When nephropathy supervenes the serum albumin falls further and the γ -globulin sometimes falls towards or into the normal range, presumably because of urinary loss, as was demonstrated in one of our patients. This urinary loss of γ -globulin undoubtedly includes L.E. factor, for this has been demonstrated in the urine (Korting and Schmitz, 1952), and we have noticed that in patients with proteinuria and a normal γ -globulin level the L.E. cells are demonstrable only with difficulty and in scanty numbers. On the other hand, the α_2 -globulin rises to normal levels when proteinuria is present. This is found in the nephrotic syndrome whatever the aetiology, and presumably represents selective retention by the damaged kidney of the high molecular weight α_2 -globulin.

It seems likely that the reason we have rarely found actual increases in the serum α_2 -globulin, as has been reported by other workers, is because we have expressed the protein values in absolute figures and not as percentages, which in this instance, at least, would be misleading.

Even though the serum protein changes in systemic lupus erythematosus are not specific they have diagnostic value in a negative sense. This disease is most unlikely in a patient with a normal serum γ -globulin level in the absence of considerable proteinuria. Unfortunately, changes in the other protein fractions are too slight and too inconstant to be helpful.

In systemic lupus erythematosus the serum proteins probably have little prognostic value, for though those patients with a very low albumin and a normal or only slightly raised γ -globulin level did progress to an early death, this can be forecast from the invariable presence of severe nephropathy.

Summary

The total serum proteins and electrophoretic fractions were measured in a group of patients with systemic lupus erythematosus and compared with the results obtained from a healthy control group.

Eighteen untreated patients with systemic lupus erythematosus but without persistent proteinuria showed statistically significant increases in the total protein and γ -globulin levels and reductions in the albumin, α_2 - and β -globulin levels that were probably significant. The raised γ -globulin was quantitatively the most striking change, and was above the upper normal limit in 17 of the 18 patients.

Seven patients with systemic lupus erythematosus and persistent proteinuria (five were untreated, two were on small doses of steroids) were compared with the 18 patients without proteinuria and showed significantly lower total protein and albumin levels and a higher α_2 -globulin level. The γ -globulin level was lower, but not significantly so. The α_2 -globulin level in the patients with proteinuria was not different from that of the healthy controls, but the γ -globulin was still significantly raised.

Therapeutically induced remissions were accompanied by a reversal of the serum protein changes towards normal, but it was exceptional for the γ -globulin actually to reach normal levels.

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TUBERCULOSIS IN THE FAMILY

BY

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Recent years have seen a fall in the mortality and the incidence of all forms of tuberculosis in children and adults, and it is sometimes assumed that tuberculosis is becoming a relatively unimportant disease. The fall in tuberculous morbidity, however, is much slower than the fall in mortality, and tuberculosis remains among the most important of communicable diseases. In children the source of infection is now almost always an adult contact with pulmonary tuberculosis. The observations described here on tuberculous children and the adults in contact with them indicate the continuing significance of this aspect during a time when many changes are occurring in the management of tuberculosis and in the type of disease seen. The cases described were observed over a period of seven and a half years between 1951 and 1958. The district covered by the two chest clinics and the hospital group is primarily residential, and the overall incidence of tuberculosis is not unduly high. The type of tuberculous disease seen in 87 children under 14 who were treated in the paediatric department is shown in Table I. The disease was classified as primary or disseminated. *Primary* was taken to include mediastinal adenitis with or without segmental collapse, pleural effusion, cervical adenitis, abdominal adenitis, primary cutaneous lesions, and positive tuberculin tests in children under 4 years of age. *Disseminated* included meningitis, miliary tuberculosis, bone and joint disease, renal disease, and adult-type pulmonary disease.

