Though several papers have been published on the part played by allergy in staphylococcal infections (Elek, 1959), nothing of practical value has so far emerged from experiments involving allergy. This line of investigation is unpromising.

Conclusion

Antitoxic immunity is only one factor in the control of infection generally. There is a close parallel between staphylococcus antitoxin and haemolytic streptococcus (scarlet fever) antitoxin in that both protect rabbits against intravenous lethal doses of culture without disposing of all the invaders: temporary recovery from the inoculation is followed by abscess formation (metastases) in various sites.

In man, also, staphylococcal and streptococcal infections may persist in spite of procedures designed to raise the concentration of serum antibodies to the highest possible level. Nevertheless, there is evidence, which appears adequate, that staphylococcus antitoxin will prevent some fatalities from staphylococcal infection in human subjects, and that the administration of alpha toxoid may be useful in many cases of superficial infection.

Suggestions have been made in this paper for "improving" antigens and antibodies in various ways. But humoral immunity is not the full story: there is an elusive "something else," and the study of staphylococcal infection—and indeed of infection generally—"will have taken a great step forward when the nature of this other factor is brought to light" (*Brit. med. J.*, 1937).

REFERENCES

Blair, J. E. (1937). *Proceedings of the Second International Congress of Microbiology, London, 1936*, p. 518.
—— (1958). In *Bacterial and Mycotic Infections of Man*, edited by R. J. Dubos, 3rd ed., p. 325. Pitman, London.
Boivin, A., and Izard, Y. (1937). *C.R. Soc. Biol. (Paris)*, **124**, 25.
Branch, A. (1938). *Canad. med. Ass. J.*, **39**, 391.
Brit. med. J., 1937, **2**, 860.
Burnet, F. M. (1929). *J. Path. Bact.*, **32**, 717.
—— (1930). Ibid., **33**, 1.
—— (1931). Ibid., **34**, 471.
—— and Freeman, M. (1932). Ibid., **35**, 477.
Dolman, C. E. (1934). *Canad. med. Ass. J.*, **30**, 601; **31**, 1, 130.
—— (1956). *Canad. J. Microbiol.*, **2**, 189.
Downie, A. W. (1937). *J. Path. Bact.*, **44**, 573.
Ede, S., Davis, G. M., and Holmes, F. H. (1959). *J. Amer. med. Ass.*, **170**, 638
Elek, S. D. (1959). *Staphylococcus Pyogenes and its Relation to Disease*. Livingstone, Edinburgh and London.
Fisher, M. W. (1959). *Nature (Lond.)*, **183**, 1692.
Glenny, A. T., and Stevens, M. F. (1935). *J. Path. Bact.*, **40**, 201.
Holt, L. B. (1936). *Brit. J. exp. Path.*, **17**, 318.
Jochmann, G. (1924). *Lehrbuch der Infektionskrankheiten*, 2nd ed. Springer, Berlin.
Kitching, J. S, and Farrell, L. N. (1936). *Amer. J. Hyg.*, **24**, 268.
Kleiger, B., and Blair, J. E. (1943). *Arch. Surg. (Chicago)*, **46**, 548.
Lowenstein, P. S. (1931) *Amer. J. med. Sci.*, **181**, 196.
Macdonald, T. C, and Taylor, F. (1951). *Lancet*, **2**, 558.
Murray, D. S. (1935). Ibid., **1**, 303.
Negro, R. C., Gentile-Ramos, I., and Galiana, J. (1956). *An. Fac. Med. Montevideo*, **41**, 263.
Okell, C. C. (1932). *Lancet*, **1**, 761, 815, 867.
—— and Parish, H. J. (1928). Ibid., **1**, 748.
Otten, M. (1907). *Dtsch. Arch. klin. Med.*, **90**, 461.
Panton, P. N., and Valentine, F. C. O. (1929). *Brit. J. exp. Path.*, **10**, 257.
—— —— (1932). *Lancet*, **1**, 506.
Parish, H. J., and Clark, W. H. M. (1932). *J. Path. Bact.*, **35**, 251.
—— and Okell, C. C. (1927). Ibid., **30**, 521.
Ramon, G., Richou, R., Mercier, P., and Holstein, G. (1946). *Rev. Immunol. (Paris)*, **10**, 71.
Soper, W. B. (1912). *Proc. N.Y. path. Soc.*, **12**, 223.
Stuart-Harris, C. H. (1959). *Brit. med. J.*, **1**, 1606.
Tasman, A., Brandwijk, A. C., Marseille, A., van Ramshorst, J. D., and van der Slot, J. (1952). *Antonie v. Leeuwenhoek*, **18**, 336.
—— and van der Slot, J. (1953). Ibid., **19**, 256.
Valentine, F. C. O. (1936) *Lancet*, **1**, 526.
Wittler, R. G., and Pillemer, L. (1948). *J. biol. Chem.*, **174**, 23.

