endocrine tissues as well as those of other structures, such as liver, kidney, skin, bone, etc. The post-mortem appearances noted were those of microsplanchnia comparable to a state of severe and premature senescence. The combination of the typical skin changes with gonadal atrophy is distinctive. The biochemical investigations strongly suggest functional hypopituitarism with adrenal hypofunction in this case. The multiple features and variation around a common and unforgettable clinical pattern cannot, however, be explained on a purely endocrine basis nor by the effects of reduced function of the liver or kidney alone. The clinical picture of the syndrome varies as a result of other factors superimposed on what is probably a single inherited trait. Modifications of the final syndrome may then be largely dictated by the relative degrees of hypofunction of various vital endocrine and metabolic organs and their resulting imbalances. The basic cellular disturbance as shown in the skin, hair, and body structure remains constant and determines the typical physical features. A deficiency of synthesis in one enzyme system vital to all cells may be responsible and so set in train the diverse pathological consequences encountered. This is probably an inherited heterozygous recessive character, and an analogy may perhaps be drawn to galactosaemia, Hartnup disease and Wilson's disease—conditions in which a tissue enzyme defect has been established.

Summary

The biochemical investigations and necropsy findings are described in a male patient of 62 years with Werner's syndrome. It is suggested that the condition is due to a generalized enzyme defect which causes premature senescence.

Our thanks are due to Dr. G. Scarlett, who referred this case to us, to Dr. Cotton Kennedy and Mr. D. Neill for their help with the laboratory investigation, and to Dr. Colin Brennan for clinical supervision. It is a pleasure also to acknowledge the invaluable secretarial help of Miss Joan Coburn. We wish to thank Organon Laboratories Limited for the supply of compound S.

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EPIDEMIOLOGY OF "SUDDEN, UNEXPECTED, OR RAPID" DEATHS IN CHILDREN

BY

JOHN L. EMERY, M.D., D.C.H.

Department of Pathology, the Children's Hospital, Sheffield

Fatal disease in children after the perinatal period falls into four fairly distinct groups: (1) unnatural accidents; (2) neoplastic disease; (3) congenital abnormalities of form or function; and (4) rapid, unexpected death occuring either at home or shortly after admission to hospital. Our hospital beds are filled with the children of the first three groups, but the children of group 4 are rarely seen by a paediatrician, and even more rarely by the conventional paediatric research team, and there is a tendency to overlook them or assume that the deaths in this group are outside the responsibility of the hospital.

In Sheffield we are fortunate in that, through the co-operation of the coroner, the general practitioners, and the pathologist in charge of the local regional hospitals, virtually the whole of the natural deaths in children, from a fairly well circumscribed community of over half a million, have tended to pass through a single paediatric pathology department. The variation in the types of death probably reflects as complete a picture of infant mortality as is seen anywhere in the country.

When we first began doing necropsies for the coroner we were struck by the similarity in anatomical findings between the children referred to the coroner as possible cases of home suffocation and the children dying in hospital after a short illness. A careful study of the histories of a series of 50 such "sudden deaths" was carried out in conjunction with the hospital almoner; this confirmed the findings of Bowden and French (1951) that the majority of histories given to the coroner were incomplete. In over 90% there was a history of symptoms beginning at least 48 hours before death (Emery and Crowley, 1956). It thus seemed that it was something of "chance" whether a child died at home or in hospital. For that reason we have now surveyed the deaths of children who, from the histories available, had symptoms for 48 hours or less prior to death, irrespective of the site of death.

Material and Selection of Cases

During the seven years from June, 1949, to May, 1956, we carried out 1,250 necropsies in which the clinical histories were available and adequate for study. Of these deaths, 654 occurred over the age of 7 days. Only these are discussed in the present paper, as the pathological features causing death are likely to be different under this age.

Of the 654 children, 249 had died with a total history of symptoms for 48 hours or less, and from what appeared to be natural acute illnesses. There were a further 10 deaths from unnatural accidents, such as road accidents, and 8 children died as a result of a "cold" operation in hospital.