TABLE I.—Type of Tuberculous Disease in 87 Children

Primary Disease (62 Cases)		Disseminated Disease (25 Cases)	
Bronchial adenitis only	27	Meningitis only	10
" " with		" " with miliary	4
segmental collapse	11	Miliary only	2
Pleural effusion	9	Bone and joint	6
Cervical adenitis	7	Renal	1
Abdominal	3	Adult-type pulmonary	2
Cutaneous	2		
Aged 3 and under with positive tuberculin test	3		

Tuberculosis in childhood may be diagnosed after the investigation of suspicious clinical symptoms or by examination of the child contacts of adult cases of tuberculosis in the chest clinic. The diagnosis in these 87 cases was made by the hospital clinician in 64 cases (39 primary and 25 disseminated) and at the chest clinic in 23 (all primary).

The clinical features of tuberculous disease in childhood are so varied as to cover the whole field of medical or surgical diagnosis among children. The principal features encountered are shown in Table II.

TABLE II.—*Clinical Features in 87 Tuberculous Children*

Vague ill-health	30	Other skin lesions	2
Loss of weight	10	Phlyctenular conjunctivitis ..	2
Pyrexia of uncertain origin ..	6	Abdominal pain	9
Irritability	12	Cervical adenitis	8
Drowsiness	9	Enlarged spleen	2
Convulsions	3	Limb pain	8
Neurological signs	4	Back	3
Cough	15	Deformity	4
Chest pain	16	Limp	5
Signs in chest	12	Dysuria	2
Erythema nodosum	7	No symptoms	4

The early diagnosis of tuberculous meningitis provided the most urgent problems. Meningitis was present in 14 children while 19 others required lumbar puncture to exclude the diagnosis. There were other clinical features of note. Abdominal pain was a prominent feature in five children with primary intrathoracic disease, and in one an appendectomy was performed. Enlargement of the spleen was not seen in miliary disease, but was noted in two small children who had large primary complexes. Chest pain and cough were more common than expected, although in general neither symptom was severe. Only four children were completely free from symptoms among the 23 diagnosed on contact examination at the chest clinic.

Tuberculin-testing

The clinical manifestations being so varied, it is generally agreed that tuberculin-testing plays an important part in the diagnosis of tuberculosis in childhood. All the children in this series had positive tuberculin tests. No convincing example of tuberculosis of any type with a persistently negative tuberculin test was found.

During the period 1955–8 tuberculin tests were performed on 920 children admitted to hospital and 69 (7.5%) were positive or doubtful positive. In 33 (48%) of these 69 and 3.5% of the total tested tuberculosis was diagnosed. Figures are unfortunately not available for the earlier period. The children tested were a sample of hospital in-patients selected by symptoms which might be caused by tuberculosis.

By comparison the incidence of positive tuberculin tests in local school-children of 13 prior to B.C.G. inoculation was 11% in 1954–5 and 7% in 1957–8. These figures are similar to the incidence of positive reactions of children in hospital with symptoms compatible with tuberculosis, but the hospital group was composed of much younger children, and nearly half the positive reactors required treatment for tuberculous disease.

Sources of Infection

A probable source of infection was found in 74 of children (Table III) and in 13 it was not known. Two possible adult sources of infection were present in nine instances, but only the most probable is shown in Table III. A likely source of infection was found

TABLE III.—*Sources of Tuberculous Infection in 74 Children*

	Father	Mother	Grand-parents	Uncles/Aunts	Siblings	Others	Milk	Total
Probable infecting contact ..	20	9	10	8	2	10	—	59
Known sputum-positive ..	17	8	8	6	1	6	—	46
No. of children infected ..	26	10	11	9	2	10	6	74

in 85% of the children, and in 78% the disease appeared to be of human origin. Among the 13 children for whom no source could be found were five whose homes were in streets where tuberculous adults were known to live. Sources of human infection outside the family included a tuberculous landlady, dwellers in the same block of flats, and a greengrocer. No case of tuberculosis in a child could be traced to a school infection.

Milk-borne Disease.—During 1951–2 five cases of tuberculosis (two of cervical adenitis, two of abdominal adenitis, and one of spinal disease) occurred in children whose family milk supply had been from a local dairy, where heavy tuberculous infection had occurred. During 1954 a boy aged 5 developed abdominal adenitis after drinking tuberculous milk while on holiday.