OBSERVATIONS ON 100 CASES OF LEUKAEMIA IN CHILDHOOD

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[WITH SPECIAL PLATE]

Deaths attributed to leukaemia at all ages in England and Wales have increased two and a half times in the last two decades (Registrar-General's Statistical Review, 1938–57). In childhood there is now a peak incidence between the ages of 2 and 4 years (Hewitt, 1955). Acute leukaemia accounts for nearly 25% of cases of malignant disease admitted to the Hospital for Sick Children, Great Ormond Street. In this paper a survey of clinical and radiological findings is presented and an analysis made of the form and duration of remissions induced by antileukaemic agents. Steroids are prominent in treatment, and the place of antimetabolites has been firmly established since the original studies of Farber *et al.* (1948) on folic-acid antagonists and of Burchenal *et al.* (1953) on 6-mercaptopurine. Remission therapy can lengthen life and can change the clinical course of the disease. It can also affect pathology; references to infiltration of the kidneys (Pierce, 1957) and intracranial structures (Sullivan, 1957) are made in this paper.

Material

This report is based on 100 cases admitted to the Hospital for Sick Children between September, 1951, and March, 1957. The diagnosis was confirmed by marrow examination in every case. Twenty other children attending with leukaemia during the same period are omitted because 17 of them were treated elsewhere after confirmation of the diagnosis and three were suffering from lymphosarcoma with leukaemic termination.

TABLE I.—*Age and Sex Distribution in* 100 *Cases of Leukaemia in Childhood*

Age on Admission (Years)	Males	Females	Total
0–1	1	3	4
1–2	3	4	7
2–4	15	10	25
4–6	10	12	22
6–8	11	12	23
8–10	7	6	13
Over 10*	4	2	6
Total	51	49	100

* Twelve years is maximum age for admission.

The age and sex distribution are shown in Table I. Sex incidence was equal. Aetiological factors were not investigated, as those children who died between 1953 and 1955 had already been included in a study on the antecedents of childhood leukaemia (Stewart *et al.*,

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1958); three of our series were mongols, an incidence similar to that of the above survey.

Clinical Features

A summary of the presenting symptoms and signs is shown in Table II. The average duration of history was six weeks. Eight children had had symptoms for

TABLE II.—*Initial Clinical Picture* (100 *Cases*)

Main Symptoms	No. of Cases	Main Signs	No. of Cases
Pallor	54	Pyrexia	80
Malaise	51	Lymphadenopathy	75
Limb pain	37	Splenomegaly	73
Anorexia	23	Hepatomegaly	69
Bruising	23	Petechiae or ecchymoses	65
Neck swellings	12	Ulceration of mouth or fauces	11
Vomiting	12	Skin infiltration	4
Cough	8	C.N.S. signs	4
Backache	5	Proptosis	3
Dyspnoea	5		

less than one week; three had been ill for over one year. Pallor, limb pain, and skin haemorrhages were prominent initial symptoms. A few patients presented with swellings involving skin (four cases), bone (two cases), vulva (one case), and parotid glands (one case). In three cases proptosis was a presenting feature; hemiplegia was an initial manifestation in two, while facial and third-nerve palsy were presenting signs in one case each.

