TABLE IV—SIGNIFICANT PHYSICAL CONDITIONS APPARENTLY COINCIDENTAL TO PSYCHIATRIC ILLNESS

Physical condition	No. of patients
Respiratory system:	
? Active pulmonary tuberculosis (2); chronic bronchitis (3); upper-respiratory-tract infections (4)	9
Alimentary system:	
Dental conditions (8); peptic-ulcer symptoms (2); hæmorrhoids (2)	12
Cardiovascular system:	
Symptomless mitral incompetence (1); auricular fibrillation (1); hypertension (2)	4
Orthopædic conditions:	
Fractured ankle; prolapsed intervertebral disc; fractured jaw	3
Gout	1
Idiopathic hypercholesterolæmia	1
Severe varicose veins and varicose eczema	1
Ophthalmic conditions (excluding errors of refraction) ..	1
Iron-deficiency anæmia	2
Total	34 (*16*%)

Of the remaining patients, 69 (34%) were found to have, or developed whilst in hospital, physical illnesses which required attention or further investigation. 18 (9%) of these had multiple physical abnormalities. The physical conditions are detailed in tables II–IV, and the terms concomitant, consecutive, and coincidental may be respectively employed.

Table III shows that 9 patients (4%) developed presumably iatrogenic conditions whilst having modern drug therapy. 3 of these had venous thrombosis of the legs whilst receiving phenelzine, and 1 also had a small pulmonary embolism. None of them was particularly debilitated, or confined to bed, before the thrombosis occurred, though 2 had minor varicose veins. I have not seen another report of this complication of phenelzine therapy.

Discussion

Many patients in whom their own doctors have found no physical abnormality are being referred to the psychiatric outpatient clinics instead of to medical outpatient clinics. Greater vigilance is therefore required on the part of psychiatrists to avoid labelling physical, and potentially treatable, disease as " functional ".

Comroe (1936) was one of the first to become aware of this situation; he found that of 100 patients in a general medical clinic with the diagnosis of neurosis, 24% developed organic disease within 8 months, and in many of these it was present when the original diagnosis was made. Meyer (1958), in a general review of the relation of psychiatry to surgery, has emphasised that because symptoms arise in the midst of an emotional crisis the possibility of organic disease is not excluded. This is further borne out by cases 5, 6, and 7 of the present study, in which a spurious psychogenesis had been attributed to real physical illness. The likelihood of such a mistake will be considerably lessened if one remembers that neurotic reactions are rare in patients of mature years with good previous personalities and no past history of similar episodes.

Cases 1–3, 6, 10, and 11 all showed organic mental syndromes; of these, cases 1, 3, and 6 in particular complained a priori of none of the usual symptoms, but of more nebulous things like depression and listlessness. Organic symptoms should be specifically looked for and inquired after, and the scheme for examination put forward by Mayer-Gross (1954), with particular care in testing for orientation, memory, attention and adaptability, lability of mood, and use of numbers, can be applied simply and quickly in all cases.

A psychiatric opinion is often requested after patients have been " through the mill " in other special departments, and therefore the physical states which may be found are uncommon or atypical. For example, Eilenberg and Scobie (1960) have emphasised the tendency to misinterpret the symptoms of acute porphyria as hysterical.

Finally, the need for a full physical examination of every psychiatric case, irrespective of whether the patient has been referred from another doctor or hospital, is self-evident but often forgotten, as is well illustrated by cases 6 and 10. Furthermore, the full use of all ancillary diagnostic aids is essential. Every patient admitted to this unit has a routine urine examination, chest X-ray, blood-count, erythrocyte-sedimentation rate, and Wassermann reaction. Many important physical conditions would have been missed without.

Summary

The physical disorders amongst 209 psychiatric inpatients have been analysed.

In 5% major physical illness, first discovered on admission to a psychiatric unit, was the principal diagnosis. In 21% physical conditions contributed to the onset of psychiatric illness, in 8% they resulted from it, and in 16% they were unrelated to it.

The dangers of imputing a spurious psychogenesis, and of overlooking organic mental syndromes, must be avoided.

A full physical examination, with radiological and pathological investigation if indicated, is important.

