the cause of the disturbances in our patients. None showed radiological evidence of emphysema, and because emphysema was less likely to be present in younger patients the results in the under 35-year-old patients were considered separately. In these younger patients the A–aDo$_2$ and Vd/Vt ratios were disturbed just as severely during their attacks of asthma as in those patients who were more than 35 years old. Furthermore, the return of the Pao$_2$ measurements to more normal levels on recovery helps to differentiate " variable " or " reversible " airways obstruction due to asthma from irreversible obstruction due to chronic bronchitis and emphysema.

Our results indicate that the Paco$_2$ alone is not an adequate estimate of respiratory failure in bronchial asthma. The respiratory defect in asthma, at least before the terminal stage is reached, is predominantly one of V/Q disturbance rather than alveolar hypoventilation, and consequently the Paco$_2$ is nearly always normal.

The frequent failure of the A–aDo$_2$ and Vd/Vt to improve after isoprenaline inhalation may at first seem surprising. However, it can be readily explained if ventilation is preferentially increased to already overventilated alveoli and if perfusion is preferentially increased to already overperfused alveoli and thereby fails to diminish venous admixture. Halmagyi and Cotes (1959) and Daly and Howard (1965) similarly found that bronchodilators failed to improve arterial desaturation in patients with airways obstruction.

All our patients felt considerable subjective improvement during recovery, but in four there was no improvement in the P.E.F.R. and in the others the P.E.F.R. failed to return to normal levels ; this failure of changes in objective tests of airways obstruction to match subjective improvement is a common clinical observation. On the other hand, subjective improvement was invariably associated with an improvement in the Pao$_2$ and in the A–aDo$_2$. These observations in the recovery phase could be accounted for by an increase in ventilation or decrease in perfusion of alveoli with a low V/Q ratio—that is, a decrease in venous admixture. It is possible that this is the mode of action of corticosteroid drugs, in contrast to that of sympathomimetic drugs such as isoprenaline. The latter do not appear to cause a consistent reduction in the A–aDo$_2$ and in venous admixture.

It is clear, therefore, that tests of airways resistance and uneven ventilation are not alone adequate for the full assessment of the severity of bronchial asthma, and particularly the response to therapeutic agents. For many years practically all assessments of drugs in the treatment of bronchial asthma have been made on the basis of the relief of bronchospasm measured by tests of airways resistance. There are now good reasons for a search for drugs which will also improve the disturbance of V/Q ratios. For routine clinical purposes, however, measurement of Pao$_2$ and calculation of the A–aDo$_2$ and Vd/Vt are not necessary, because the hypoxaemia, whatever the type and degree, is readily correctable by the administration of oxygen.

Summary

The arterial oxygen tension, alveolar arterial oxygen difference, and physiological dead space have been measured in 11 controls and in 15 patients during and after acute attacks of asthma, severe enough to require steroid therapy. The results were consistently abnormal during an attack of asthma but returned to more normal levels on recovery. It is concluded that uneven ventilation–perfusion ratios occur during attacks of asthma and give rise to arterial hypoxia more often than is appreciated on clinical evidence.

Isoprenaline produced inconsistent changes in the ventilation–perfusion abnormalities, and it is concluded that these factors are important in the assessment of drugs for the treatment of bronchial asthma, and that tests of airways resistance are not alone adequate for the assessment of response to treatment.

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Summer and Death from Neuroblastoma

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It has been shown that the peak incidence of acute leukaemia is in the summer (Lee, 1962) and that peak mortality is also in the summer (Lee, 1967). Its age distribution and naturally occurring remissions and relapses distinguish acute leukaemia from other forms of neoplastic disease. It is therefore important to determine whether this unexpected seasonal distribution is limited to acute leukaemia.

Most solid tumours affect middle-aged or elderly people. Their mortality (Allan, 1966) and the incidence of the first symptom of new cases (Lee and Gardner, 1965) are highest in the winter months ; this seasonal pattern can reasonably be related to coincidental respiratory infections. Now such infections are likely to be of less consequence in children.

Furthermore, neoplastic diseases in children generally run a more rapid course than in adults, so that opportunities are fewer for infections to occur and for determining the clinical course. I have therefore made a study of neoplastic disease in children. The date of onset of disease, however defined, is always open to question. Did the patients notice their symptoms just then ? and why ? Why were they admitted on that day ? To avoid this type of difficulty a study was made of the seasonal distribution of deaths from neoplastic disease in children.