Initial Haematology in the Acute Cases (98 Patients)

Table III shows that leucocytosis (30 cases) was encountered more often than leucopenia (25). Leucocytosis was nearly always accompanied by abnormal cells in the peripheral blood (26 out of 30); in contrast, cases without leucocytosis frequently had only mature cells in the differential count (32 out of 68). Fourteen

TABLE III.—*Representative Peripheral Leucocyte Count in Untreated Stage* (98 *Cases of Acute Leukaemia*)

Total White Blood Cells	No. of Cases	Predominant Cell Type		
		Polymorphs (No. of Cases)	Lymphocytes (No. of Cases)	"Blast" Cells (No. of Cases)
Under 5,000 per c.mm. (leucopenia)	25 } 68	4*	51†	13
5,000–15,000 per c.mm.	43 }			
Over 15,000 per c.mm. (leucocytosis)	30	3‡	8§	19
Total	98	7	59	32

* 1 had leukaemic cells. † 18 had leukaemic cells. ‡ 3 had leukaemic cells. §[4 had leukaemic cells.

children had a haemoglobin level over 75% (11 g. per 100 ml.) when first seen, and in six of these leukaemic (blast) cells were not seen initially in the peripheral blood. Bone-marrow examination disclosed a normal picture on the first occasion in three children; in a further case the marrow was aplastic and in another hypoplastic. The marrow in all other cases was already leukaemic on initial examination. Precise subdivision of leukaemic cells into lymphoblastic and myeloblastic types was not attempted, because differentiation between these stem cells is not feasible by ordinary haematological techniques. Special categories recognizable in this series by their haematological findings and clinical course were acute monoblastic, acute plasma-cell, and chronic myeloid leukaemia.

Acute Monoblastic Leukaemia (5 Cases)

Cells resembling primitive monocytes were found in blood and bone marrow. Ulceration of skin and oral mucous membrane was frequent. There was a rapid deterioration in all five. Remission was not obtained in the two cases treated.

Plasma-cell Leukaemia (1 Case)

S. M., a female aged 7 months, developed pallor, refused to feed, and vomited blood. Slight jaundice was present. Petechiae were found on the soft palate. There was marked enlargement of the liver and spleen. The haemoglobin level was 48% (7.1 g. per 100 ml.). Initial leucocyte count was 8,400 per c.mm., with 64% lymphocytes and 36% polymorphs. Primitive cells were also absent in the only subsequent blood count. The bone marrow contained numerous round reticular basophil cells, compatible with either erythroid or plasma-cell origin. Filter-paper electrophoresis of the patient's serum showed an abnormal pattern (α_1 globulin high, α_2 globulin low, β globulin possibly raised; no comment was made regarding the γ-globulin band). Progress of the disease was rapid and the infant died after two weeks in spite of blood transfusion and cortisone therapy.

At necropsy the liver, spleen, and kidneys were enlarged. The bone marrow showed a uniform gelatinous, reddish-pink appearance. Microscopically, there was a general infiltration by abnormal cells involving extensively the bone marrow, liver, and spleen, and foci of infiltration were present in the kidneys, lungs, and lymph nodes.

Cytology of Leukaemic Cells.—The infiltrate consisted of large cells which varied from 15 to 20 μ in diameter. They had disproportionately large, rounded nuclei which, in

TABLE IV.—*Details of* (*a*) *Five Cases of Monoblastic Leukaemia and* (*b*) *Two Cases of Chronic Myeloid Leukaemia*

Age	Sex	Length of History	Presenting Symptoms	Enlarged			Haemoglobin (g. per 100 ml.)	Initial Leucocyte Count (per c.mm.)	Differential Leucocyte Count	Bone-marrow Cell Count	Treatment	Survival After Diagnosis
				Liver	Spleen	Lymph Nodes						
(a) Five Cases of Monoblastic Leukaemia												
8 mths	F	2 mths	Upper respiratory infection	+	+++	+	6·5	5,800	63% monoblasts	100% monoblasts	Cortisone	4 mths
9 ,,	M	7 ,,	Skin lumps; sore throat	+	+	+	10	6,700	24% monoblasts	100% monoblasts	Nil	3 ,,
9 yrs	M	1 week	Bleeding	0	0	0	7·5	29,000	100% monoblasts	100% monoblasts	Transfusion	2 days
11 ,,	M	6 mths	Rash on arms and legs	+	0	0	7·0	5,300	65% monoblasts	100% monoblasts	,,	2½ mths
12 ,,	F	1 mth	Sore throat	+	++	Neck only	3·6	77,800	82% monoblasts	100% monoblasts	Cortisone, aminopterin, 6-mercaptopurine, nitrogen mustard	4 ,,
(b) Two Cases of Chronic Myeloid Leukaemia												
7 yrs	F	21 mths	Joint pains and fever	+	+++	+	7·7	256,000	76% polymorphs	22% premyelocytes	Deep *x*-ray therapy	3 yr 6 mth
8 ,,	F	4 ,,	,, ,,	0	+	0	12·1	133,000	99% polymorphs	35% premyelocytes	,, ,,	5 yr 3 mth