Variation in Proportion of Deaths During the Seven Years

The total annual number of children examined during the period of study was remarkably stable, being: 1949–50, 88; 1950–1, 92; 1951–2, 98; 1952–3, 100; 1953–4, 90; 1954–5, 99; 1955–6, 87. The proportions

of rapid deaths in these corresponding years were: (excluding road accidents and cold operative deaths) 1949–50, 22 (25%); 1950–1, 37 (40%); 1951–2, 33 (33%); 1952–3, 42 (42%); 1953–4, 46 (51%); 1954–5, 31 (31%); 1955–6, 38 (43%). These figures suggest an increase in the proportion of rapid deaths over the years studied.

It is possible that the general population of children coming to the hospital during this period may have changed, but the only change known to have occurred was an increase in the number of children sent from hospitals in surrounding cities for further investigations. This would increase the number of deaths from diseases of more than 48 hours' duration. The rapid deaths came, of course, from places within a relatively short distance from the hospital. If the numbers of rapid deaths had in actuality remained the same our overall proportions would have shown a diminution. Since our proportions show a tendency to increase, it would seem justifiable to conclude that there was a real increase in the proportion of children dying from acute diseases during this period.

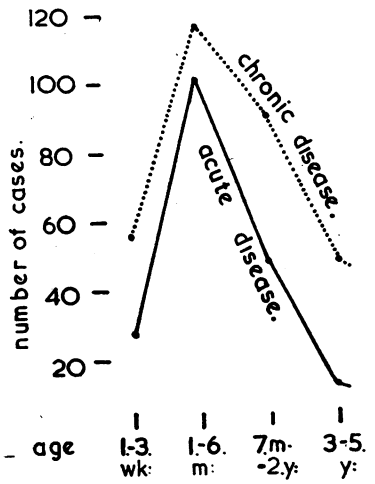

FIG. 1.—Number of children examined dying of disease of under 48 hours' duration, and those of longer duration.

Age at Death

The relative numbers of children dying from disease with symptoms for 48 hours or less compared with the other deaths at the same time in the hospital are expressed in Fig. 1. These two curves show a peak in the age group 1–6 months. The latter part shows a relative increase in deaths from chronic disease. The proportion of very acute diseases was remarkably constant up to the age of 1 year. From the age of 1 year onwards an increasing proportion of deaths occurred from diseases of longer duration.

Time of Year

The total deaths for the different months of the seven years, together with the numbers of children dying from acute disease, are given in Fig. 2. The percentage of acute deaths related to the total number of deaths in the different months is shown. The greatest number of deaths occur during the period December to February, but the proportion of deaths from very acute illness is higher during the later winter months than during the later summer months.

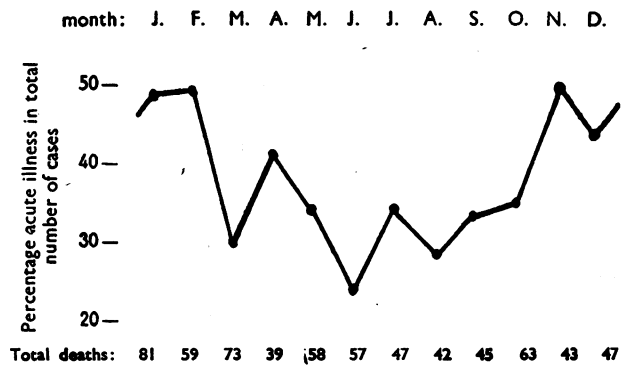

FIG. 2.—Number of children dying in a five-seven-year period; number dying of acute disease and their relationship at different months of the year (excluding road accidents and cold operations).

Site and Day of Death

Of the 249 deaths from acute disease, 120 occurred at home, 13 in the ambulance on the way to hospital, and 116 after admission to hospital. In view of the observation that cot deaths appear to occur more often at the week-end than the rest of the week, it was thought worth while to relate the site of death to the day of the week. The results of this are shown in Fig. 3.