I am grateful to Dr. Desmond Curran, Sir Paul Mallinson, and Dr. Maurice Partridge for permission to study and report on their cases, and to Dr. Curran in particular for much helpful advice and encouragement.

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CYTOMEGALIC INCLUSION DISEASE AND PNEUMOCYSTIS CARINII INFECTION IN AN ADULT

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CYTOMEGALIC inclusion disease is a viral infection which has been recognised in infants for some years (Farber and Wolbach 1932, Wyatt et al. 1950, Seifert 1954, Nelson and Wyatt 1959). It may be localised to the salivary glands, when it is usually found incidentally at necropsy, or it may be a severe, sometimes fatal, generalised illness (Worth and Howard 1950). In adults, cytomegalic inclusion disease is rare and takes a different form. It may be confined to a single organ in association with other diseases, notably those of the reticuloendothelial system (Hamperl 1956). In a more generalised form, it is often accompanied by other systemic diseases (Fisher and Davis 1958).

Pneumocystis carinii is thought to be a protozoon and was first alleged to be responsible for interstitial plasma-cell pneumonia of infants by Vaněk and Jírovec (1952).

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This disease was initially recognised in central Europe (Rossle 1923, 1928, Ammich 1938). Later, cases were reported from Scandinavia (Linell 1949, Gormsen 1950), Great Britain (Baar 1955), North America (Lunseth et al. 1955), and Australia (Reye and ten Seldam 1956). An association between this condition and cytomegalic inclusion disease has been observed in infants (Dittrich and Seifert 1953, Baar 1955, Berdnikoff 1959). This form of combined infection appears to be extremely rare in adults (Hamperl 1956, Symmers 1960).

Clinical Report

A man, aged 25, was admitted in April, 1959. For two years he had had chronic gingivitis which improved temporarily after gingivectomy in November, 1958. Throughout 1958, he had had variable non-irritant lesions on the skin of his back and shoulders. He attended elsewhere for dermatological advice during this time; the diagnoses included neurodermatitis, eczema, and tinea; and he was treated with X rays, local hydrocortisone (1% cream), and chlortetracycline (1% cream).

His general health was good until December, 1958; he then gradually developed breathlessness on exertion, nocturnal sweats, anorexia, loss of weight, tiredness, and fever. He had a cough, producing mucopurulent sputum with a few scanty hæmoptyses. He had had slight pruritus ani for some years, and had hæmorrhoids which bled occasionally. In February, 1959, a painful, indolent anal fissure developed, and gradually extended backwards and forwards from the anal margin. This enlarging ulcer had a shallow edge and a deep centre. In April, 1959, a small papule appeared in one nostril. The papule ulcerated and slowly increased in size.

He was wasted, febrile, and ill. There was moderate generalised gingivitis. A few scaly brownish lesions were seen on the skin of his back and shoulders. There was no enlargement of lymph-nodes, and no abnormalities were found in the cardiovascular system (blood-pressure 120/75 mm. Hg), lungs, abdomen, or central nervous system. The anal ulcer extended 3 in. in the natal cleft behind the anus and 1 in. anteriorly; it was covered by a purulent exudate. A small papule was seen at the tip of the left nostril.

Investigations

The hæmoglobin ranged from 94 to 108% (13·9–16·0 g. per 100 ml.) and the white-cell count from 7300 to 10,800 per c.mm. (the differential count was normal). His erythrocyte-sedimentation rate was also normal (2 to 8 mm. in the first hour) except during an attack of bacterial pneumonia when it rose to 30 mm. The serum-albumin was between 3·3 and 4·5 g. per 100 ml., falling to 2·1 g. on Aug. 20, 1959. The serum-globulin was between 2·3 and 2·4 g. per 100 ml.