addition to moderate general basophilia, contained coarse clumps of chromatin of irregular arrangement, one to three or more large nucleoli, and a well-defined nuclear membrane. The cytoplasm was sometimes inconspicuous, sometimes pale and immolated, but was frequently homogenous and deeply staining, with a slight or moderate basophilia. The nuclei commonly occupied an eccentric position in the cytoplasmic mass, and sometimes there was a faint perinuclear halo of paler cytoplasm. Occasional cells possessed two or even more nuclei. There were some mitotic figures. In sections of spleen and bone marrow stained with methyl green and pyronine an appreciable portion of the neoplastic cells showed a definite coloration of thin cytoplasm. The appearance supported the evidence obtained from bone-marrow smears during life, that the neoplastic cells were primitive forms of plasma cells.

Chronic Myeloid Leukaemia

The two cases are summarized in Table IV. They were characterized by a long history, polymorphonuclear leucocytosis in the peripheral blood, and an excess of myelocytes in the marrow. Aged 8 and 12 years respectively, they were treated with *x* rays and transfusions and survived for three and five years.

Radiology of 50 Acute Cases

Complete or partial skeletal surveys on 50 patients showed radiological changes in 33 (66%). This incidence is likely to be higher than that of an unselected series, because radiographs were often requested on account of skeletal symptoms. The femora and tibiae were the most frequently involved (Table V); only once were

TABLE V.—*Skeletal Survey* (50 *Cases*)

Bone *X*-rayed	No. of Cases	Abnormal	
		No.	%
Femur	44	26	59
Tibia and fibula	42	24	57
Spine	26	8	31
Humerus	33	9	27
Radius and ulna	28	8	29
Skull	16	4	25
Hands	9	2	22
Pelvis	27	5	18
Ribs	27	2	7

they radiologically normal in the presence of bone changes elsewhere. The skull showed infiltration in four cases (Special Plate, Fig. 1). Radiological changes were present in the spine in eight cases (Special Plate, Fig. 2), and in two of these preceded evidence of leukaemia in the peripheral blood.

P.B., a female aged 3 years, had had lumbar pain for two months and a limp for two weeks; restricted movement in the lower spine was the only clinical sign. Radiographs showed anterior wedging of the fourth and fifth lumbar vertebrae. Initial blood count and marrow findings were within normal limits. Haematological evidence of leukaemia appeared three months later. The patient lived for eight months receiving remission therapy.

L.D., a female aged 8 years, presented with a three-months history of backache and abdominal pain. On admission there was unilateral proptosis with third-nerve palsy on the same side. Bone pain became a prominent feature. Radiologically there was progressive collapse of vertebral bodies, and extensive rarefaction involving several long bones, with the subsequent development of pathological fractures. The serum calcium rose to 14.6 mg. per 100 ml. The marrow contained primitive cells at an early stage, but leukaemic cells were not found in the peripheral blood until several months after radiological changes appeared. Her response to remission treatment was poor.