Deaths from Neoplastic Disease in Children

The various types of neoplastic disease in children aged 0–14 in England and Wales during the years 1958–64 caused the

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deaths shown in Table I. Leukaemia heads the list and accounts for 44% of all the deaths from neoplastic disease in this age group. Then come neuroblastomas and renal tumours. These are the commonest types of tumour. Rarer tumours of many different types produce the remainder of the deaths. The present report deals mainly with neuroblastomas.

TABLE I.—*Number of Deaths from Neoplastic Disease in Children of Both Sexes Aged 0-14, by Type**

	Age in Years		
	0-4	5-9	10-14
Leukaemia†	1,067	834	536
Neuroblastoma	269	76	40
Renal tumours	254	113	16
Other tumours of the lymphatic and haemopoietic system	159	172	200
Miscellaneous tumours of brain and nervous system	349	375	278
Remainder	342	171	327
Total	2,440	1,741	1,397

*All data in Tables I–V refer to England and Wales 1958–64, and are derived from copies of the official register of deaths, by courtesy of the Registrar General.
† Effectively acute myeloid or chronic leukaemia in children. There are few cases of acute myeloid or chronic leukaemia in children. Even though some, with treatment, survive for a long time, they remain haematologically cases of acute leukaemia.

The International Statistical Classification of Diseases, Injuries, and Causes of Deaths used by the General Register Office divides most tumours only by anatomical site of primary. Hence it is impossible to divide neuroblastomas certainly from other tumours of the same organs. In order to do this, a special study has been made in collaboration with the General Register Office. Copies of entries in the official registers of deaths for the years 1958–64 have been obtained for all ages for tumours of the sympathetic nervous system and of the adrenals. For children aged 0–14 certificates were obtained for renal tumours for the years 1959–61. Entries for tumours of the eye were examined for neuroblastomas, but none was found; and a partial survey of the entries for tumours of the brain was also made. An unknown but probably small number of neuroblastomas will have been missed because they were ascribed by the certifying doctors to some other anatomical site than the sympathetic nervous system, adrenals, eye, or brain. The seasonal distribution of deaths was similar in those neuroblastomas ascribed to the adrenal glands, and those classified with other organs or left by the certifying doctors without anatomical description. While those tumours associated with the adrenal glands by the certifying doctors can be accepted as having their origin in these glands, the doctors were not required to state the site of origin of tumours. Consequently, those tumours not associated with the adrenal glands are a mixture of those known to have their primary growth elsewhere and those merely not fully described. No comparison is thus possible between tumours beginning in the adrenal glands and tumours beginning elsewhere.

Analysis of the deaths from neuroblastomas showed a marked and consistent excess of summer deaths. The excess was present in both children and adults (Table II), there being in the whole series 32% more deaths in summer than in winter. A similar summer excess mortality has not so far been demonstrated in tumours related to neuroblastomas. These are either much rarer as causes of deaths—for example, retinoblastoma, phaeochromocytoma—or, like the neuroblastomas, are combined with other tumours in the standard coding processes. Large and specially designed studies will be needed to trace the seasonal pattern of mortality of these tumours.

There were nine deaths (five in the summer, and four in the winter) from ganglioblastomas—intermediate between the highly malignant neuroblastomas and the benign ganglioneuromas. These have not been included in the analysis of neuroblastomas.

TABLE II.—*Number of Deaths from Neuroblastomas by Age and Quarter*

Age	January to March	April to June	July to September	October to December	Total
0- 4	57	77	77	58	269
5- 9	17	21	20	18	76
10-14	10	14	8	8	40
15 and over	13	25	19	16	73
All ages	97	137	124	100	458*

*The calendars of deaths by single numb r months vary irregularly.

D

Mortality of children from disease is even today greater in winter than in summer, and the neuroblastoma deaths do not conform to the general pattern (Table III).

TABLE III.—*Number of Deaths from Neuroblastoma in Children of Both Sexes Aged 0-14 by Quarter, and Expected Number Based on Deaths from All Diseases*

	January to March	April to June	July to September	October to December	Total
Neuroblastoma	84	112	105	84	385
Expected deaths*	115·25	92·40	79·59	97·78	385·02

$\chi^2 = 22·68.$ D.F. 3, $P < 0·0005.$
* Standardized for age. Deaths from all causes minus violence, which, like neuroblastoma, causes more deaths in the summer than in the winter.