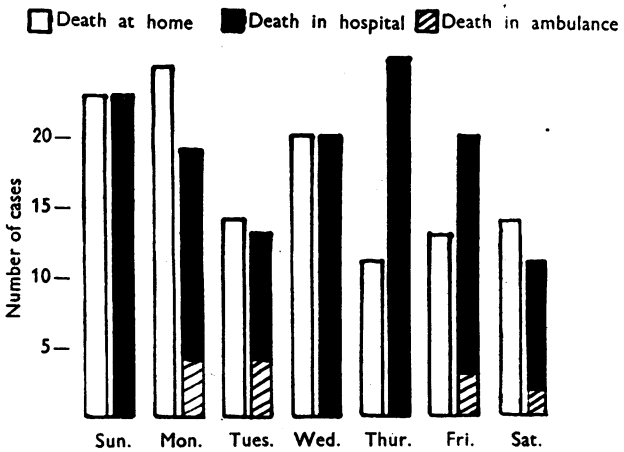

FIG. 3.—Number of deaths from acute illness on different days of week, and site at which deaths occurred.

Since it is sometimes uncertain which side of midnight a child died, we have classified the day of death as including the previous night. A common history is that the child was alive when fed at approximately 11 p.m. and was found dead at 8 a.m., and on that basis we felt it best to assume that death occurred after midnight—that is, deaths occurring during the Sunday night after the child had been put to bed, and in which the child was found dead on the Monday morning are grouped as Monday deaths. There are two points of interest in Fig. 3: first, the relatively slight overall difference in the total number of sudden deaths during different parts of the week; and, second, the difference between the site of death in the latter half of the week and those at the week-end. On Thursday—that is, Wednesday night and Thursday—approximately the same number of children died as on Sunday night and Monday, but the site of death is quite different. There would appear to be a tendency for death to occur at home during the week-end and in hospital during the week.

"Face-down in Pillow"

What appeared to be an accurate description of the position in which the child was found dead was available in 84 children. The position of the child related to its age is expressed in Fig. 4. These figures have only relative value, as we are not able at this point to state the exact proportion of children who would normally sleep in either the face-up or the face-down position. Two things, however, appear: one is

that there seems to be a relatively large proportion of deaths "face down" during the first month, when it is extremely unlikely for a child to be able to turn itself on to its face unless it was virtually placed there originally; and, secondly, the relatively even distribution of face-down position was not found over the age of 9 months. These figures may be biased, as there is a tendency to report the position of a child being found dead face-down and not record the position when the child was face-up. A large number of histories are definite one way or the other, and this point is always recorded when taking histories from coroners' cases. The face-down position does not presumably occur in ambulance deaths, as the children are under constant supervision during this time, but these cases are not included in Fig. 4.

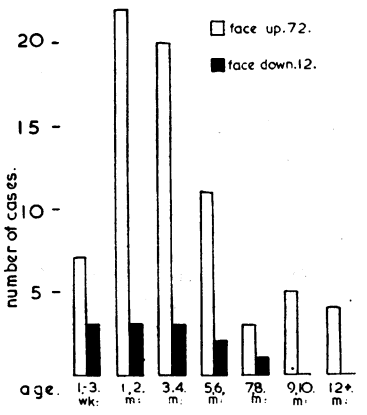

FIG. 4.—Position in which child was found dead related to age of child.

Necropsy Findings

It is not proposed to discuss pathological problems to any extent. Why one child dies with such a minimal amount of, say, pneumonia as to require careful histology to reveal it, and another child survives gross pulmonary infection, is one of the most intriguing problems of pathology. Here are listed only the general pattern of morbid anatomical lesions found. Of the 249 cases, disease of long standing was found in 83; in 37 of these the deformity had been previously known to exist; in 46 the diagnosis was made only after death. The deformities formed a wide range, including many congenital abnormalities of the heart, mongolism, bilateral hydronephrosis with infection, diaphragmatic hernias, etc. Of the remaining cases, lesions which were possibly of pathological significance were found in 145, and in 21 no morbid anatomical diagnosis of any known significance was seen. These 21 children varied in age from 23 days to 5½ months: seven died in bed with parents, two in hospital, nine face-up, three face-down.