Serial chest radiographs showed fine nodular opacities throughout both lungs, with partial clearing after the administration of steroid drugs. The sputum was examined many times; acid-fast bacilli were not seen and all cultures for *Mycobacterium tuberculosis* were negative. The Mantoux test was negative at a strength of 1/10. The fæces contained no pathogenic organisms, and swabs from the anal fissure showed debris and gram-negative bacilli; culture produced a growth of *Bacillus proteus* and a coliform organism. Blood-cultures were repeatedly sterile. The Wassermann reaction and the Kveim test were both negative. Examination of the sternal marrow showed a nucleated-cell count of 178,000 per c.mm. There was generalised hyperplasia of all normal elements and plasma cells were present. Tissue was taken for microscopic examination from the anal and nasal lesions, and a scalene node was also removed. The anal lesion consisted of a non-specific granulomatous ulcer; the nasal lesion was ulcerated, granulomatous, and densely infiltrated with polymorphonuclear leucocytes and lymphocytes; there were no eosinophils or vascular damage. The scalene node showed some reactive hyperplasia but was otherwise normal.

Progress and Treatment

An initial diagnosis of miliary tuberculosis was made in view of his high fever, severe constitutional symptoms, and the radiological findings. He was treated with streptomycin 1 g. daily, isoniazid 100 mg. twice daily, and *p*-aminosalicylate 6 g. twice daily for twelve weeks. There was no response to treatment and, because of the negative reaction to tuberculin, the diagnosis was abandoned. Other diagnoses which were considered included sarcoidosis, the reticuloses, and Wegener's granulomatosis. After two months, prednisone 10 mg. three times daily was added to the antituberculous regimen. This produced a temporary improvement in his symptoms; the pyrexia subsided for several weeks, his appetite improved, and he gained weight. The anal lesion, however, had progressed remorselessly to involve a wide area of his buttocks, extending several inches on each side of the natal cleft (fig. 1a). The nasal lesion broke down into a chronic ulcer which eroded the nasal cartilages and spread to the lip (fig. 1b). An indolent paronychia of the left index finger developed. In the last month of life, fresh ulcers appeared on the dorsum of the tongue and the lower lip. Local radiotherapy was given to the ulcerated areas, but without any convincing benefit. Three weeks before

Fig. 1a—Perianal ulceration.

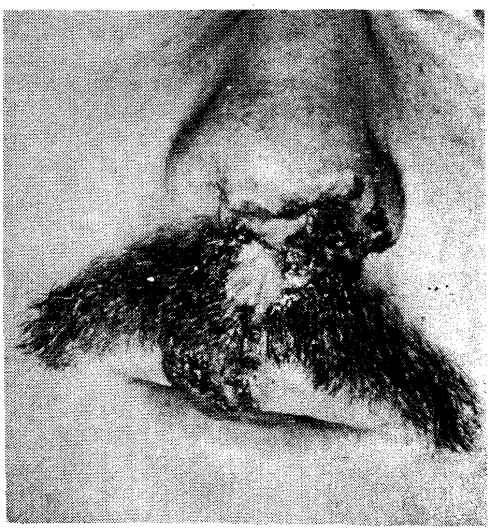

Fig. 1b—Ulcer of nose spreading to upper lip.

death he had severe bronchopneumonia which partially responded to treatment with erythromycin 500 mg. six-hourly, and chloramphenicol 500 mg. six-hourly for ten days; but he steadily became weaker, dying some four and a half months after admission. Latterly there was central cyanosis with increasing tachypnœa and early clubbing of the fingers.

Postmortem Appearances

External

The body was severely emaciated. The epidermis lying between the nasolabial folds was largely desquamated from an underlying smooth, moist dermal surface. The perianal ulcer, its base covered by serofibrinous exudate, extended over the buttocks with an ill-defined, undermined edge. The nasal and finger lesions were similar, though smaller. Numerous small lesions, some pustular, others dry and encrusted, were distributed irregularly over the skin of the thorax, abdominal wall, scapular regions, and inner aspects of thighs.

Internal

The lining membranes of the nose, mouth, pharynx, and larynx were ulcerated and covered with purulent exudate; ulcerated plaques were present on the dorsum and lateral margins of the tongue. The trachea was congested and contained a little mucopus, but was not ulcerated.

