Two skulls were also cracked through lack of precautions. Now there is evidence that non-traumatic risks are present which if numerically fewer are no less unpleasant or hazardous.

Summary

The foregoing occurrence of acute pulmonary oedema with neurological disturbance followed promptly after completing the "mess trick" and the "fainting lark." Syncope in each case occurs through well-established physiological vascular changes. Lung trauma is considered to be an improbable cause of pulmonary oedema. Neither cerebral thrombosis nor cerebral haemorrhage is thought to be likely as a cause of neurological disturbance. A proved connexion exists between pulmonary oedema and cerebral damage: both conditions have been confirmed at post-mortem examination. With lesser degrees of cerebral damage recovery from pulmonary oedema may occur.

The infliction of discrete lesions to the hypothalamic pre-optic nuclei in experimental animals is regularly followed by acute and severe pulmonary oedema. Uninhibited vasomotor impulses in these animals will move blood from regions of high constrictor potential into lung vessels possessing low constrictor potential. The pulmonary oedema that follows is essentially neuro-haemodynamic in origin. By applying to man the principle elicited by this experimental work, an unusual symptom-complex after the fainting lark or mess trick becomes understandable. The presence is postulated, in these people, of unsuspected anatomical and morphological anomalies in the ultimate arterial supply to the hypothalamus and upper brain-stem; this, coupled with the very marked reduction in overall cerebral blood flow that accompanies a dedicated performance of the fainting lark, is calculated to deprive of blood both the oedemagenic centre in the hypothalamus

(presumed to exist in man) and parts of the upper brain-stem. It would be tantamount to their sustaining arterial shutdown. Therefore this reversible neural disturbance most probably causes neuro-haemodynamic changes which result in pulmonary oedema and a variable neural dysfunction in the upper brain-stem.

I am indebted to the Director-General of Medical Services, Royal Air Force, for permission to publish, and to the Medical Branch of the Ministry of Aviation for placing their clinical records at my disposal.

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PULMONARY OEDEMA AND INTRACRANIAL LESIONS

BY

PETER RICHARDS,* M.A., M.B., M.R.C.P.

Research Assistant to the Neurosurgical Unit of St. George's Hospital at Atkinson Morley's Hospital, Wimbledon

Pulmonary oedema is a frequent necropsy finding in subjects with a variety of intracranial lesions. Weisman (1939) found it at necropsy in 70% of 686 patients with traumatic or spontaneous intracranial haemorrhage and in only 2% of 200 controls. Cameron (1948) found a similar incidence and also noted that it was common at necropsy in patients dying from hypertensive disease (86%), chronic nephritis (74%), complete coronary obstruction (68%), and mitral stenosis (65%). In contrast, Paine *et al.* (1952) claimed that pulmonary oedema and congestion was less common in patients dying with "significant disease of the central nervous system" (46%) than in those who died with other major illnesses (60%). Moreover, they found evidence of hypertension and/or heart disease in three-quarters of those with lesions of the central nervous system and concluded that an essentially cardiac origin of the oedema was likely.

Little attempt has been made to correlate particular lesions of the central nervous system in man with the occurrence of pulmonary oedema, with the exception of Baker (1957), who demonstrated consistent bilateral damage to the dorsal nuclei of the vagus and to the medial reticular nuclei in 10 patients with bulbar poliomyelitis dying with pulmonary oedema, but not in five others without oedema.

In experimental animals a variety of injuries to the central nervous system provoke pulmonary oedema in different species. These procedures include non-specific rise in intracranial pressure in guinea-pigs (Campbell and Visscher, 1949) and dogs (Harrison and Liebow, 1952), intracisternal injections of thrombin and fibrinogen in rats and rabbits (Cameron and De, 1949) and dogs (Sarnoff and Berglund, 1952), discrete bilateral lesions of the anterior hypothalamus or paraventricular nuclei in rats (Gamble and Patton, 1953; Maire and Patton, 1956), and either bilateral lesions of the vagal nuclei, transection of the cervical cord at C7, or bilateral vagotomy in guinea-pigs (Borison and Kovacs, 1959). Bilateral vagotomy has long been known to precipitate pulmonary oedema, and this, as well as oedema produced by the other methods mentioned, is often accompanied by multiple discrete haemorrhages throughout the lungs which were first described by Valsalva (1740).