Table VI shows that metaphysial translucent bands of rarefaction were the commonest findings in the long

TABLE VI.—*Bone Changes* (33 *Cases*)

	No. of Cases	%
METAPHYSIAL TRANSLUCENT BAND	29	88
CORTICAL INVOLVEMENT	20	61
Round translucent areas	13	
Sclerosis	7	
Spontaneous fracture	6	
Generalized rarefaction	2	
PERIOSTEAL INVOLVEMENT	9	27
Irregularity	5	
Double contour	4	
Subperiosteal calcification	3	

bones (Special Plate, Fig. 3), occurring in 88% of all cases with *x*-ray changes. Cortical changes (61%) came next in order of frequency, often taking the form of translucent areas in the diaphysis; these areas were sometimes extensive and the cause of spontaneous fractures (Special Plate, Fig. 3); occasionally sclerosis was seen. Periosteal involvement (27%) consisted of irregularity, double contour, or subperiosteal calcification (Special Plate, Fig. 4). Epiphysial changes were not observed in this series, although we had previously seen epiphysial involvement of the femoral head resembling Perthes's disease in a 12-year-old boy with chronic myeloid leukaemia.

Treatment

The series included 30 patients ("untreated cases") who were seen mainly in the early part of the period under review and received, at most, blood transfusions or antibiotics. There were also 63 patients ("treated cases") who received one or more courses of steroids, aminopterin, or 6-mercaptopurine. It should be noted that amethopterin ("methotrexate") was not available in Great Britain during most of the review period. The remaining cases included two cases of chronic myeloid leukaemia and five cases of acute leukaemia treated with agents subsequently judged to be inoperative.

Table VII shows that half the "untreated" children had died within three months of their first symptoms, while it was seven months before the same proportion

TABLE VII.—*Results of Treatment: Survival from Onset of Symptoms*

	Supportive Treatment Only	Supportive and Anti-leukaemic Treatment
50% dead	3 months	7 months
75% ,,	6 ,,	11 ,,
100% ,,	1 year	2 years, 6 months

TABLE VIII.—*Relation of Chemotherapy to Survival*

Chemotherapy	No. of Cases	Average Survival in Months	
		From Onset	After Treatment
None	30	3·0	—
Cortisone	16	5·5	4·0
Cortisone and aminopterin	17	8·8	6·5
Cortisone and 6-mercaptopurine	9	10·8	8·6
Cortisone, aminopterin, and 6-mercaptopurine	15	13·3	10·7

had died among the "treated" group. All untreated children died within one year, at which time nearly a quarter of the treated group were still alive. The longest survival, 30 months, was observed in a boy aged 5 years with acute undifferentiated leukaemia; he had five remissions, the highest number in the series.

Table VIII shows the average survival time in months after the first symptom according to the drug(s) given during the whole course of the illness. The average survival time increased progressively from 5.5 months

when steroids were the only agents given, up to 13.3 months when all three antileukaemic agents were used.

General Pattern of Remissions

Serial examinations of the bone marrow were not performed as a routine, and we have used the term "complete remission" to imply (1) abeyance of all symptoms and signs; (2) a sustained satisfactory haemoglobin level (over 11 g. per 100 ml.); (3) the disappearance of abnormal cells from the blood and a return to normal of the total and differential leucocyte count. The term "partial remission" implies an amelioration in symptoms, signs, and blood picture short of the above criteria. In patients who received a transfusion as well as remission treatment, improvement sustained for at least six weeks was required because a short remission sometimes follows a transfusion.

Of the 63 treated patients, 34 (54%) had at least one complete remission, while a further 14 (22%) underwent partial remissions. Thus temporary improvement occurred in 76% of the treated cases. The number of cases remitting after a second, third, and fourth course was 16, 6, and 3, respectively. A second remission (partial or complete) occurred in 46% of patients who had complete initial remission and in only 15% of those who had had partial first remissions.

Steroid Remissions

Thirty-five children were treated solely with steroids as their first course of remission therapy. In this group there were 18 complete and 8 partial remissions, giving an improvement rate of 74%. Fourteen children received a second course of steroids, and five had a remission. Experience was mainly with cortisone, the dosage of which varied from 50 mg. daily for five days to 300 mg. daily for several weeks. The lowest dose which induced a complete remission was 100 mg. daily given for a week to a 7-year-old boy. Thirteen children received less than 200 mg. daily during the first week of cortisone therapy, and only four of these had a remission; in contrast, 22 courses of 200 mg. or over during the first week were followed by 14 remissions, a significantly better result ($P = <0.02$). A remission followed an increase in dosage to 300 mg. daily in two cases in which a dosage of 200 mg. had failed.