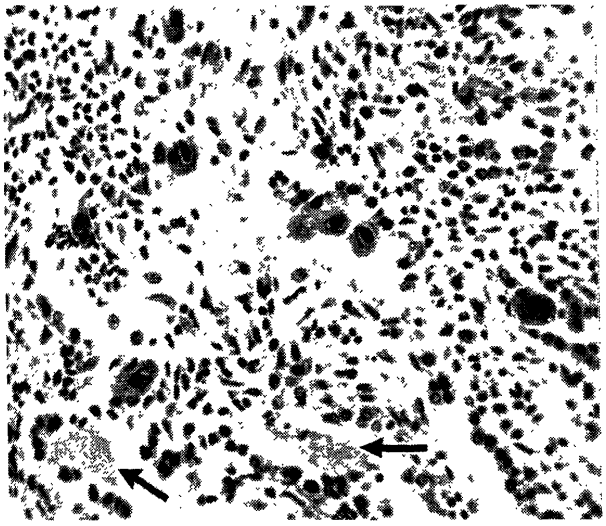

Fig. 2—Lung showing interstitial pneumonia and cytomegaly with inclusions. Aggregates of pneumocystis lie in alveoli (arrows). (Hæmatoxylin and eosin. ×230.)

Lungs.—In the right lung (weight 485 g.): the lower lobe was partially collapsed; there was extensive fibrinous exudate over the diaphragmatic and lateral pleural surfaces associated with an empyema (about 250 ml.) from which coagulase-positive *Staphylococcus aureus* was later cultured. Section of the lung showed a uniform grey-white consolidation of all lobes with a hæmorrhagic zone adjacent to the empyema. Bronchi at the base contained small quantities of mucopus; the remaining bronchi contained mucoid material only. The pulmonary arterial tree was normal.

The left lung (weight 480 g.) was of firm consistence; its cut surface showed extensive areas of grey-white consolidation sharply defined from limited areas of aerated tissue. Small quantities of mucoid material were present, mainly in the bronchi of the lower lobe. The main pulmonary arteries appeared normal. The hilar and mediastinal lymph-nodes were moderately enlarged and rather fleshy, with foci of carbon pigmentation.

Other organs.—The pericardial sac contained approximately 7 ml. of brown-stained fluid and showed a slight fibrinous exudate over the apex.

The spleen (210 g.) was moderately enlarged and soft. The liver (1950 g.) was enlarged and rather flabby, with a pale cut surface, showing occasional hæmorrhagic foci. The lobular pattern was maintained.

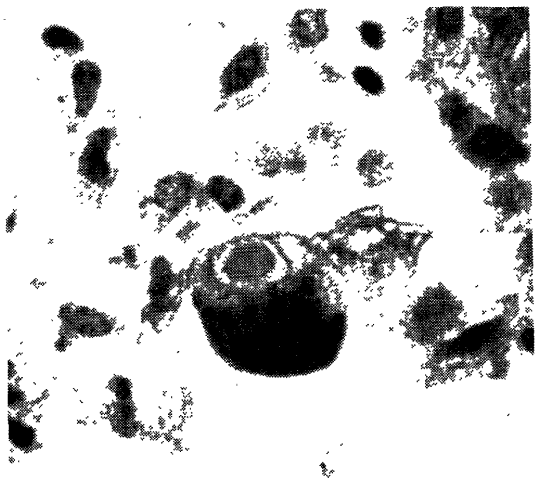

Fig. 3—Lung. Cytomegalic inclusion cell showing typical intranuclear and intracytoplasmic inclusions. (Giemsa. ×700.)

The only lesion seen in serial sections of the brain was a solitary, pale brown, circumscribed focus 0·5 cm. in diameter situated in the cortical grey matter of the left parietal lobe.

