PAPERS AND ORIGINALS

Epidemic Neuromyasthenia: Outbreak among Nurses at a Children's Hospital

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Summary

Between August 1970 and January 1971 nearly 150 of the staff of a London teaching hospital were affected by an illness with features in common with what is currently known as epidemic neuromyasthenia. Symptomatology was protean, clinical findings minimal, relapses frequent, and results of laboratory investigations, including virological studies, were generally negative. Most of the patients were nurses. Care was taken to minimize anxiety and fear in a vulnerable population, and laboratory investigations were limited in number for this reason.

Introduction

In the late summer of 1970 an outbreak of an illness occurred among members of the nursing staff of the Hospital for Sick Children, Great Ormond Street, London, which had features in common with outbreaks reported from many different parts of the world. These have been described under a variety of names —poliomyelitis-like illness (Gilliam, 1938; Jackson, 1957), Iceland disease (White and Burtch, 1954), Akureyri disease (Sigurdsson and Gudmundsson, 1956), Royal Free disease (Royal Free Medical Staff, 1957; McEvedy and Beard, 1970a), benign myalgic encephalomyelitis (Innes, 1970; McEvedy and Beard, 1970 b), and epidemic neuromyasthenia (Miller *et al.*, 1967; Graybill *et al.*, 1972). There have been other reports of outbreaks with similar symptomatology (Hill, 1955; Geffen and Tracy, 1957).

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Reviews of these disorders have been published (Acheson, 1959; Henderson and Shelokov, 1959; Shelokov, 1972), and also there have been at least two leading articles on the subject (*Lancet*, 1956; *British Medical Journal*, 1957). A similarity in the clinical and epidemiological patterns can be seen in outbreaks of this syndrome of unknown aetiology in the United States, Iceland, Denmark, Australia, South Africa, Germany, Greece, and the United Kingdom. This paper describes the outbreak which affected the staff of the Hospital for Sick Children.

Incidence and Epidemiology

During the six months from August 1970 to January 1971 136 cases were seen and from February to June 1971 only sporadic cases. A few cases occurred in other hospitals within the group. In the week beginning 15 August 1970 two nurses presented with certain complaints which will be described in detail. Within a week four more nurses presented with similar histories, and many more followed. By the first week of September an outbreak of this curious syndrome was apparent among the nurses. There were no communicable illnesses reported in the community such as influenza, poliomyelitis, or other unexplained epidemic illness, though nurses were also being seen with illnesses in no way resembling the syndrome.

At least 145 persons were affected and there were probably other unidentified cases. Most of the nurses and resident domestic staff came under the care of one of us (M.J.D.). Others were registered with doctors outside the hospital. Of the 145 cases recognized 124 were among nurses, of whom 103 were student nurses and 21 were seniors. There were six cases among the medical staff and 15 among other staff, including domestic and administrative, physiotherapists, and medical social workers. Most of the patients were women but at least four men were affected. Of these, two were doctors and two were on the administrative staff. The staff numbered about 1,900, and therefore the minimum incidence of symptomatic disease was 7-8%. Of the 1,900 staff 800 were nurses, 190 were doctors, and the remainder were other personnel. Thus 15% of the nurses were affected, 3% of the medical staff, and about 2% of the remainder.

There were two fairly distinct waves, the first between 15 August and 23 September 1970, and a second which finished

towards the end of January 1971. Isolated cases were seen during the next six months (fig. 1). There were 33 cases in the first wave, and most of them were student nurses. In fact, over a half were attending daily classes in the nurses' training school immediately before the start of the outbreak. A sister tutor who had taught these nurses was also affected. During the second wave all levels of the nursing staff were affected together with some doctors, domestic staff, and others. On careful investigation none of the children who were inpatients during this period had similar symptoms.

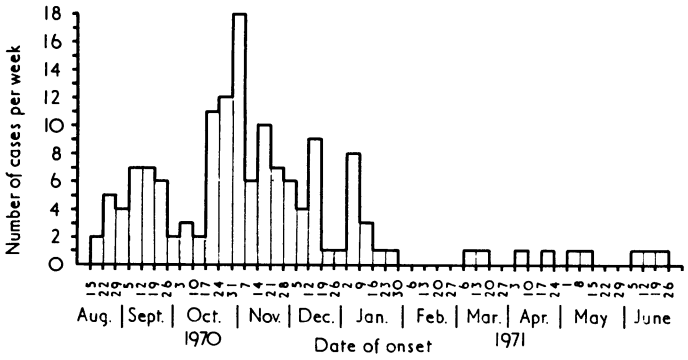

FIG. 1—Occurrence of cases between August 1970 and June 1971. Two fairly distinct waves can be seen.

