provides an epidemiological tool to estimate bone mass in groups of subjects. ${ }^{8}$ All our observations were made by a single trained observer, and a formal test of repeatability showed no evidence of systematic variations that could have led to the difference observed.

Three case-control studies using controls from the general population, rather than people who had fallen, showed an increase in risk of fracture with reduced Singh grade. ${ }^{11-13}$ In contrast, two similar studies using dual photon absorptiometry showed only small differences in the bone mineral content of cases and controls. ${ }^{514}$ One interpretation of these findings is that the Singh index reflects some aspect of bone morphology that is more closely related to bone strength than is the bone mineral content as measured by photon absorptiometry.

The study population comprised an unselected series of elderly patients with hip injuries resident in two adjacent health districts. The cases included $92 \%$ of all patients in the districts who underwent inpatient treatment for hip fracture during the one year study period. The controls were subject to selection by those factors that determine attendance at the casualty department by elderly people who fall and injure their hips. We think it unlikely that these factors are closely related to bone mass and hence it is unlikely that selection bias produced the large differences in the bone mass of cases and controls.

Three interacting factors may contribute to the risk of hip fracture: bone strength, the risk of falling, and the effectiveness of the neuromuscular responses that protect the skeleton against trauma. Our study was designed to examine two of these factors while allowing for the third. We conclude that at ages below around 75 years reduced bone mass, or osteoporosis, is a strong independent risk factor for fracture. Above that age it may be less important than neuromuscular protective responses.

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#### Abstract

A review study examined the clinical course of measles diagnosed in children being treated for malignant disease in Newcastle upon Tyne during 1973-86. Of the 17 cases diagnosed, five were fatal. Factors associated with a favourable outcome were a typical rash and Koplik's spots, which were accompanied by a detectable serum antibody response and the disappearance of measles giant cells from nasopharyngeal secretions. Pneumonitis severe enough to require assisted ventilation was invariably fatal. Pneumonitis and encephalitis were the main complications. Treatment included immunoglobulin, interferon, and ribavirin, but none could clearly be shown to be effective.

The comparatively low mortality in this series may have been due to the extensive use of the fluorescent antibody technique in Newcastle during the study period and therefore detection of less severe cases as compared with other reports.

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## Introduction

Despite the availability of a safe measles vaccine for years and the significant reduction in measles in the United States as a result of a statutory immunisation policy ${ }^{1}$ fewer than $60 \%$ of children in Britain are currently immunised against the disease. ${ }^{2}$ This may reflect a lack of concern among some of the health care professions and a misguided tendency in Britain to regard measles as a comparatively mild childhood disease with few sequelae, scarcely worth preventing. Consequently the incidence of measles in Britain is high enough to expose children who are at special risk to a potentially lethal infection.
Serious measles infections have long been recognised as a lifethreatening complication of childhood cancer. ${ }^{34}$ In this group of children the occurrence of severe measles without rash (or with an atypical rash) and presenting as giant cell pneumonia or encephalopathy with a high mortality has been well documented. ${ }^{3.7}$ In view of atypical clinical signs which may occur in immunosuppressed children and the lack of a comprehensive viral diagnostic service in some hospitals a proportion of unexplained deaths in the past may have been due to unrecognised measles. ${ }^{8}$
In order to clarify the serious consequences of measles infection in children having treatment for cancer Gray et al have reported the experience of four large paediatric oncology units; they found that only three of 22 children survived the infection and that one of these was left severely handicapped. ${ }^{9}$ None of the units had the benefit of a rapid viral diagnostic service during the period of study, and so probably only the most obvious and serious cases were recorded.

For many years the virology department of the Royal Victoria Infirmary, Newcastle, has employed the fluorescent antibody technique as a routine test for the rapid diagnosis of infection with viruses causing respiratory or febrile illnesses, or both, including measles. ${ }^{10}$ We have therefore reviewed the experience of measles in a paediatric oncology unit in Newcastle.