Histological Examinations

The lungs showed a fairly generalised, bilateral interstitial pneumonia. The alveolar septa were thickened and infiltrated, mainly by small lymphocytes and, to a lesser extent, by plasma-cells. The alveolar lining epithelium was cubical in many areas and frequently shed into the alveolar lumina which contained numerous lipid-laden phagocytes. Large cells, typical of cytomegalic inclusion disease, were present in all lung fields, being particularly striking in some areas (fig. 2). The intranuclear inclusions were strongly basophilic; they stained red or red-brown in phloxine-tartrazine preparations and blue with Mallory's phosphotungstic-acid/hæmatoxylin. Between the intranuclear inclusion masses and the nuclear membrane, which often showed margination of nuclear chromatin, there was in most instances a clear halo. Within the cytoplasm there were clusters of small inclusions, shown well in Giemsa preparations as small blue bodies (fig. 3). Scattered irregularly throughout the lungs, sometimes densely, were honeycomb masses of light-refracting bodies, characteristic of the cysts of *Pneumocystis carinii*. These masses reacted strongly to periodic-acid/Schiff and to the methenamine silver stain of Gomori, and with a lesser intensity, to the Weigert-Gram (fig. 4) and Gridley stains (1953). Some of the cysts contained four or eight distinct spores; others

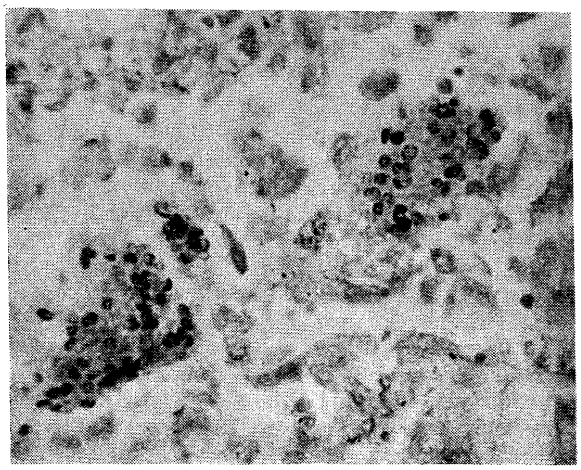

Fig. 4—Lung. Clusters of pneumocystis cysts containing spores. (Weigert/Gram. ×480.)

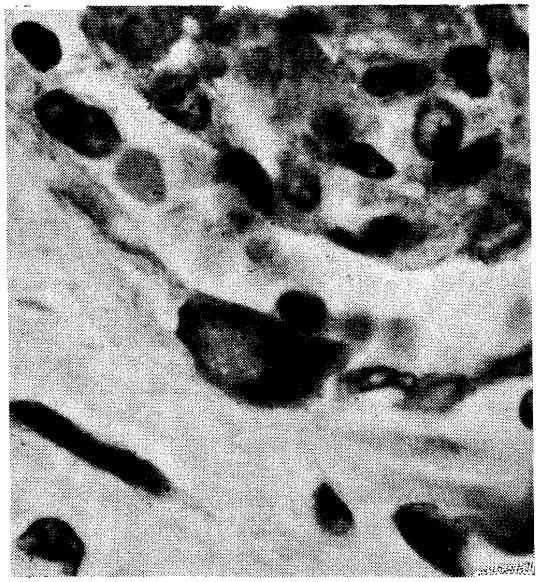

Fig. 5—Skin lesions. Capillary in granulation tissue showing inclusions in nuclei and cytoplasm of endothelial cell. (H. & E. ×870.)

appeared degenerate and void of spores. Occasional spores or spore-bearing cysts were located with the alveolar septa.

The Skin Lesions

The lesions around the mouth and in the perianal region were non-specific granulomatous ulcers. Secondary infection contributed to most of the lesions in the mouth or pharynx. A careful search failed to show evidence of parasitic and fungal infection in these sites. In the circumoral and perianal lesions, and in the ulcerated plaques on the tongue, intranuclear inclusions were found in some of the cells (presumably endothelial) lining, or in close relation to, the lumina of the capillaries of the granulation tissue (fig. 5).

Elsewhere, the smaller skin lesions consisted of encrusted, non-specific superficial ulcers, or small intradermal abscesses. Occasional small, herpetiform vesicles occurred in the hypertrophic squamous epithelium of the tongue.

The cellular focus of the brain lesion consisted of astrocytic cells with granular nuclei, oligodendrocytes, microglial cells, and a few surviving neurones in a rather vascular stroma. Search for both inclusion bodies and protozoa proved negative, although unusual amounts of extracellular granular material positive to periodic-acid/Schiff were present. The nature of this lesion is uncertain; the histological appearances suggest either an early astrocytoma, though in an unusual site, or alternatively a hamartomatous glial nodule.