Changes in the Management of Tuberculosis

During the period of observation many changes occurred in the management of tuberculous disease. Effective and prolonged chemotherapy, thoracic surgery, B.C.G. inoculation, the disappearance of sanatorium waiting-lists, and a more radical approach to the treatment of primary disease are factors which have played a part. The widespread use of isoniazid, an adequate number of beds for tuberculous adults, and B.C.G. inoculations are all factors which made their appearance between 1952 and 1954. That there has been a considerable change in the type of case seen in children and their contacts is shown in Table IV, in which the type of tuberculosis seen is compared with the estimated period of contact with the source of infection. A short period of contact was considered to have occurred when the adult source of infection had recent disease, or short or very intermittent contact with the child, while long-standing contact was considered to have occurred when the adult disease was severe or chronic, and the child lived in the same house or saw the adult repeatedly.

TABLE IV

	1951–4	1955–8
Children with primary disease ..	37	25
“ „ disseminated disease ..	17	8
Contact—Short	10	19
adult or Long	34	11
milk Unknown	10	3

The change in the character of the disease seen is further shown by the observation that 15 of the 25 children with primary tuberculosis in the period 1955–8 had mediastinal adenitis only, while of the 11 cases of long-standing contact 6 were due to sputum-positive tuberculous grandfathers.

In this latter period the incidence of adult cases with short contact with children was doubled and the incidence of disseminated disease in the children was

halved, while a source of infection could not be found in only three of the 33 children seen.

Diagnosis of the Adult Contacts

Most of the adult contacts were diagnosed in chest clinic practice, and the tuberculous children in the present series who were found on contact examination of these patients form only a proportion of the primary infections diagnosed in the chest clinic. In many other instances a family history of tuberculosis was found when children were admitted to hospital, although in a number of cases the information was not obtained without repeated questioning.

When no information could be gained from the family history of a child who appeared to have tuberculosis the family contacts were thoroughly investigated. It was usually found expedient to radiograph the suspect adults immediately after discussion of the child with the paediatrician. Seven previously unsuspected cases of tuberculosis in adults were revealed in this manner, five in the father, one in the mother, and one in an elder sister of 17. Six of these seven previously unsuspected cases of tuberculosis had tubercle bacilli in their sputum. Although few in number these adults were the source of an undue proportion of the most serious cases in children. Of their child contacts, one died of miliary tuberculosis, while two others were cases of tuberculous meningitis with disastrous permanent brain damage.

Four children died of tuberculosis. One, mentioned above, was a child of 18 months with extensive miliary disease affecting all organs. Another was a child of 12 months admitted to hospital with convulsions and hemiplegia. She was a contact of an elderly man with open pulmonary disease who lived in the flat above. The other two were both mongol mental defectives, aged 9 and 13, admitted to hospital with advanced meningitis and living only a few days.

Two other children, both under 3 years old, were left with permanent severe brain damage from meningitis. These two children, with the two mentioned above who were under 2 years of age, form 25% of the 16 children under 2 seen in this series.

Although the incidence of serious tuberculous disease in childhood and the contact of children with infectious tuberculous adults both show a substantial reduction over the past seven years, the need for continued vigilance is indicated by the cases seen during 1958.

Case Reports

Case 1.—A carpenter aged 41 failed to regain normal strength after "Asian 'flu" in November, 1957. He was referred for chest x-ray examination and found to have a large apical cavity on the day his 5-year-old daughter became unwell. His family doctor's alert appreciation of the possibility of tuberculosis led to the very early diagnosis of miliary and meningeal tuberculosis in the child, with complete recovery on treatment. His 9-year-old daughter was also treated for primary tuberculosis.

Case 2.—A 5-year-old child from Ireland developed tuberculosis cervical adenitis. No source could be found.