This paper presents clinical and pathological observations on pulmonary oedema complicating lesions of the central nervous system made in the course of a study of respiratory infections in this neurosurgical unit. Particular attention has been paid to the incidence, the associated lesions of the central nervous system, the lobar distribution of oedema, associated heart disease and hypertension, and to the clinical and radiological features.

*Now at the Royal Hampshire County Hospital, Winchester.

Methods

A prospective survey was made for five months (July–November, 1962), covering all patients who died from intracranial lesions and for whom permission for necropsy was obtained. This amounted to consecutive deaths with the exception of five for which permission for necropsy was not granted, seven in cases of pulmonary embolism proved at necropsy, and one death from carbon monoxide poisoning.

The hospital necropsies were performed by Professor T. Crawford and Dr. M. R. Crompton. Dr. R. Pearce carried out those ordered by the coroner on accident cases. Only at coroners' necropsies was the brain cut fresh; the remainder were sectioned after fixation by Dr. M. R. Crompton. Of the 88 necropsies, 80 were attended personally.

A control group was formed by taking consecutive necropsies from all the other departments of St. George's Hospital during July–November, 1961, apart from the neurosurgical and neurological units. Subjects under 15 years were excluded, as were those who died with pulmonary embolism (as in the series), those dying from uraemia, and those with clear pathological evidence of coronary occlusion or recent myocardial infarction. The incidence of oedema was high in these groups and there were no comparable cases in the series.

Pulmonary oedema at necropsy in this study is defined as the appearance of copious frothy fluid from the cut surface of the lung. The absence from other regions of the lung of oedema as defined does not exclude the possibility that minimal oedema was present. Visscher *et al.* (1956), after a careful review and discussion of the possible methods of estimation of pulmonary oedema, concluded that gross observation at necropsy provided as reliable and accurate an estimate of the presence and degree of oedema as any method. Vascular congestion, which may or may not be associated with oedema, is frequently severe, and for this reason lung weights are not a reliable guide to the severity of oedema.

Apart from those with a blood-pressure of more than 150/95 on admission, hypertension was also regarded as having been present previously, even if not evident on admission, if some or all of the following findings were present: a history of hypertension, hypertensive retinopathy, a large heart clinically and radiologically, proteinuria, and a left ventricular-wall thickness at necropsy of 2 cm. or more. "Significant heart disease" apart from hypertensive disease refers to the presence of one or more of the following pathological findings: old or recent infarction, atheroma narrowing the lumen of a main coronary artery to less than one-third on cross-section, recent thrombus in a coronary artery, or valvular disease.

Care was taken not to overload the circulation with intravenous fluids. Prolonged airway obstruction was also avoided. A tracheotomy was performed when the airway could not be kept clear of secretions by catheter suction, postural drainage, and bronchoscopic aspiration.

Results

There were 88 patients and 101 controls. Pulmonary oedema was found at necropsy in 52.3% and 29.7% respectively. The average age, incidence of hypertension and/or significant heart disease, and the incidence of pneumonia are summarized in Table I. The incidence of hypertension and/or significant heart disease was significantly raised only in those with pulmonary oedema in the

control group. Pneumonia was equally common in those with pulmonary oedema in the two groups.