Principal Lesions Found in a Survey of 249 Deaths in Children Giving a History of Disease of Less Than 48 Hours' Duration

Disease of long standing			83
Diagnosed during life		37	
Heart disease	12		
Chronic sepsis	0		
Diagnosed after death		46	
Heart disease	8		
Chronic sepsis	10		21
No pathological lesion found			112
Acute infection of respiratory tract			
Acute infection of upper respiratory tract	24		
Laryngotracheobronchitis	35		
Acute suppurative bronchiolitis	13		
Bronchopneumonia	30		
"Necrotizing bronchitis"	10		
Oedema of the lung			57
Meningitis			14
Septicaemia			35
Onset of a known infectious disease			11
Waterhouse–Friderichsen syndrome			19
Pertussis			7
Acute hepatitis			5
Polioencephalitis			5

The general pattern of lesions found does not differ greatly from that seen in other surveys (Bowden and French, 1951), and can best be assessed from the Table and the age distribution of some of the common cases in Fig. 5.

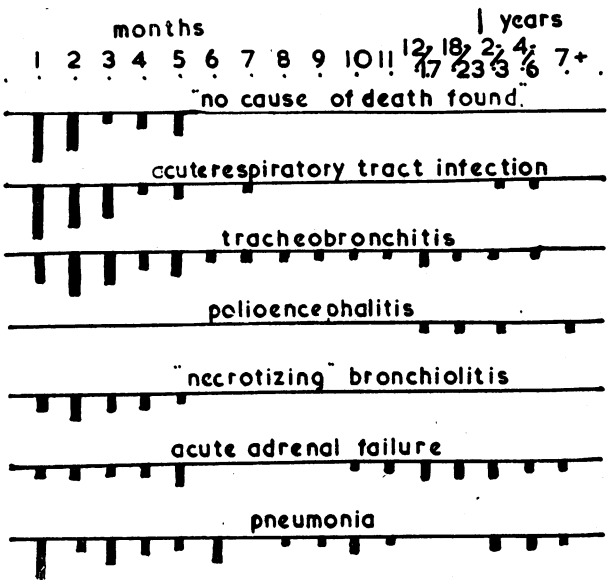

FIG. 5.—Relative age distribution of some of the lesions found in present series of child deaths.

The first most striking feature is the high proportion of child deaths coming into this survey. Here are combined both early hospital deaths and home "cot" deaths. In a series of 150 hospital deaths in 1955, 66 were in children dying within 24 hours of admission (*B.M.J.*, 1957). A difficulty in assessing the relative incidence in the general population is that the certification of these deaths is very variable in some areas. Death from "suffocation" is recorded in some localities; in others "acute pneumonia" will cover the same cases. In a study of accidents in childhood, Boucher (1958) records 415 deaths from suffocation out of a total of 692 children dying at home under the age of 4 years in 1955, and in the years 1950–4 the death rate per million from accidents under the age of 1 year was 749 "suffocation" compared with 28 burns and scalds, and 6 motor accidents. This ratio is reversed in later childhood. Deaths ascribed to accidental suffocation per annum are quoted at 200 (*B.M.J.*, 1958), and 20% of a series of 1,400 deaths in 1955 (Banks, 1958). Swinscow (1951) gives the figures from 1940 to 1949 at between 446 and 911 a year.

In the present series there appears to have been an upward trend in the proportion, varying from 25% to 46%, and one would expect that, in an area which does not contain a hospital liable to attract children likely to die from chronic and rare diseases, the proportion of deaths in this category would approach 50% of all infant deaths. The deaths were not all in children who had been completely normally formed, but congenital abnormalities of themselves likely to cause death accounted for less than 10%. The residue were to all appearances normally formed, and but for this "natural accident" of fulminating illness would presumably have had a normal expectation of life. Over half of the children died either at home or on the way to hospital, and a large number of those who reached hospital died within minutes or a few hours of admission. It is probably an understatement to say that three-quarters of these children died before they were even examined by a paediatrician.

Our figures show, in common with all other surveys, an increased proportion of child deaths in the category under 1 year and a diminishing proportion over this age. Also, from a study of the time of the year and the relative proportions of sudden death, we find that, on top of the known annual variation in the time of these acute deaths (Bowden and French, 1951 ; Stowens, 1957), the proportion of sudden deaths, as well as the absolute numbers, is also much higher in this period.

