3 mm agar within two hours, light chain bound to serum takes three hours, and that bound to IgM eight to 12 hours.

Concentration of urine up to ×300 is essential to exclude low levels of Bence Jones protein and this is best done by vacuum dialysis in collodion thimbles of urine, initially passed through 1·0 μ and 0·2μ filters to remove bacteria. The Table shows the results when this technique was used in 1159 cases of various disorders.
The Emergence of New Tumour Lines during Therapy
J. R. Hobbs (Westminster Hospital Medical School, London)

During the relapse from an initial response to treatment with cyclophosphamide or melphan, evidence that their tumour had 'changed its spots' was found in 45% of 155 patients in the first MRC myeloma trial. These changes all seemed to evolve a tumour with a faster growth rate and this occurred either alone, growth rate escape (2%), or with other changes: Bence Jones escape 1 (32+3%) was seen as a disproportionate increase in Bence Jones proteinuria relevant to the initial proportions of Bence Jones to whole protein and in a few patients Bence Jones appeared where it had not formerly been detected in urine concentrated 300 times (de novo 3%). Mutation escape 1 (5%) was the emergence of a new paraprotein closely related (eg, one amino acid difference) to the parent one: non-paraprotein escape 2 (3%) was seen as terminal reticulo-sarcoma with very little paraprotein, but enough to relate the primitive tumour to the initial myeloma. In this series monocytic leukaemia 3 has not yet been seen.

All these new lines emerged mostly two to five years after treatment and have rarely been witnessed in the natural history of the disease. Successful prolongation of life could have allowed a natural tumour progression to show, but if the treatment, which acts by altering DNA, may have induced mutants, the most prolific of which are seen in the relapse. This explanation could also apply in patients given immunosuppressive therapy for renal transplants. Cytotoxic drugs are best reserved for otherwise fatal diseases.

References

Fibrin in the Kidney in Myelomatosis
A. Milford Ward and F. E. Preston (The Children's Hospital, Sheffield)

Renal involvement in myelomatosis is a frequent occurrence both as a mode of presentation and as a cause of death. The nature of the renal involvement is varied but the precise mechanism by which renal failure occurs is obscure. Attention has recently been focused on the role of fibrin in the development of renal lesions, in both the experimental and clinical situations. The deposition of fibrin has been shown in the renal glomeruli in proliferative glomerulonephritis but not in membranous glomerulonephritis or in the nonproliferative phases of the nephrotic syndrome. This correlation of fibrin with proliferation has been confirmed in the experimental model. We have conducted a retrospective study of the renal histology in a necropsy series of 32 cases of myelomatosis. Intravascular fibrin was demonstrated within the glomeruli of more than one third of the cases and this was usually associated with proliferation of the mesangium. The presence of intravascular fibrin and mesangial proliferation was not associated with any particular immunoglobulin abnormality or with the presence or concentration of Bence Jones proteinuria. In addition to fibrin within the glomerular capillaries, fibrin was also demonstrated in intertubular capillaries in three cases of myelomatosis with acute tubular necrosis.

Although the precise significance of the presence of fibrin within the renal glomerulus in myelomatosis is obscure, we believe that it may be of importance in the pathogenesis of the renal dysfunction which occurs in myelomatosis, and that this merits further study.

Production of Lymphomata following Intrapleural Inoculation of Silica
Margaret M. F. Wagner and J. C. Wagner (Pneumocystis Research Unit, Penarth)

Crystalline silica was injected into the right pleural cavity of Wistar rats at 6-10 weeks of age. Alkaline-washed quartz, less than 5μ in size, was used. Approximately 37% developed tumours belonging to the reticulosarcoma group, whilst another third had an altered or hyperplastic reaction. Very few tumours have been reported previously following exposure of various animals to silica by other routes. The distribution of the tumours was from 300 to 1 000 days in a spread out fashion. They were mainly found in the medastinum and on the diaphragm, as were the benign silicotic nodules. The majority of tumours were believed to be malignant histiocytoses, although some malignant lymphomas with a predominant lymphoblast or mature lymphocyte were found. A few spindle cell sarcomas were also found.

In order to study the development of these tumours, rats were killed at five-week intervals after intrapleural injection of silica. The distribution of the dust was noted and it was found to reach the tracheo-bronchial lymph nodes and the region of the thymus. Eventually it entered the thymus. The thymus appeared to be involved in the tumours: likewise silica and tumour tissue was also, but not always, found in the spleen, liver, and occasional abdominal lymph nodes.

Rats have also been given intraperitoneal coal and carbon, but no tumours have developed. Three different types of silica have been used, and tumours have developed with all three types when given by this route. However, when the silica was given intravenously and intraperitoneally, tumours were not found.

Two Cases of Haemangioepicytoma Arising in the Uterus
Hilda R. Harris (Maerol General Hospital, Wrexham)

The first case occurred in a woman aged 39 years, who for three months had