Clinical Manifestations

A typical case presented as a hitherto healthy young woman who felt generally unwell, had a sore throat, and a mild headache. In a day or two the headache would become much worse and be accompanied by lethargy and nausea. Pain in the neck and back would develop, possibly also vomiting, and perhaps photophobia. She would be unfit for work, have limb pains, be depressed, and be dizzy on standing. Mild analgesics would have made no impression on the headache, which would probably be described as the worst ever experienced. The patient would look ill. She would have no fever or only a transitory rise in temperature not exceeding 38·5°C. Examination would show slightly injected conjunctivae; a red throat; perhaps a slight, whitish-grey exudate on the tonsils and pharyngeal wall; moderately enlarged, tender cervical lymph nodes; usually no skin rash; no abnormality of the heart or lungs; and, notably, no splenomegaly. Stiffness of the neck would often be complained of, certainly pain in the neck or back on flexion, and also photophobia. Ophthalmoscopy would usually find no abnormality, but in two patients the retinal veins were distended and one had papilloedema for a short time. Usually there would be no other significant neurological finding, though sluggishly reacting pupils were noted in one patient.

Some patients had mild diarrhoea at first; some had severe pleurodynia; some had transient skin rashes; some had subjective weakness of limbs; some suffered curious sensory symptoms, including numbness and pins and needles in the limbs; and some had bladder symptoms consisting of hesitancy, frequency, and retention. On exercise, such as ascending stairs, some complained of rapid fatiguability and stiffness in the legs, but no abnormalities of gait were seen.

The symptoms and signs lasted about two to three weeks and then resolved gradually over a period of several weeks, resulting in a total duration of symptoms of six to 12 weeks (tables I and II).

Another striking feature of the illness was the occurrence of definite symptomatic relapses over prolonged periods in at least 28 patients without clearly precipitating or associated events such as menstruation. The interval between apparent recovery and relapse varied from two to six months, but often during the period of apparent recovery the patients were not entirely restored to normal health, complaining of vague symptoms such as lethargy or depression. In these patients exacerbation would be a more accurate term than relapse. Some patients relapsed two or three times and it was up to 12 months before they fully recovered.

TABLE I—*Symptoms and their Incidence in 145 Patients*

	No. (%) of Patients		No. (%) of Patients
Headache	82 (56·5)	Abdominal pain	8 (5·5)
Sore throat	60 (41·3)	Photophobia	8 (5·5)
Nausea	53 (36·5)	Diarrhoea	8 (5·5)
Back pain	39 (26·8)	Earache	7 (4·8)
Malaise	38 (26·2)	Loss of voice (laryngitis)	6 (4·1)
Vomiting	38 (26·2)	Sensory symptoms (paraesthesiae)	5 (3·4)
Neck pain	37 (25·5)	Faintness	4 (2·7)
Tiredness	28 (19·3)	Jaw pain	3 (2·0)
Limb pains	25 (17·2)	Bladder symptoms	3 (2·0)
Depression	18 (12·4)	Anorexia	3 (2·0)
Dizziness/giddiness	15 (10·3)	Subjective limb weakness	2 (1·3)
Sore eyes	14 (9·6)	Blurred vision	2 (1·3)
Cough	14 (9·6)	Diplopia	1 (0·6)
Coryza	10 (6·8)	Painful joints	1 (0·6)
Chest pain	9 (6·2)		

TABLE II—*Abnormal Physical Signs and their Incidence in 145 Patients*

	No. (%) of Patients
Pharyngeal infection	88 (60·8)
Cervical lymph node enlargement	34 (23·4)
Neck stiffness	16 (11·0)
Injected conjunctivae	14 (9·6)
Pyrexia	13 (8·9)
Photophobia	8 (5·5)
Rash	6 (4·1)
Slight splenomegaly	2 (1·3)
Distended retinal veins	2 (1·3)
Papilloedema	1 (0·6)
Sluggish pupillary reactions to light	1 (0·6)
Fits in known epileptic	1 0·6))
Arthritis	1 (0·6)

Management

Treatment was unsatisfactory and consisted of symptomatic measures. Simple analgesics were of little value for the headache and back pain but pentazocine, dihydrocodeine, and dextropropoxyphene were more helpful. Antiemetics were useful but antidepressants were valueless. Short-wave diathermy was not of much help. In the very early stages of the epidemic the number of investigations—particularly lumbar punctures, electroencephalography, and electromyography—was limited so as not to create an atmosphere of anxiety in a vulnerable population. Though this would handicap the discovery of the aetiology of the illness this policy was thought to be correct.