Continuous treatment with steroids from one active leukaemic phase through remission until the next relapse carried no apparent advantage over the administration of separate short courses in the few cases analysed (see Table IX). More data on this point are desirable. In two children given cortisone continuously for over three months vertebral collapse developed. This complication was not encountered as a direct result of short courses of cortisone, though one patient showed deterioration of pre-existing leukaemic vertebral damage.

TABLE IX.—*Comparison of Short Courses and Prolonged Course of Steroid Therapy*

First Steroid Therapy	No. of Cases	Remission in Months		
		Shortest	Longest	Average
Short courses (less than one month)	6	1	7	4·5
Long course (continued until next relapse)	9	1	7	4

Other side-effects were slight, even when cortisone was administered continuously for four weeks in a daily dosage of 200–300 mg. Four children developed hypertension and three others had pyodermia. Two children had temporary rises in blood urea level, reaching 430 mg. per 100 ml. in one. This effect was thought to be partly related to the rapid shrinkage in size of a heavily infiltrated liver and spleen.

Remissions induced by steroids were usually quicker and more distinctive than those following antimetabolite therapy. In febrile cases the earliest clinical sign of an impending remission was a prompt return of the temperature to normal. Remissions followed in 81% (26 out of 32) of children in whom pyrexia had resolved within three days of starting steroid therapy, but in only 23% (5 out of 22) of those still febrile on the third day. The subsequent clinical picture of remission was a return of well-being, fading of purpura, and diminution of hepatic, splenic, and lymph-node enlargement.

Haematological evidence of remission usually occurred 10–14 days after starting treatment, and often resulted in severe leucopenia in cases where the leucocyte count was already low. A fall in the haemoglobin level was another early change, and in one-third of cases was in excess of 4 g. per 100 ml. Failure to meet this situation by timely transfusion was probably the cause of death in one cortisone-treated patient whose haemoglobin level was low initially. Transfusion was given in the first ten days of therapy during 41 out of 86 remission courses in which steroids were concerned, alone or in combination. Second or subsequent transfusions were necessary in six children in whom the first transfusion had failed to prevent a fall in haemoglobin level of over 4 g. per 100 ml.

The clinical and haematological findings before steroid therapy were analysed to see if any reliable method existed of foretelling the chance of a remission. Table X shows that relatively unfavourable signs for

TABLE X.—*Influence of Initial Leucocyte Count and Predominant Cell on Remission with Steroid (First Course)*

Predominant Cell	Remissions			
	None	Partial	2–6 Months	Over 6 Months
Neutrophil	4	1	0	0
Lymphocyte	5	6	13	6
Blast cell	5	7	6	0

Total Count	None or Partial	Over 2 Months
Under 5,000 per c.mm. ..	6	8
5,000–15,000 ,, ,, ..	15	13
Over 15,000 ,, ,, ..	11	3

developing a remission were peripheral leucocytosis and neutrophil predominance in the differential count. Severe anaemia, a clinical history of under one week, and absence of generalized adenopathy in cases showing other systemic leukaemic effects were also indications that a steroid remission was unlikely. Relatively favourable signs were the absence of leucocytosis or a differential count which was predominantly lymphocytic. No guide was obtained from haemorrhagic manifestations or the degree of enlargement of liver or spleen.

6-Mercaptopurine Remissions

In 24 children the first course of 6-mercaptopurine was sufficiently free from overlap with other agents to judge the separate effect of this drug. Three complete and five partial remissions resulted, giving an over-all

remission rate in this small group of 33%. Only one child in five experienced remission after a second course. The usual dosage was 2.5 mg. per kg. per day and the range fell between 25 and 100 mg. daily. 6-Mercaptopurine was usually discontinued if the total leucocyte count fell below 1,000 per c.mm., and, using this precaution, no severe toxic effects were encountered even after prolonged therapy. In seven cases azaserine (diazoacetylserine) was combined with 6-mercaptopurine, but no synergic effect was manifest in these few cases, and therapy had to be discontinued in two owing to oral sepsis or gastro-intestinal bleeding.