## Patients and methods

From 1973 to 1986, 401 children were treated in Newcastle for either leukaemia or solid tumours. Any of these children attending clinics or admitted to hospital with respiratory or febrile illness or rash were investigated for possible viral infection. Throat and nose swabs were collected for viral culture and nasopharyngeal secretions for examination by the indirect fluorescent antibody technique and culture. ${ }^{11}$ Skin lesions were investigated by electron microscopy, the fluorescent antibody technique, and culture for Herpesvirus hominis and varicella zoster. Paired serum samples were collected whenever possible from all patients and tested by complement fixation against the common respiratory viruses, measles, and the herpes-virus group, including cytomegalovirus.

Nasopharyngeal secretions were tested by the fluorescent antibody technique for the common respiratory viruses (respiratory syncytial virus, adenovirus, influenza $A$ and $B$, and parainfluenza viruses) and for measles virus, as described. ${ }^{1012}$ If nasopharyngeal secretions were limited in quantity measles was given priority over other viruses sought. ${ }^{12}$ Measles rabbit antiserum used in earlier fluorescent antibody tests was prepared, absorbed, and evaluated in the virology department, ${ }^{12}$ but later a rabbit antiserum produced with highly purified virus was obtained from Finland. Rabbit antisera to the other viruses were similarly prepared, absorbed, and evaluated in Newcastle. ${ }^{10}$ All specimens were also cultured for the common respiratory viruses and herpes viruses. A detailed review of other viral infections in children with cancer in Newcastle has been reported. ${ }^{13}$

When there was known contact with measles and collection of samples was possible nasopharyngeal secretions were examined at regular intervals throughout the incubation period. When measles was diagnosed serial samples of nasopharyngeal secretions were examined by the fluorescent antibody technique and culture throughout the illness and occasionally sputum or bronchial secretions were studied when available to confirm lower respiratory tract disease.

If death occurred and permission for necropsy was granted secretions from the lower respiratory tract and samples of lung and brain (if indicated) were examined by the fluorescent antibody technique and culture for measles and other viruses, in addition to the normal histopathological and microbiological investigations. Electron microscopy was used selectively. Some patients were included in a continuing double blind study of interferon versus placebo.

## Results

Measles was diagnosed in 17 (4.2\%) of the 401 children during their treatment for cancer. The table gives the details of these cases and the outcome of the infections. None of the patients was known to have had measles previously or to have been immunised against it. In patients with a history of contact with measles this was either in a sibling or friend or at school. We do not have comprehensive records of children who had been either immunised or infected with measles virus before the onset of their cancer and who subsequently came into contact with measles.

## ENCEPHALITIS

In three children the illness consisted mainly of encephalitis. One (case 1) was diagnosed post mortem by brain histology, the fluorescent antibody technique, and electron microscopy. No specimens were examined before death. Cytomegalovirus was isolated from the lungs but no evidence of measles was detected by either the fluorescent antibody technique or isolation from specimens of lung or temporal lobes when examined in Newcastle but was shown histologically in specimens of the parieto-occipital cortex and midbrain examined at another centre. ${ }^{7}$ Another patient (case 8) recovered from encephalitis only to die of his leukaemia six months later, and the third patient (case 16) survived after intramuscular and intrathecal interferon but was left with severe neurological handicap. These last two patients were diagnosed by serology alone. Nasopharyngeal secretions were not examined during their original measles infections, and measles could not be detected in nasopharyngeal secretions from either patient after
encephalitis had developed. Though one of these patients (case 16) was exposed to measles over three months before the onset of encephalitic symptoms, her measles complement fixation antibody titre remained undetectable until three weeks after the onset of encephalitis, after which it rose over four weeks to $1 / 1280$. Measles antibody was not detected in cerebrospinal fluid tested during the period when the blood titre began to rise, but none was examined when it was at its maximum.