The apparent variation in site of death during the week and week-end could be a reflection of the patient–doctor relationships at different times of the week—that is, in a number of cases, when I have been able to discuss the child's death later, it seems that the parents knew that the child was ill. They did not realize that it was severely ill, and thought that they would wait until the doctor was back or on duty again on Monday before calling him in, or taking the child to the surgery. It would seem likely that this increased death rate at home at the week-ends is a reflection of this attitude of parents to the medical profession. Parents have also stated that they have known that their own doctor was not on duty at the week-end, and that one of the partners would be called in, and for that reason they had delayed calling in a doctor.

The feature, however, which is probably of even more importance is that an almost similar number of deaths occur during the week-days as at the week-end, which suggests that, even if the doctors had been called to the children, in a large number of instances the death could not certainly have been prevented. On the other hand, we know of many instances in which, but for the prompt intubation and aspiration in the reception rooms of the hospital, children would have died from tracheobronchitis.

Summary

A study was made of 249 children over the age of 7 days who died in Sheffield during the years 1949 to 1956. During these seven years the number of deaths from disease with symptoms of less than 48 hours' duration appeared to remain constant, and possibly increased relative to other diseases.

The proportion of rapid deaths from disease of longer standing appeared to remain constant up to the age of a year. Over that age rapid death became less common.

Death face-down in a pillow showed no particular age distribution.

Of the deaths 120 occurred at home, 13 in an ambulance, and 116 in hospital.

Rapid deaths appeared to be both absolutely and relatively more common in the winter than in the summer months of the year.

While the total number of deaths varied little on different days of the week, there appeared to be a greater tendency for deaths to occur at home at the week-end, and in ambulance or hospital on a week-day.

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DIURETIC EFFECT OF HYDROFLUMETHIAZIDE

BY

J. H. JONES, M.B., M.R.C.P.
Registrar in Clinical Pathology

AND

J. VERRIER JONES, B.M., M.R.C.P.
Lately Senior House Officer in Medicine
Queen Elizabeth Hospital, Birmingham

Following the synthesis of chlorothiazide, a benzothiadiazine derivative, various studies, including those of Ford *et al.* (1957) and Bayliss *et al.* (1958), showed that it was the most effective compound yet produced in the search for non-mercurial and non-carbonic-anhydrase-inhibiting oral diuretic agents.

Hydroflumethiazide (6-trifluoromethyl-7-sulphamyl-3, 4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide) is a new benzothiadiazine derivative. This paper reports the response of 21 oedematous patients treated with this drug, and also the effect of a single dose of hydroflumethiazide on the pattern of urinary excretion in five non-oedematous males.

Preliminary studies (Kobinger and Lund, 1958; Holbolth *et al.*, 1958; Sele, 1958) have shown that hydroflumethiazide is an effective oral diuretic and is between 15 and 20 times more active than chlorothiazide in comparable dosage. The present studies confirm this diuretic effect and in addition show that hydroflumethiazide does not significantly inhibit carbonic anhydrase.

Method

Twenty-one consecutive patients with oedema were treated with hydroflumethiazide. The patients were observed for a minimum of three days before hydroflumethiazide was given, except for five cases whose clinical condition did not justify delay. With three exceptions the duration of hospital treatment was between three and four weeks. Half the patients had received various diuretics, and all except three of the cases of heart failure (cases 7, 11, and 12) had been digitalized before admission. Throughout their stay in hospital patients received a low-sodium diet (15 mEq daily). Potassium supplements were not given as a routine. Hydroflumethiazide was given in a dose of 100 or 200 mg. at 6 a.m. and 12 noon on four consecutive days per week. Patients were weighed daily, and 24-hour urine collections were made from midnight to midnight. Weekly blood counts were performed, and serum electrolytes were measured at least once a week. In nine patients urine electrolytes were measured daily.

In the study of the effect of a single dose of hydroflumethiazide the subjects were five adult male convalescent patients who had never been oedematous. On the control day urine was collected under liquid paraffin every two hours for the first 12 hours, and the urine passed in the last 12 hours was collected and studied as a single specimen for each patient. The volume and sodium, potassium, and chloride content of each specimen were measured, and on the specimens