Laboratory Investigations

Haematological.—Routine blood examination included the determination of haemoglobin level, red cell morphology, total and differential white cell count, erythrocyte sedimentation rate, and a Paul-Bunnell screening test (Monospot, Ortho Diagnostics).

Biochemical.—Liver function and serum creatine phosphokinase levels were estimated only in some patients.

Bacteriological.—Throat swabs from all patients were examined for bacterial pathogens and for *Mycoplasma pneumoniae*. Mycoplasma complement-fixing antibody tests were also performed on acute and convalescent sera.

Cerebrospinal Fluid Examination.—Lumbar punctures were performed on only three of the patients and the cerebrospinal fluid examined for cells, protein, and sugar levels. Bacteriological and virological examination was also carried out.

Virological.—These consisted of attempts to isolate a virus from the nasopharynx, faeces, and cerebrospinal fluid and serological tests.

ATTEMPTS TO ISOLATE VIRUS

Materials.—Nose, throat, and rectal swabs were collected separately in 3 ml of virus transport medium and either inoculated into cell cultures directly on arrival in the laboratory or stored at −20°C before inoculation. A wide variety of cell cultures (primary and continuous lines of monkey kidney, rabbit kidney, human embryo-lung fibroblasts, and human embryo-kidney cells) were used as well as human embryo-trachea cultures and suckling mice.

Cell Cultures.—These were examined microscopically for cytopathic effects. The inoculated cells were then harvested and, after freezing and thawing, cells and supernatants were passaged in the same cell cultures. Primary monkey cells were also tested for haemadsorption with human group O erythrocytes.

Organ Cultures.—Six pairs of nose, throat, and rectal swabs were examined at the Central Public Health Laboratory, Colindale, using human embryo-trachea organ cultures. In the same laboratory the materials were also inoculated into a range of cell cultures similar to those used in our own laboratory.

Suckling Mice.—Rectal and throat swabs from 14 patients were pooled and inoculated by the intracerebral and intraperitoneal routes into litters of 24-hour-old mice. They were observed for 28 days. Two mice from each litter were killed seven days after inoculation and suspensions of mouse brain and muscle were inoculated into further litters, the former intracerebrally and the latter by the intramuscular route.

SEROLOGICAL TESTS

Paired sera were tested for antibody to the following viruses by the techniques shown. (1) Complement-fixation test: cytomegalovirus, adenovirus, herpes simplex, influenza A and B, parainfluenza 1 and 3, mumps, and E.B. virus. (2) Haemagglutination-inhibition test: rubella, measles. (3) Virus neutralization test: Coxsackie B viruses types 1-6.

ELECTRON AND IMMUNE ELECTRON MICROSCOPY

Sera from patients in the acute and convalescent phases of the disease were examined at the Royal Postgraduate Medical School. Serum deposits were examined after differential centrifugation by the electron microscope technique of negative staining. Immune electron microscopy was used to examine the acute-phase sera after interaction with recovery-phase serum in the hope that aggregates of an agent might have been formed (Almeida and Waterson, 1969). Similar tests were carried out on supernatant fluids and cell homogenates of lymphocyte cultures from patients in the acute phase of the disease.

Other Laboratory Investigations

Immunoglobulin (IgM, IgG, and IgA).—Levels in acute and convalescent sera were determined.

Interferon.—Serum taken in the acute phase of the illness and supernatants of cultured lymphocytes were tested for the presence of interferon by inhibition of the cytopathic effects of Sindbis virus in monolayer cultures of human embryo-lung fibroblasts.

Phytohaemagglutin Stimulation of Peripheral Lymphocytes.—Lymphocytes taken in the acute phase of the illness were examined for their response in culture to PHA by measurement of the uptake of tritiated thymidine in triplicate cultures. Simultaneous controls were set up with lymphocytes from healthy adults of a similar age.