## OTHER CASES

The illness in the remaining children varied from mild to fatal. There was a history of contact with measles in only six of the children, and five were given prophylactic intramuscular immunoglobulin. In the two (cases 9 and 12) not given immunoglobulin the incubation period was normal and both developed a typical measles rash. In the three children given immunoglobulin (cases 6, 7, and 15) the incubation periods from time of known contact were 60,34 , and six days, though more recent contact could not be excluded. In cases 7 and 15 there was a typical rash and both children showed prolonged excretion of virus with persistence of giant cells in the nasopharyngeal secretions. One of these patients (case 7), who had pneumonitis, was not examined until three weeks after onset of the rash and giant cells were detected for a further nine days, diminishing after treatment with immunoglobulin. ${ }^{7}$ In case 6 (included in interferon trial) there was no rash and virus was detected for 13 days. Giant cells were present for six days along with a rhinovirus, but the patient had a good recovery.

## FATAL CASES

Of the five patients who died, none had a typical rash. One (case 4) was only six months old and succumbed very rapidly with pneumonitis. Two other patients (cases 2 and 3) were diagnosed late in the illness; both had atypical rashes, which were discrete and macular and mainly confined to the trunk, and severe pneumonitis. In cases 2 and 5 pneumonitis was already present when measles was diagnosed. One child (case 3) had had a fever of unknown origin for 10 days. In these patients giant cells persisted in the nasopharyngeal secretions in undiminishing numbers up to the time of death. Measles specific giant cells were detected in the bronchial secretions in case 2 during life and in the lungs in cases 3 and 5 at necropsy; the virus was isolated throughout the illness and no immune response was detected by complement fixation in any of these patients.
Prolonged excretion of virus was common, as assessed by fluorescent antibody positive cells in serial nasopharyngeal secretions, but in those who survived the numbers of giant cells diminished progressively with a decline in isolation rate. The complement fixation immune response was variable among those tested. The highest titres ( $1 / 512$ and $1 / 1280$ ) occurred in patients who developed a delayed encephalitis.
Five children had treatment with immunoglobulin, three with interferon, and four with either interferon or placebo. One patient was given ribavirin by both continuous inhalation and intravenous injection.

## Discussion

The mortality from measles in children having treatment for cancer in Newcastle was $29 \%$ ( $5 / 17$ ), which is considerably lower than that reported from other centres. ${ }^{9}$ This may reflect the inclusion of more mild cases recognised through the routine accessibility to rapid diagnostic techniques and which would have been missed had these virological facilities not been available for patients with no typical clinical signs of measles.
This study allows factors which have been associated with a favourable outcome to be assessed. Of the patients who died, only one had received a prophylactic injection of immunoglobulin, and he later developed a delayed encephalitis. Four other children had received immunoglobulin and all survived. The typical rash or presence of Koplik's spots was invariably associated with recovery, and these signs were usually accompanied by a measurable complement fixation immune response. A delayed immune response was usually associated with the onset of pneumonitis and prolonged excretion of virus, as found by other workers whether or not a rash was present. ${ }^{4}$ Three of the five patients with an atypical rash died.
Eleven patients developed pneumonitis and four died. Once pneumonitis had become severe enough to require intermittent

Our study does not provide enough data to decide which treatment, if any, is most beneficial. Neither type of malignancy, nor regimen of treatment, nor age or sex appeared to be particularly associated with the development of measles or its outcome. Despite a few clinically mild cases virological results showed that among those patients from whom serial specimens were obtained only three had truly mild infections, as judged by the detection of giant cells for only a brief period. Nevertheless, no case of measles should be taken lightly as most are a source of infection to others for a considerable time after onset and a serious danger to other immunocompromised patients.

Measles is also important nationally. Six deaths from measles have so far occurred out of a total of 630 children with acute lymphoblastic leukaemia treated according to the latest MRC UKALL VIII protocol (O B Eden, personal communication). As the survival rate of children with cancer steadily improves deaths from incidental causes such as infection assume greater importance.

How then can children with cancer be protected from measles? Immunisation of immunosuppressed patients with a live attenuated vaccine has been reported from Japan, ${ }^{15}$ but its safety has yet to be established. In 1976 Pullan et al suggested that at the initial diagnosis of leukaemia all unimmunised siblings should be given measles immunisation and kept isolated from the patients for two weeks until excretion of the live vaccine had stopped. This may be effective for preschool children, but current emphasis is to encourage children given treatment to lead a normal life, including attendance at both nursery and school, where they may be exposed to many unimmunised children. Fourteen of the 17 children in this study who developed measles did so after the age of 2 years, and all but one of these could have been immunised in the first year of life.