Case 3.—A boy of 12, examined as a contact, developed an apical focus. His grandfather, who lived in the same house, became unwell with cough and sputum, and was found to have open tuberculosis. The boy was virtually symptom-free and his lesion cleared with chemotherapy.

Case 4.—A 34-year-old engineer felt "run-down" for three months. Mass x-ray examination of his chest showed

tuberculous cavities, and tubercle bacilli were found in his sputum. Both his sons were infected—one aged 8 had mild pleural pain and hilar adenitis, and the other, aged 5, had loss of weight, massive adenitis, and segmental collapse.

Case 5.—A girl of 12 developed a pleural effusion, and tubercle bacilli were isolated from the fluid. No source of infection was found in her large family or at her school. An elderly man with chronic fibroid phthisis and tubercle bacilli in his sputum lived in the same row of cottages, and the girl said she had often passed him as he was coughing.

Case 6.—A boy of 6 was admitted to hospital with general ill-health and a low-grade pyrexia. A tuberculin test was positive and he had hilar adenitis. No tuberculosis was found in his family, but an elderly man living in the flat above him had become unwell and was found to have pulmonary tuberculosis with tubercle bacilli in his sputum. The boy had often visited him.

*Case 7.**—A girl aged 18 months was admitted to hospital with convulsions and hemiplegia. A choroidal tubercle was seen in the fundus oculi. Tubercle bacilli were isolated from the cerebrospinal fluid. In spite of intensive treatment with streptomycin, isoniazid, P.A.S., and steroids she remained spastic, and developed optic atrophy and mental defect. In retrospect it seems that she did not recognize her parents for three days before admission, and had been unwell for two weeks. On x-ray examination of her family contacts, her father, a 41-year-old stoker, was found to have advanced bilateral cavitated tuberculous disease with tubercle bacilli in his sputum. He had a chronic cough. His brother and sister had had tuberculosis in the remote past, but he had never attended a chest clinic. He had been a prisoner of war in the Far East. Eighteen months after his return home in 1946 his 6-months-old son had died of meningitis, the infecting organism not being known. It seems probable that this infant had tuberculous meningitis. The tubercle bacilli isolated from this man's sputum and his daughter's cerebrospinal fluid were resistant to isoniazid, and only partially sensitive to streptomycin. As he had never received any previous treatment, it would appear that his infection was due in part to primarily drug-resistant organisms.

Thus, an account which is mainly of improved prognosis for tuberculous children and adults ends on the sinister notes of drug-resistant organisms and unsuspected infectious disease, the most pressing problems in the modern management of tuberculosis.

Discussion

In the observations described above there was rarely any conclusive evidence that any individual child was infected by a particular adult. Taken together, however, they indicate the importance of close contact with adult cases in the causation of tuberculosis in children, and are in accord with the observations in a much larger series in Sheffield in the period 1947–52 (Briggs *et al.*, 1955), when a human source was found in 81% of 401 cases of miliary, meningeal, or primary tuberculosis in children. They show, too, the particular dangers of the "sputum-positive" adult in the home, which was emphasized by van Zwanenberg (1955) in a survey of the contacts of 483 cases in Suffolk in 1949–53. Other observers, however, have found a lower incidence of contact with known cases. Half of a group of London school-children dying of tuberculosis between 1948 and 1952 had no history of tuberculous contact (Bentley *et al.*, 1954). In a tuberculin survey of East London school-children a source of infection was found in 41 out of 154 tuberculin-positive children, but in only 19 was the index case in the child's family

*This child has since died (of bronchopneumonia).

(Silver, 1958). In an earlier survey in Edmonton, in 1952-3, Davies (1955) observed that one or more known cases of tuberculosis resided in 65% of the streets of the borough, a condition in which infection of children outside their homes might be common.