Deaths from Neuroblastoma

The excess summer mortality from neuroblastoma is found at ages 0–4, 5–9, and 10–14, and on the rarer occasions when the tumour is diagnosed in adults (Table IV). The summer excess mortality is found in both males and females.

TABLE IV.—*Number of Deaths from Neuroblastoma in Summer (April–September) and in Winter (October–March) by Age and Sex*

Age	Males			Females			Total		
	Summer Deaths	Winter Deaths	Summer Excess (%)	Summer Deaths	Winter Deaths	Summer Excess (%)	Summer Deaths	Winter Deaths	Summer Excess (%)
0- 4	91	69	32	63	46	37	154	115	34
5- 9	24	21	14	17	14	21	41	35	17
10-14	12	9	33	10	9	11	22	18	22
15 & over	25	17	47	19	12	58	44	29	52
All ages	152	116	31	109	81	35	261	197	32

A simple test of the proportion of deaths occurring in the summer was performed for each age group with more than 35 deaths (0, 1, 2, 3, 4, 5–9, 10–14, 15–19, 20 and over). The results of these, taking account of direction, were summed. The resultant, expressed as a standardized normal deviate, is highly significant of a summer excess (P < 0·001).

The death rate from neuroblastoma is high in the first and second months of life, then falls, and rises to a new peak at about the second birthday (Fig. 1). Mortality data by single month of age for England and Wales for all neoplasms is available only for the years 1963 and 1964. But these limited data suggest that the high early death rate is not a general feature of neoplastic disease in children. The summer excess mortality is smaller in the age range 0–5 months than it is in the rest of the first year of life or in the second year (Fig. 2). While this difference is not statistically significant, it could be plausibly associated either with the limited exposure of the infants aged
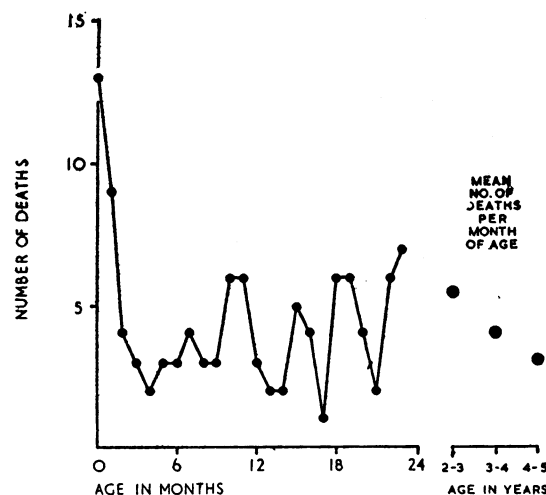

FIG. 1.—Number of deaths from neuroblastoma by single months of age in children 0-2 years, both sexes. England and Wales, 1958-64.

less than 6 months to the general environment or with the high proportion of infants dying with neuroblastoma who have gross hepatic metastases (Wieberdink, 1957).
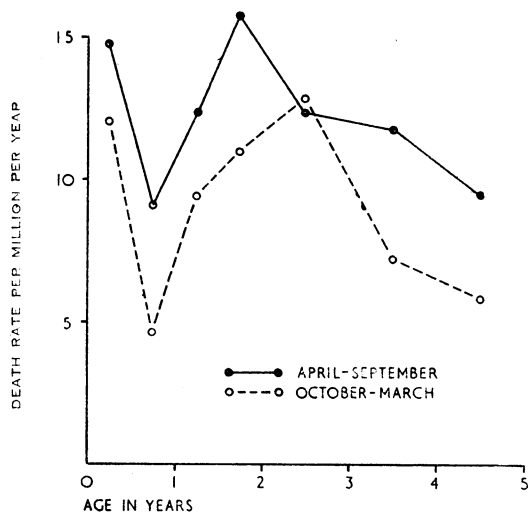

FIG. 2.—Death rates from neuroblastoma by season and age in children 0-4 years, both sexes. England and Wales, 1958-64.

The summer excess mortality from neuroblastoma in adults (Table IV) is present both in the twenties and in middle age (Table V). The diagnosis of neuroblastoma in an adult is an uncommon one, and has been the subject of controversy (see Willis, 1960). It is interesting that the deaths in adults proved to have a seasonal distribution similar to that of the deaths in childhood.