Lymphocyte Cultures.—Attempts were made to set up long-term cultures of peripheral lymphocytes from three patients in the acute stage of the illness. A number of 2-ml and 10-ml cultures containing 2×10^6 lymphocytes/ml of culture medium consisting of MEM-suspension medium (Flow Laboratories Ltd.), 20% fetal calf serum, 1% glutamine, penicillin 200U/ml, and streptomycin 200 μg/ml were set up from each of the patients.

Results

Haematological investigations were carried out on 58 patients. In all cases haemoglobin levels and red cell morphology were normal and the E.S.R. was not raised. Total white cell counts ranged from 3,000-9,000/mm³ but in five patients the counts ranged from 9,500-12,300/mm³, and from 1,600-2,500/mm³ in four. The mean polymorph count was 56% (range 27-85) and the mean lymphocyte count 36% (range 12-68) of the total. In 20 of the patients between 1-5% of lymphocytes were "atypical" forms but in two patients there were 10% and 70%. The Paul-Bunnell screening tests gave positive results in 48 patients.

Liver function tests on 12 patients showed normal levels of serum bilirubin, transaminases (SGOT and SGPT), serum proteins, and alkaline phosphatase in all cases except one where there was a slight rise in both the transaminases and the α2- and γ-globulin levels. Serum creatine phosphokinase levels were normal in the small number of patients tested.

The cerebrospinal fluid of the three patients in whom it was examined contained normal levels of protein and sugar, there was no pleocytosis, and no organisms were isolated.

Group A β-*haemolytic streptococci* were the only pathogens isolated from throat swabs, and were found in five patients. *Mycoplasma pneumoniae* was not isolated.

VIROLOGICAL INVESTIGATIONS

The only viruses isolated were Coxsackie B1 from the throat of one patient, adenovirus type 3 from throat and rectal swabs of another patient, and adenovirus type 5 from the throat of a third patient (table III).

TABLE III—*Results of Cultures for Virus Isolation*

Culture System	No. of Isolates/No. of Specimens		
	Throat Swab	Rectal Swab	Cerebrospinal Fluid
Cell cultures:			
Primary monkey kidney (Patas) ..	1*/16	0/16	0/1
Primary monkey kidney (Rhesus)†	0/6		
Continuous monkey kidney (V3A)	0/39	0/38	0/1
Continuous monkey kidney (Vero)†	0/6		
Continuous rabbit kidney (RK13)	0/39	0/38	0/1
Human embryo lung (HEL/GOS) ..	2‡/29	1§/38	0/1
Human embryo lung (W138)† ..	0/6		
Human embryo kidney†		0/6	
Organ cultures:			
Human fetal trachea†	0/6		
Animal inoculation:			
Suckling mice	1*/14¶	0/14¶	0/1

*Covsackie B1.
†Tested at the Central Public Health Laboratory, Colindale.
‡Adenovirus type 3, 5.
§Adenovirus type 3.
¶Tested at first in a pool of 14 specimens.

In the serological tests no significant rise in antibody or seroconversion was obtained to cytomegalovirus, adenovirus, herpes simplex, influenza A and B, parainfluenza 1 and 3, mumps, E.B. virus, rubella, measles, or *Mycoplasma pneumoniae*. In one patient there was a rise in neutralizing antibody to Coxsackie B5 from <1:10 to 1:30.

In the complement-fixation antibody tests many sera were anticomplementary. These sera, which were not obviously lipaemic and not contaminated by bacteria or fungi, were then tested systematically for their anticomplementary activity. Titrations were performed on serial twofold dilutions of inactivated serum against a standard dose ($2HD^{50}$) of guinea-pig complement. Of 14 sera taken in the acute phase 12 (83%) were

anticomplementary (titres 1:2 to >1:128), but of 16 convalescent sera from these 14 patients only seven (43%) showed a similar abnormality. The titres of anticomplementary activity in acute sera were also generally higher than that in the convalescent sera from individual patients. Anticomplementary activity could be reduced but not eliminated by addition of guinea-pig complement (1:10) in some of the sera.

ELECTRON AND IMMUNE ELECTRON MICROSCOPY

Ill-defined aggregates were found in some of the acute sera, particularly those that had been shown to have anticomplementary activity. Unfortunately the aggregates were equivocal in appearance and no definite diagnosis could be reached from them. Similar unsatisfactory results were obtained from the cultured lymphocyte preparations.