No particular combination of gross pathological lesions of the brain was found to be associated with pulmonary oedema (Table II). Histological study of the anterior

TABLE I.—Age, Cardiovascular Disease, and Pneumonia in 88 Subjects with Intracranial Lesions and in 101 Controls

	Series		Controls	
	Pulmonary Oedema	No Oedema	Pulmonary Oedema	No Oedema
No. of subjects	46	42	30	71
Average age in years	49.4	53.3	63.7	64.2
Hypertension and/or significant heart disease	18 (39.2%)	18 (43.8%)	16 (53.3%)	31 (43.6%)
Pneumonia	7 (15.5%)	5 (11.8%)	4 (13.7%)	32 (45.3%)

TABLE II.—Necropsy Findings in 88 Subjects Dying with Intracranial Lesions During July to November, 1962

Intracranial Lesion	Pulmonary Oedema	No Oedema
Cerebral compression	10	16
Cerebral compression with brain-stem distortion, haemorrhage, or infarction	28	21
Brain stem injury without cerebral compression	5	4
Neither cerebral compression nor brain-stem injury	3	1
Total	46	42

hypothalamic region in 106 consecutive subjects with ruptured intracranial aneurysm at this hospital has failed to reveal any consistent lesions associated with pulmonary oedema. Anterior hypothalamic lesions were found in 65 of the 106 cases, and pulmonary oedema occurred in one-third of those with and one-third of those without hypothalamic lesions (Crompton, 1963).

Pulmonary oedema was found in 26 (61.9%) of 42 subjects dying within 36 hours of accident, haemorrhage, or operation, and in 20 (43.4%) of 46 subjects dying after a longer period.

The distribution of oedema was very variable, the commonest being unilateral or bilateral upper-lobe oedema predominantly affecting the apical segments (19 cases). Pulmonary oedema was generalized in 15, and in the remainder it involved one or more lobes on the same or opposite sides. Only in the 11 subjects with severe generalized oedema did the oedema appear sufficient of itself to cause death. In all these the intracranial damage was so severe as to appear irrecoverable. The pathological conditions in these cases were head injury (4), ruptured aneurysm (4), cerebral tumour (2), and intracerebral haematoma (1).

Clinical evidence of pulmonary oedema generally appeared a few hours before death, and in all cases within 24 hours. Only in those with severe generalized oedema was abundant frothy sputum a feature. Radiological changes were not found until the oedema was clinically severe. The radiological appearance was similar to early pneumonic consolidation, and was reported as such (see Fig.). Reversible pulmonary oedema was observed once. A 19-year-old girl developed generalized pulmonary oedema a few hours after the partial removal of a glioma; she recovered spontaneously within 24 hours, and eventually made a good neurological recovery. Elliot (1955) has described reversible pulmonary oedema in acute disseminated sclerosis.

Discussion

No combination of lesions in the brain, including anterior hypothalamic damage, has been found to be

particularly associated with pulmonary oedema. The possibility that symmetrical microscopic lesions of the vagal nuclei are constantly associated with it as in cases of bulbar poliomyelitis is open to further investigation. Only macroscopic observations were made on the brain-stem in this study. The more acute the intracranial lesion the more frequent was pulmonary oedema, although it was absent in one-third of those with lesions severe enough to cause death within 36 hours.

It is unlikely that injuries at brain-stem level are essential for the development of "neurogenic" oedema, since it can be produced experimentally by cervical-cord transection at C 7 (Borison and Kovacs, 1959). During this survey severe oedema was found at necropsy in a woman with a rapidly progressive suppurative myelitis of the cervical cord extending from C 4 to T 1.

It is not known whether the oedema is primarily the result of acute overloading of the pulmonary venous system either because of heart failure or a redistribution of blood, or whether it is the result of a sudden increase in permeability of the pulmonary capillaries (Visser *et al.*, 1956).

Whatever the mechanism, acute intracranial lesions can produce dramatic and fulminating pulmonary oedema within minutes of head injury or haemorrhage in young healthy subjects. It has been suggested that this is explicable entirely on the basis of heart failure (Paine *et al.*, 1952). The heart failure has been attributed either to extreme tachycardia associated with lesions of the vagal nuclei (Baker, 1957) or to bradycardia and hypertension with raised intracranial pressure (Campbell and Visser, 1949). During this survey no consistent difference in the

behaviour of heart-rate or blood-pressure has been observed terminally in patients with or without oedema.