TABLE V.—*Number of Deaths from Neuroblastoma in Summer (April-September) and in Winter (October-March) in Adults by Age*

Age						Summer Deaths	Winter Deaths
15–19..	..	..	..	..	..	18	19
20–24..	..	..	..	..	..	7	2
25–44..	..	..	..	..	..	7	4
45–64..	..	..	..	..	..	10	2
65 and over ..	..	..	..	..	..	2	2
Total	..	..	..	..	..	44	29*

* Summer excess at age 15 and over, 52%.

The summer excess mortality occurred in each year of the seven years from 1958 to 1964. With this short series no trend is apparent in its size. There is no evidence to suggest that it is a feature of special years or that neuroblastomas behave in an epidemic manner.

The excess mortality in summer is found in patients dying in teaching hospitals, in non-teaching hospitals, and at home. The summer excess mortality is thus not limited to those dying in the course of hospital treatment or while receiving terminal care at home. Few deaths from neuroblastoma were dealt with by coroners, but the summer excess mortality was also found in this group.

Discussion

A summer excess in the mortality from neuroblastoma has been observed comparable with that found in acute leukaemia. Why two such different diseases should behave in this way cannot yet be explained. Seasonal variations in disease and mortality are well known—heat stroke, hay-fever, polio, and accidental drowning in the summer ; hypothermia and pneumonia in the winter. There does not seem to be anything at present known about disease in the summer likely to provide a reasonable explanation of the behaviour of neuroblastoma, but the possibility that the summer mortality is the delayed result of the infections of winter needs examination. A number of patients

with neuroblastoma might suffer from respiratory infections during the winter which accelerated the progress of their disease, so that they died in the following summer. But the immediate effects of infections in debilitated patients are surely more prominent than their consequences some months later. While the effects of winter will certainly tail off into the following summer, it is hard to see how the bad weather and infections of winter could produce more deaths in the following summer than at the time.

If the observed seasonal distributions of morbidity and mortality in acute leukaemia and of mortality in neuroblastoma cannot be explained in terms of the effects of known features of these diseases, a new type of relationship between environment and neoplastic disease must be postulated, and its study takes on a greater interest. As a first step to the explanation of the observation, a detailed description of the progress of the disease at different times of the year is needed.

The deterioration in the condition of the patients (perhaps due to an increase in the activity of the disease) must be greater in the summer than these mortality data suggest. The direct effects of winter will undoubtedly produce some deaths, and hence reduce the apparent summer excess. Australian morbidity data for acute leukaemia, derived from a more benign winter climate, do not show the subsidiary peak in incidence in the winter that is apparent in the British data (Lee and Gardner, 1965). Further, death from neoplastic disease is due to a combination of (*a*) the effects of the disease at the time with (*b*) a summation of its effects since it became active. Whatever short-term variations there are in tumour activity much of the deterioration leading to death will, even in children, be relatively long-term ; thus it can hardly be seasonal. More direct measures of the current activity of neoplastic disease—for example, blast-cell counts in acute leukaemia, and measurements of catecholamine excretion in neuroblastoma—are urgently needed as indications of the effects of season.

The studies thus outlined would give information on whether the disease did change, and, if it did, when and to some extent how it changed. The observed changes in mortality could be the result of changes limited to the early stages of the disease that occurred months before. But the similarity of the seasonal distribution of the clinical onset of acute leukaemia and the mortality from acute leukaemia suggests that the seasonal effect is felt by patients at all stages of the disease.

Further mortality data are needed to clarify the distribution of mortality by single calendar months and to enable a longer series of summers and winters to be studied. Data for 1965 are awaited and efforts are being made to collect data for years earlier than 1958.

Morbidity data are also needed to demonstrate the effects of season on earlier stages of the disease. Coding difficulties make analysis of the National Cancer Registration Scheme material exceedingly difficult, and so a start has been made on the analysis of hospital notes.

Case records of patients with neuroblastoma, collected by the Medical Research Council as part of a study of the influence of vitamin B_{12} on the disease, have been analysed by month of primary treatment. These data are probably the most useful in solid tumours, in contrast to the first symptom in acute leukaemia. Of 94 cases, 53 received their primary surgical treatment or radiotherapy in the period April to September and 41 in the period October to March, a 29% summer excess. So far as they go these clinical data confirm the high summer incidence of the mortality.