OTHER INVESTIGATIONS

Serum Immunoglobulins (IgM, IgG, and IgA).—These were estimated in acute and convalescent phase sera from 14 patients. There were no significant changes in levels of immunoglobulins in paired sera from individual patients and the levels were within the normal range in all cases.

Interferon.—Circulating interferon was not found in acute-phase sera from the patients or in the supernatants of the lymphocyte cultures.

PHA Stimulation of Peripheral Lymphocytes.—Four patients were tested in the acute stage of their illness. There was no impairment in the response to PHA and there was also no difference in the activity of lymphocyte cultures to which PHA was not added (unstimulated activity) between the patients and healthy controls.

Lymphocyte Cultures.—In the cultures of lymphocyte from three patients there was a fall in cell numbers at first to about 20-25% of the original inoculum and the remaining cells remained viable. In the cultures from one of the patients multiplication of cells occurred, allowing subcultures to be made. Unfortunately, after 9, 15, and 18 weeks these cultures were lost because of a technical failure of the incubator.

Discussion

This outbreak of illness has much in common with previously described outbreaks of what is currently known as epidemic neuromyasthenia (Henderson and Shelokov, 1959; Shelokov, 1972). As in most reported epidemics, the disease was restricted exclusively to young and middle-aged adults with women predominantly affected, particularly nursing staff. The illness started in late summer and lasted through the autumn, which concurs with the descriptions of over half the outbreaks (Hill, 1955; Geffen and Tracy, 1957; Shelokov, 1972).

The protean symptomatology and the contrastingly minimal clinical findings were characteristic. Headache, backache, neck and limb pains, associated with malaise, fatiguability, and depression are prominent symptoms in most previous descriptions of the disease. Respiratory and gastrointestinal disturbance have been often reported and sore throat, though not a feature in every epidemic, was prominent when present. In fact, though the exact frequency differs, the 10 or 11 commonest symptoms in the present outbreak are very similar to those reported elsewhere and were almost identical with those found during the Royal Free epidemic (Royal Free Medical Staff, 1957; McEvedy and Beard, 1970 a).

The paucity of positive clinical findings was also very typical, yet the physical signs seen by us were in keeping with those reported in the literature. Nevertheless, the objective neurological abnormalities were less prominent than in many reports. Apart from the pharyngeal injection, rarely reported, tender, enlarged cervical lymph nodes, injected conjunctivae, and skin rash have all been seen and the absence of splenomegaly has been noted.

Careful examination found little evidence of neurological involvement. There was no real evidence of weakness, reflex changes, or cranial nerve involvement except in three patients with fundal changes and in one with sluggishly reacting pupils. Bladder symptoms resolved spontaneously. The question of a functional disorder was considered early on in the epidemic in light of suggestions by McEvedy and Beard (1970 a, b), in their retrospective investigations of the Royal Free epidemic in 1955, that epidemic hysteria was a likely explanation for that and other similar outbreaks of the disease. In the first fortnight of the present outbreak we deliberately limited the number of investigations in order to prevent anxiety and fear in a theoretically susceptible population. This was possible since one of us (M.J.D.) saw every patient and was able carefully to explain the possible nature of their illness and also to be reassuring about the outcome.

There was no similar illness in the community nor among the children who were patients in the hospital at the time of the present outbreak. In previously reported epidemics poliomyelitis was at times prevalent in the community, but this was clearly not the case in the present outbreak. In the second wave, particularly, there was a wider age range from late teenage to middle age. Though previous psychiatric illness is not necessary for the development of a hysterical reaction it is worth mentioning that only seven of those affected had definite histories of a previous psychiatric disorder. Epidemics of hysteria in schools, convents, prisons, and other establishments are known to run a short, intensive course (Schuler and Parenton, 1943) and would not be readily confused with the present and other similar outbreaks.

Fatiguability, malaise, headache, neck and back pain, and depression were prominent and incapacitating symptoms among those with a prolonged convalescence due to symptomatic relapses. The phenomenon of relapse has been recorded by Hill (1955), Royal Free Medical Staff (1957), and many others. The incidence of disease with a biphasic pattern is suggestive of an infective aetiology.

The small group of student nurses who were affected in the first wave had been in fairly close daily contact in classrooms. During the second wave there was a spread to all levels of staff with a correspondingly wider age range.