Sarnoff and Berglund (1952) found that the pulmonary arterial and venous pressures were elevated in dogs with experimentally induced "neurogenic" pulmonary oedema, but there was a consistent increase in systemic arterial pressure. In this series pulmonary oedema was observed in subjects who did not have systemic hypertension. However, Sarnoff and Berglund attributed the increased pulmonary pressures primarily to a shift in blood from systemic to pulmonary venous reservoirs, and not to the increased systemic peripheral resistance. No measurements of pulmonary vascular pressures have been recorded in patients with "neurogenic" pulmonary oedema. Intense vascular congestion is commonly found at necropsy both in those with and in those without oedema. The lack of prominence of the hilar shadows on the chest film is unlike the accepted picture of oedema due to heart failure, and three subjects in whom it was clinically severe had a normal jugular venous pressure when seen a few minutes before death.

Recently attempts have been made to implicate a humoral factor. Rech *et al.* (1962) induced pulmonary oedema in a normal guinea-pig as a result of cross-circulation with a vagotomized animal. No pharmacological studies on the oedema fluid have yet been reported, but they would seem to be indicated.

The variable distribution of the oedema suggests that local factors are also of importance. The position of the patient at death and in the preceding hour was recorded, but failed to explain the distribution found at necropsy. There was no correlation between the side of the intracranial lesion and that of the oedema: it was not found more commonly on the affected side when chest movements were reduced with a hemiplegia. It is possible that regional underventilation might explain the predominance of apical oedema.

The rapid development of pulmonary oedema a few hours before death is similar to experimental findings. In this survey it was frequently more severe at necropsy than had been suspected clinically or radiologically. Courtice (1953) has shown that significant pulmonary oedema may exist in the goat in the absence of radiological changes, but it is probable that the disparity between clinical and necropsy findings is largely due to rapid increase in the oedema shortly before death.

It does not seem that pulmonary oedema complicating intracranial lesions can be attributed entirely either to cardiovascular factors or to neurogenic or humoral influences on pulmonary capillary permeability, although both mechanisms may be involved. The patchy distribution strongly suggests that local factors also play an important part.

Summary

Pulmonary oedema was found at necropsy in 46 out of 88 subjects dying with intracranial lesions, and in 30 out of 101 controls. It was not associated with any particular combination of gross intracranial lesions or with consistent hypothalamic damage. The high incidence could not be attributed to hypertension, heart disease, or pneumonia. The oedema was often confined to one or both upper lobes. The reason for this distribution, and the mechanism by which "neurogenic" pulmonary oedema is produced is obscure. It is possible that a variable combination of local and general factors is involved.

Clinical signs of oedema were not found more than 24 hours before death and they preceded the radiological

Portable chest film of a 60-year-old woman 12 hours after a third and fatal haemorrhage from a basilar-artery aneurysm, death occurring two hours after this film was taken. Bilateral pulmonary oedema was found at necropsy, more severe on the right. Incidental findings were a 4-cm. cyst at the apex of the left pleural cavity, and a large air-filled cyst in the left oblique fissure.

changes, which resembled patchy pneumonic consolidation. The jugular venous pressure was not raised.

Spontaneous recovery once occurred from pulmonary oedema which developed after the excision of a glioma. Although common at necropsy and often severe, pulmonary oedema in subjects dying with intracranial lesions did not kill those who might otherwise have survived. The intracranial condition appeared irrecoverable in each case.

I am grateful to Mr. Wylie McKissock for the opportunity to make this study; to Professor A. C. Dornhorst, Professor T. Crawford, and Dr. M. R. Crompton for assistance; and to Air Vice-Marshal Sir Aubrey Rumball for suggesting this investigation.