Discussion

The initial clinical diagnoses were tuberculosis or a reticulosis. The outstanding features at this time were the severe constitutional symptoms and fever, out of keeping with the relatively slight clinical findings; the major lesion was the already advanced anal ulcer. Tuberculosis was excluded by the negative Mantoux test, failure to isolate any organisms, and failure to respond to appropriate treatment. A reticulosis seemed unlikely in view of the biopsy reports. Sarcoidosis was considered but later progress and the results of the investigations did not support this diagnosis.

The progressive extension of the nasal ulcer finally suggested the diagnosis of Wegener's granulomatosis; the general features, together with the ulceration, appeared typical of this condition (Walton 1958), though there was no involvement of the kidneys. Anal ulceration, as seen in our patient, does not appear to have been described, though the case of Short (1957) had shallow necrotic ulcers over the buttocks. Wegener's granulomatosis was the presumptive clinical diagnosis at the time of death.

From the pathological point of view, the main interest lay in the lung and skin lesions. Histologically there was no evidence of Wegener's granulomatosis. The main pulmonary lesion was a severe interstitial pneumonia associated with cytomegalic inclusion disease and a patchy pneumocystis infection. The patchiness of this infection and the pulmonary macrophage response indicated some degree of resistance on the part of the host, whose death was finally hastened by a terminal staphylococcal pneumonia and empyema. This is in contrast to the overwhelming pulmonary protozoal infections encountered in the majority of infants suffering from pneumocystosis.

The possibility of Behçet's disease was rejected because of the distribution and progressive nature of the skin lesions, together with absence of eye and joint symptoms, and central nervous system lesions (France et al. 1951, Curth 1952). The only specific features of the lesions in the skin were the presence of intranuclear and intracytoplasmic inclusions in the endothelial cells of related capillaries. These are an accepted feature of cytomegalic inclusion disease in its generalised form (Symmers 1960). Hartz and van de Stadt (1943) described similar inclusions in the capillaries in a biopsy specimen from a pedunculated anal tumour in a 35-year old coloured woman.

Generalised cytomegalic inclusion disease in the adult has been described in association with toxoplasmosis and myeloid metaplasia (Hemsath and Pinkerton 1956), myeloid leukæmia (Fisher and Davis 1958), and with *Pneumocystis carinii* infection and severe systemic diseases (Symmers 1960). In our case, if one accepts the staphylococcal lung infection as a terminal event, no severe underlying disease was found, the small brain lesion being regarded as fortuitous. Although agammaglobulinæmia or hypogammaglobulinæmia could not be excluded on the data available, the normal total serum-protein levels and abundance of plasma-cells in the bone-marrow and tissues make this unlikely. Steroid therapy, however, probably contributed to a decreased host resistance in this case, thus encouraging extension of the infections, and possibly allowing these saprophytic organisms to adopt a pathogenic role. This possibility has been demonstrated with a wide variety of bacteria, viruses, protozoa, and fungi (Kass and Finland 1953).

The pattern of generalised cytomegalic inclusion disease may vary, but the lungs, adrenals, liver, spleen, and kidneys are most commonly involved. Lesions varying from early degenerative changes to frank cellular necrosis have been described in these organs. The view advanced by von Glahn and Pappenheimer (1925) that this is a viral disease has been confirmed by the recent experimental work of Smith (1956) which also supported the probable species-specificity of the virus. Nor is the virus purely epitheliotrophic—for example, Vogel (1958) found specific inclusions in fibroblasts, heart-muscle cells, and mesothelial and endothelial cells, in a 10-year-old boy dying from the disease. He also successfully reproduced comparable endothelial inclusions in the capillaries of experimental granulomata in mice inoculated with mouse inclusion virus.