Some of the common seasonal cycles in human disease are manifestly imposed on man by changes in his environment. Cycles outside of man—in plants, or the seasons themselves—impose their patterns on vulnerable human beings. Hay-fever associated with the pollen season and hypothermia in cold spells are examples that have been mentioned. I cannot, up to now,

find any example among cycles of this type that could provide a starting-point for an explanation of the observations on acute leukaemia and neuroblastoma.

As well as these imposed responses, there are seasonal cycles in a number of physiological factors which are controlled by biological clocks within man himself. Seasonal cycles in the degree of platelet stickiness, the level of antidiuretic hormone, the excretion of the metabolic products of steroid hormones, etc. (Tromp, 1963), are likely to be the result of internal cycles whose only reference to the environment is for synchronization. It is unknown whether these cycles affect disease, but they are large enough and occur in substances that are known to affect the progress of neoplastic disease. It is in such physiological cycles that the explanation of the observed changes in neuroblastoma seems likely to be found.

Summary

Deaths from neuroblastoma are more common in the summer months in England and Wales than in the winter. The summer excess in mortality for all patients is 32% ; it is found in males and females, and in children and adults. The seasonal pattern may be due to a physiological mechanism which influences the activity of certain forms of neoplastic disease.

ADDENDUM.—Since this paper was written two series of patients with neuroblastoma have been analysed where the date of *diagnosis* was recorded. At the Children's Orthopaedic Hospital and Medical Centre, Seattle (72 cases), there were 5.7% more diagnoses in the months April–September than in October–March. At the Los Angeles Children's Hospital (111 cases) there were 13.4% more diagnoses in the months April–September than in October–March. I am grateful to these two institutions for the use of their data.

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Herpes Simplex Encephalitis Treated with Intravenous Idoxuridine

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In 1961 Herrmann, using the agar diffusion method which he had introduced with his colleagues (Herrmann *et al.*, 1960) for the detection and bioassay of antiviral drugs, reported that plaque formation by the deoxyribonucleic acid (D.N.A.)-containing viruses of vaccinia and herpes simplex was inhibited by 5-iodo-2′-deoxyuridine and by 5-bromo-2′-deoxyuridine, the inhibition being reversed by thymidine. These synthetic nucleosides were inactive against ribonucleic acid (R.N.A.)-containing viruses.

Experimental herpes simplex keratitis of rabbits was then found to be prevented or cured by the topical application of 5-iodo-2′-deoxyuridine (idoxuridine) (Kaufman, 1962), and in a clinical study of 76 patients the drug was found to accelerate the healing of dendritic ulcers (Kaufman *et al.*, 1962). Later experience was clouded by failure to distinguish between superficial and deep lesions of the cornea, and by including cases of uncertain cause as well as by the lack of critical comparison of treated and untreated cases. More recently a review of over 100 cases taken from statistically valid trials has confirmed the value of idoxuridine in treating superficial herpetic ulcers of the cornea, though it is ineffective in cases with deep stromal involvement (Leopold, 1965). It may prevent recurrent ulcers due to virus when corticosteroids are used for metaherpetic keratitis, iritis, and uveitis.

Calabresi *et al.* (1961) used idoxuridine in the treatment of advanced cancer, and found that the immediate toxic side-effects included leucopenia, stomatitis, and alopecia. Calabresi (1965) reported suppression of jennerian vaccination by idoxuridine and some beneficial effect on herpes zoster and on vaccinia gangrenosum. He thought that the systemic use of idoxuridine should be restricted to patients with cancer and to those with severe D.N.A.-virus infections. The drug might compete with thymidine—of which it is an analogue—in the synthesis of the nuclear D.N.A. of normal tissues, and it might thus be a remote cause of malignant metaplasia and of genetic injury.

Though the action of idoxuridine on the virus of herpes simplex is imperfectly understood, it is believed either to inhibit viral D.N.A.-polymerase or to be incorporated into viral D.N.A., thereby leading to the faulty transcription of messenger R.N.A. and to the synthesis of abnormal enzymes and proteins (Kaplan *et al.*, 1965 ; Prusoff *et al.*, 1965).

Against this background of uncertain antiviral activity and of possible human toxicity it was decided to use intravenous idoxuridine in a case of herpes simplex encephalitis from which

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