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IMMUNE RESPONSES IN MYELOMA

BY

A. L. LINTON, M.B., M.R.C.P.Ed., M.R.C.P.Glasg.

M. G. DUNNIGAN, M.B., M.R.C.P.Ed.
M.R.C.P.Glasg.

J. A. THOMSON, M.B., M.R.C.P., M.R.C.P.Glasg.

Medical Registrars, Glasgow Royal Infirmary

Impairment of antibody production has often been described in disease of the reticulo-endothelial system. Varying degrees of impairment have been demonstrated in Hodgkin's disease and lymphosarcoma (Dubin, 1947; Evans, 1948; Larson and Tomlinson, 1953), while in chronic myeloid and acute leukaemias antibody formation is said to differ little from normal (Larson and Tomlinson, 1953; Silver *et al.*, 1960). Formation of antibody is thought to be most severely depressed in diseases involving lymphocytes and plasma cells, and much work has been done on chronic lymphatic leukaemia and myeloma (Lawson *et al.*, 1955; Shaw *et al.*, 1960). Barr and Fairley (1961) have shown that the immunological inadequacy found in chronic lymphatic leukaemia differs from that observed in other reticulo-endothelial tumours; in chronic lymphatic leukaemia the antibody response to both primary and secondary immunization is impaired, while with other tumours the response to a second dose of antigen is normal.

In myeloma there is an obvious involvement of plasma cells; excessive proliferation of these cells with anatomically bizarre forms is typical of the disease. There is also no doubt that in most cases of myeloma the presence of an abnormal protein in the serum can be demonstrated. Finally, the undue susceptibility to infection of the patient with myeloma has often been observed (Zinneman and Hall, 1954). There is now much good evidence that plasma cells and lymphocytes are normally involved in antibody synthesis (Thiery, 1960); it is therefore an attractive hypothesis that in myeloma the plasma-cell abnormality, the dysglobulinaemia, and the recurrent infections are inter-dependent.

Some support for this hypothesis can be obtained from the work of Fairley and Scott (1961), who found evidence in favour of such a relationship in chronic lymphatic leukaemia, another disease involving antibody-producing cells. Definite evidence connecting the various features of myeloma has not been found, though several studies have been reported with inconclusive results. Porges (1956) described cases of myeloma in which there was a deficiency of normal gamma-globulin as distinct from the abnormal

protein, and he thought that the condition could be regarded as a secondary hypogammaglobulinaemia. Attempts to demonstrate any direct relationship between dysglobulinaemia and impaired antibody response have produced equivocal evidence, but the majority of the workers have claimed to show some correlation (Marks, 1953; Zinneman and Hall, 1954; Dancaster *et al.*, 1959). This could not be confirmed by Lawson *et al.* (1955), and it may be that the confusion is in part due to the small numbers of cases of myeloma usually available.

The present study was designed to try to assess the severity of immunological impairment in myeloma at varying stages, and to find out whether there was any correlation between the cellular defect, the protein abnormality, and the altered immunological response. The number of patients available was small, but it was decided to test in each patient a much wider range of immunological responses rather than use the single response to a bacterial antigen. It was thought that some definite pattern might emerge if different types of immune defence mechanisms were included—for example, rejection of skin graft and the rate of destruction of incompatible red cells.

Material

Investigations were carried out on a group of six patients with myeloma of various types. The investigation was explained to all of them, and each expressed complete willingness to co-operate. Details of the patients are given in Table I. The extent of the disease varied from a patient with solitary plasmacytoma to one with widespread bony involvement and plasma cells in the peripheral blood. The patients' clinical state was arbitrarily assessed as "good," "fair," or "poor." Full blood examination, marrow biopsy, radiological bone survey and estimation, and electrophoresis of plasma proteins were performed in each case. No patient was under treatment at the time of the survey, nor had been in the previous two months. It was therefore unlikely that any of the forms of treatment previously used (steroids, cytotoxic agents, or radiotherapy) would have influenced immune response at the time of