The association with *Pneumocystis carinii* infection was of further interest. This form of alleged protozoal infection has now become an established pædiatric hazard with a predilection for premature, debilitated, or

congenitally afflicted infants (Vaněk and Jírovec 1952, Hamperl 1952, Herzberg et al. 1952), but it has very rarely been found in adults. Isolated adult cases have been reported, associated with other concurrent diseases (Meer and Brug 1942 Jírovec and Vaněk 1955), whilst Hamperl (1956) demonstrated the infection in a case of fatal inclusion pneumonitis reported by McMillan (1947) and suggested the probability in two similar cases of Wyatt et al. (1953). Simultaneous pneumocystis and cytomegalic inclusion infections have also been described by Berdnikoff (1959) in an infant. The association of these two apparently separate and normally saprophytic infections is interesting, and perhaps not entirely fortuitous, especially since the nature of the pneumocystis organism has not yet been determined. In due course a closer relationship may be established. It is important to recognise their potential pathogenicity and their ability to produce, either alone or in combination, fatal infections in man.

There is some evidence that this danger is increased by prolonged treatment with steroids and antibiotics (Symmers 1960). Possibly more cases will occur because of the increasing use of these drugs. At present, there is no effective treatment.

Summary

A fatal case of combined cytomegalic inclusion disease and *Pneumocystis carinii* infection is described in a man aged 25. The main clinical features were a long-continued and progressive oronasal and perianal ulceration with severe constitutional disturbance, followed by increasing pulmonary distress ending in bronchopneumonia and empyema.

At necropsy, the main lesions were restricted to the lungs and skin; they included extensive grey-white consolidation of both lungs associated with staphylococcal empyema, severe ulceration in and around the mouth and in the perianal region, together with more generalised ulceration of the skin. Histologically the pulmonary lesion proved to be a severe interstitial pneumonia associated with cytomegalic inclusion disease and *Pneumocystis carinii* infection. The skin lesions were explicable in terms of giant-cell inclusion disease.

Very rarely both infections described have been found together in adults in association with serious underlying diseases; no underlying disease was identified in this patient. The nature of the infections is discussed and reference is made to the risk of converting these saprophytes into pathogenic organisms by prolonged treatment with steroid drugs and antibiotics.

We are grateful to Dr. C. S. D. Don for permission to publish this case; to Prof. A. C. P. Campbell and Prof. H. Hamperl (Bonn) for help in preparation; and to Mr. N. Mowat and Mr. G. Saville for technical assistance.

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PSEUDOTUMOUR OF THE ORBIT AND WEGENER'S GRANULOMA

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THE clinical condition known as " pseudotumour of the orbit " is a well-recognised, though relatively rare, lesion. Its cause is unknown, but recent work suggests that it belongs to the group of diseases which show chronic inflammatory reaction to a non-bacterial agent. This group includes polyarteritis and Wegener's granuloma (Walton 1956a and b, 1958). Duke-Elder (1952) describes orbital pseudotumours as " cases which are difficult to differentiate clinically from an orbital tumour, but which, on pathological investigation or by their resolution under treatment, are shown to be granulomata of chronic inflammatory origin ".

Our case was diagnosed clinically and histologically as pseudotumour of the orbit. At necropsy the condition was found to be Wegener's granuloma, an ulcerative, granulomatous lesion primarily involving the respiratory tract; and, in this case, with secondary involvement of the orbital tissue from the nasal sinuses.

Several fatal cases of Wegener's granuloma of the mouth and nose have been seen in Cumberland during the past thirty years, three of which were published by Walton (1956b), who subdivides the condition into three types: (1) associated with polyarteritis; (2) typical malignant granuloma usually involving the upper respiratory tract, and, though not histologically malignant, invariably fatal; and (3) granuloma gangrænescus—a histologically malignant sarcomatous lesion associated with extensive local destruction.

In our patient a granulomatous lesion, initially involving the orbit and ethmoidal sinus, eventually spread to the skull bones and cranial cavity. Later the lungs became involved, with cavitation and a purulent sputum. The disease progressed steadily, and proved fatal in two years. At postmortem examination, polyarteritis was found, with ischæmic necrosis and scarring of the kidneys.

Case-record

A woman, aged 35, was first seen in June, 1956, when she complained of diplopia and orbital pain of four weeks' duration. The left eye was found to be proptosed and a firm swelling, painless on pressure, was palpable under the lower lid, attached to the medial margin of the orbit, pushing the eye upwards and outwards. Both eyes were healthy, and vision was 6/6

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