When considering the relative influence of heredity and environment in the development of tuberculosis in 6,537 domiciliary contacts of 2,330 cases, Anderson *et al.* (1957) concluded that closeness of contact with the index case and the degree of infectivity of the case were the main factors in the development of tuberculous disease in children or adults living in the same house, irrespective of relationship. Whether children are infected by their relatives or by other adults, in their homes or elsewhere, would seem to depend mainly on the location of the infectious adult. The disappearance of sanatorium waiting-lists may well have been among the most important factors in the lowered incidence of tuberculous disease in children in recent years. In the mainly residential area of Surrey, where the patients in the above series lived, it is not surprising that the main source of infection should be within the home, while a number of children who appeared to have been infected from outside the home lived in blocks of flats.

It seems unlikely that there is anything exceptional in the observations we describe. They show, however, the value of co-operation between paediatrician and chest physician. For the paediatrician, tuberculosis remains one of the main clinical problems, a cause of morbidity and mortality as great as poliomyelitis, rheumatism or pyogenic infection, while tuberculin-testing of ill children appears to be an investigation of increasing value as the general level of tuberculous infection falls. For the chest physician, a tuberculous child is indicative of an infectious adult, occasionally of an undiscovered case. The danger to children of the open case of tuberculosis serves to emphasize the need to find and treat infectious disease, and to offer protection with B.C.G. to all children and adolescents likely to be in contact with tuberculous infection.

Summary

During the period 1951-8 a series of 87 tuberculous children were seen in the paediatric department of the Kingston Hospital Group: 62 had primary disease and 25 had various forms of disseminated disease.

A likely source of infection was traced in 74 of the 87 children. 68 appeared to have been infected by 59 tuberculous adults in contact with them—36 by parents, 22 by grandparents, uncles, aunts, and siblings, and 10 by adult contacts outside the family. Six children were probably infected by tuberculous milk. No source of infection was found in 13 cases.

Comparison of the periods 1951-4 and 1955-8 shows that the incidence of disseminated tuberculous disease in children fell from 17 to 8 cases; the incidence of prolonged contact between tuberculous adults and children fell from 34 to 11; and the incidence of an unknown source of infection in a child fell from 10 to 3 cases.

These observations emphasize the continuing need to regard tuberculosis as a serious problem, and to realize the danger to children of the tuberculous adult.

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USE OF HYDROXYDIONE IN PSYCHIATRY*

A CONTROLLED EXPERIMENT

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Ever since Bleckwenn (1930) and Horsley (1936) wrote on the use of intravenous barbiturates in psychiatric disorders, almost every new drug with narcotic or anaesthetic properties has been investigated by psychiatrists for the purpose of facilitating interviews, providing relaxation, reinforcing reassurance, uncovering repressed material, or promoting abreactions.

It was natural that, after the report on the anaesthetic properties of certain hormones by Selye (1941), these, too, should be investigated by psychiatrists. Selye (1942) stated that the most powerful anaesthetic actions are exhibited by steroids oxygenated at opposite ends of the molecule and having no double bonds in the rings. There was no correlation between hormonal and anaesthetic action.

Hydroxydione (21-hydroxypregnane-3,20-sodium hemisuccinate) is now widely used for its anaesthetic properties. Its empirical formula is $C_{25}H_{35}O_6Na$. This substance has no hormonal action and no salt-retaining properties in man unless given in very large doses. Its administration is safe, the LD_{50} being three times that of sodium thiopentone.

The action of the drug has been studied by Gordan *et al.* (1956), who report a decrease in cerebral blood flow, inhibition of oxygen uptake, and a decreased glucose uptake such as is found in pethidine and barbiturate anaesthesia. *In vitro* experiments were carried out by Elliott *et al.* (1957), and the effect of hydroxydione was compared with that of other anaesthetics. The findings of these and other authors suggest that the main action of the substance is on oxidative reactions, and especially on the inhibition of the entrance of glucose into the tricarboxylic acid cycle. Though Batt and Dally (1958) and O'Flanagan and McGuinness (1958) have written on the uses of hydroxydione in psychiatry, no controlled investigation has yet been carried out.

Experimental Method

It was decided that in order to assess the value of hydroxydione, it was necessary to compare its action

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