There is no effective treatment for established measles, though interferon and immunoglobulin may be worthy of further study. Ribavirin acts against measles in vitro ${ }^{16}$ and when given by inhalation may appreciably shorten the disease in normal children. ${ }^{17}$ Early diagnosis is needed so that treatment may be started before severe complications ensue. This means that patients with even apparently mild upper respiratory tract infection, cough, or fever should be investigated for measles. Prophylactic immunoglobulin should certainly be given when a history of contact is known. ${ }^{18}$

In the absence of effective treatment eradication of measles by immunisation appears to be the only rational answer. In the United States measles has virtually been eliminated, fewer than 4000 cases a year having been recorded over the past few years. This has been achieved by a system of compulsory immunisation, so that over $90 \%$ of the population is now immunised. ${ }^{1}$ To eliminate measles from England and Wales $96 \%$ of children would have to be immunised by 2 years of age. ${ }^{19}$ Campbell reviewed some of the reasons why there has been failure to control measles. ${ }^{20}$ Compulsion in Britain is neither politically nor socially acceptable. Education remains a means of persuading both the public and health care professions that measles immunisation is worth while.

The risk of fatal measles infection is not confined to immunosuppressed children. Barkin reviewed 454 deaths from measles occurring in the United States between 1964 and 1971-that is, before the compulsory measles immunisation programme beganand in only $17 \%$ of cases was there an underlying disease. ${ }^{21}$ The primary causes of death were respiratory complications in the younger children and neurological complications among 10-14 year olds. Miller reviewed 270 deaths attributed to measles in England and Wales from 1970 to 1983; over half occurred in otherwise normal people. ${ }^{22}$ Figures relating to morbidity are not readily available apart from the 175 cases of subacute sclerosing panencephalitis that occurred over the same period. Nevertheless, Pollock reported that 140000 cases of measles were recorded in England in 1980 and that according to data for 1963, $10 \%$ of all cases result in complications. ${ }^{2}$ He also reported that many parents refuse to have their child immunised against measles because they have been advised against it by a nurse or doctor.

It is not universally acknowledged that eradication of measles is a worthwhile goal, ${ }^{23}$ but while argument continues children are dying. If a proportion of doctors are so unaware of the dangers of measles that they fail to recommend immunisation and in some
cases actively oppose it then it follows that widespread ignorance of the severity of measles is also likely to exist among the public. Most parents questioned on Tyneside were unaware of the symptoms and complications of measles and did not believe immunisation to be effective in preventing the disease. ${ }^{24}$ Not only does measles immunisation prevent the disease but it has been shown that the workload in general practice related to measles can be reduced by $40 \%$, even when a domiciliary visit is needed to immunise the child. ${ }^{25}$

Fifty nine per cent of children born in 1981 in England and Wales had been immunised against measles by the end of $1983 .{ }^{26}$ For the Northern region 68\% of children delivered in 1982 had been immunised against measles whereas $86 \%$ had received diphtheria, tetanus, and poliomyelitis vaccine, with an uptake of $98 \%$ in some districts-for example, North Tyneside. ${ }^{27}$ If such a high uptake can be achieved for diseases that are recognised as serious then surely a more widespread recognition of the severe consequences of measles should lead to an increased uptake of the vaccine. There are only two recognised contraindications to measles immunisationnamely, cytotoxic or other immunosuppressive treatment, including corticosteroids, and allergy to bacitracin or neomycin.
Every effort must be made to achieve very high acceptance rates for measles immunisation. This can be done only if all health professionals and the public take measles seriously. Until such a change in attitude is achieved it rests with virologists to provide a rapid and adequate diagnostic service and with paediatric oncologists to make the best use of it for the benefit of their patients. Only then will deaths be kept to an absolute minimum.

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