Another important feature of the illness has been the few abnormalities found in the peripheral blood, liver function tests, and cerebrospinal fluid. In a number of outbreaks attempts have been made to identify a bacterial or virological cause. No significant results have been forthcoming. One of us (A.J.S.) who concurred in the clinical diagnosis had previously investigated a similar outbreak (Steigman, 1951). Stools and throat swabs were inoculated intracerebrally and orally into 72 rhesus monkeys pretreated with cortisone. All remained well for 30 days and when killed had no histological evidence of damage. Negative results were also obtained in many litters of suckling mice, adult mice, and in cell cultures of HeLa cells and rhesus-monkey kidney cells, despite many blind passages. Evaluation of the importance of the relatively few atypical lymphocytes in the peripheral blood of many of our patients is difficult, though this is the type of cell often seen in viral infections. These, together with a number of positive Paul-Bunnell screening tests, might have suggested infectious mononucleosis, but E.B. virus infection was excluded by serology.

The results of the other intentionally limited laboratory investigations were singularly unhelpful in establishing an infective aetiology for the illness. The failure to identify a virus clearly may be attributed to the methods used, but even by less routine procedures such as organ cultures and immune electronmiscroscopy no evidence of a viral aetiology could be found. We also failed to find indirect evidence of a virus infection—for example, the presence of circulating interferon. There were, however, some findings which must be interpreted with caution but which could be evidence of some process, possibly an

infection, causing an immunological response. These were a high incidence of anticomplementary activity in sera, with higher levels in the first paired sera, from individual patients and from the results of electronmicroscopy showing "complexes" in the serum. It is now established that anticomplementary activity is a simple test showing the presence of immune complexes in the serum. In fact, the presence of anticomplementary activity was the first suggestion that immune complexes could be present in the circulation with Australia antigen (Shulman and Barker, 1969).

Lymphocyte cultures was decided on because of the relative ease with which lymphocytes from conditions such as certain lymphoproliferative disorders and infectious mononucleosis proliferate in vitro. Though this is possible in some normal people massive numbers of lymphocytes are required. In the present study only 4 and 20 $\times$ 10^6 lymphocytes were used in separate cultures and yet in one of the sets of cultures proliferation readily occurred, permitting subcultures to be made in which proliferation continued. The usefulness of this investigation was limited by the disappointing loss of the cultures through a technical mishap at a relatively early stage. Some of the proliferating lymphocytes had, however, been examined by electronmicroscopy without providing any positive information.

This report of the syndrome of epidemic neuromyasthenia adds to the literature on a puzzling condition, since its aetiology remains unknown. Though it seems to be somewhat uncommon the attack rate in communities in which it has been described is high. Perhaps it is uncommon because the broad spectrum of the relatively mild symptoms may not be readily recognizable in the general community, whereas in relatively restricted populations departures from communal norms are more easily recognized (Graybill *et al.*, 1972). We have used the term "epidemic neuromyasthenia" for this unexplained illness for the same reasons as Henderson and Shelokov (1959). It resembles in many ways outbreaks they have studied (Shelokov *et al.*, 1957). This term seems to be the least objectionable in the limits of our present understanding. Acheson (1959), however, thinks that "benign myalgic encephalomyelitis" is more suitable. Both terms would seem to be acceptable but clearly they are not entirely satisfactory.

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Medicines Evaluation and Monitoring Group: Central Nervous System Effects of Pentazocine

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Summary

Hospital-based drug monitoring facilities have been used to investigate the frequency of perceptual disturbances in inpatients receiving pentazocine and the occurrence of dependence upon this drug after discharge from hospital. A pilot study was carried out in which seven out of 70 hospital inpatients receiving pentazocine reported such episodes, while in a prospective study, 9 out of 132 patients receiving pentazocine and 1 out of 112 receiving cyclimorph, dihydrocodeine, or pethidine reported their occurrence. A total of 135 patients who received pentazocine for disorders likely to require long-term analgesia were followed up for six months after their discharge from hospital. 24 had received pentazocine after discharge; two required an increase in dosage and four expressed a preference for pentazocine.

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Introduction

Since the introduction of pentazocine in 1967 bizarre central nervous system disturbances such as hallucinations, euphoria, and feelings of depersonalization have been reported following its administration (De Nosaquo, 1970; Edison, 1969) and the occurrence of dependence has also been recorded (Hart, 1969; Mungavin, 1969; Sandoval and Wang, 1969; Scholar *et al.*, 1969). An investigation was conducted to estimate the frequency with which hospital inpatients receiving pentazocine