In some cases a study of the leucocyte count during treatment gave the first information that a remission was impending. In two complete remissions the earliest sign was a diminution in circulating leucocytes about the third day, which became most marked at the eighth and tenth days respectively. In two partial remissions an initial drop appeared between the third and seventh days, reaching a lowest level on the nineteenth and twenty-eighth days, respectively.

Aminopterin Remissions

Fourteen children had a first course of aminopterin which was uninfluenced by overlap with the other agents. Two complete and three partial remissions resulted, giving a remission rate in this small group of 38%. Ten other children received a first course which consisted both of steroids and of aminopterin simultaneously, and six remissions resulted; this rate was no different from that when the first course consisted of steroids alone.

The usual dosage of aminopterin was 0.25–0.5 mg. daily, but it was possible sometimes to raise the dose cautiously to 1.0 mg. daily, and three of the aminopterin remissions were obtained in this way. Liability to oral ulceration after aminopterin therapy necessitated observation in hospital. Daily inspection of the buccal mucosa allowed early recognition of patchy desquamation and whitening inside the lips and on the palate. In such cases it was possible sometimes to forestall oral ulceration by withdrawal of the drug for a few days; lozenges containing folinic acid (citrovorum factor) were sometimes given for a presumed topical effect. Leucopenia, rash, and alopecia were additional complications.

In some cases the leucocyte count gave information about an impending remission before clinical improvement occurred; in the case of two complete remissions a diminution in circulating leucocytes took place within three days of starting treatment, with maximum effect on the seventh and fourteenth days respectively.

Meningeal Syndrome

With increased survival in cases of acute leukaemia, symptoms of meningeal involvement have become more frequent. Sullivan (1957) reported the development of a meningeal syndrome in a quarter of cases of acute leukaemia treated with cortisone or chemotherapy at the Anderson Hospital and Tumor Institute of Texas Medical Center. Radiographs of the skull often showed widening of the sutures, and the cerebrospinal-fluid pressure was sometimes increased, often with pleocytosis and increased protein. Systemic hypertension and obesity were also observed. It was concluded that antileukaemic drugs probably cross the blood–brain barrier in reduced concentration, and may fail to influence intracranial infiltration though the systemic lesions may be under more satisfactory control. Sullivan suggested that irradiation of the skull, or aminopterin given intrathecally, may relieve symptoms due to meningeal involvement. In our series of 100 cases several had neurological signs, but only one had the symptoms and signs of the meningeal syndrome.

C.F., a male aged 8 years, had pallor, lassitude, and limb pain. His acute leukaemia went into partial remission after administration of steroids and 6-mercaptopurine. Two months later he became deaf and developed proptosis. *X*-ray examination of the skull showed evidence of extensive leukaemic infiltration. He was given aminopterin, but soon developed headaches, vomiting, and neck stiffness. Papilloedema and retinal haemorrhages were present. The cerebrospinal fluid was not examined. A further course of steroids was given, but failed to control the meningeal phase of the disease; death occurred during a convulsion.

After our analysis had been completed, another example of the meningeal syndrome was received into the hospital for treatment.

P.F., aged 10, presented with pallor and purpura, found to be due to acute leukaemia. The first examination showed 360,000 leucocytes per c.mm. A remission followed treatment with steroids and 6-mercaptopurine. Two months later she developed headache, vomiting, and vertigo. On admission, papilloedema and retinal haemorrhages were present. A radiograph of the skull was normal. The cerebrospinal fluid contained 1,835 leucocytes per c.mm., of which the majority were leukaemic (blast) cells; protein 10 mg. and sugar 80 mg. per 100 ml. Deep *x*-ray therapy to the posterior fossa in a total dosage of 500 r over ten days resulted in improvement in the papilloedema and reduction in cerebrospinal-fluid pleocytosis to 95 per c.mm. The patient was discharged two weeks later in full remission and without meningeal signs.

Infiltration of Kidneys

Many treated cases showed enlarged kidneys at post-mortem examination. This renal enlargement usually went unrecorded in life, but was a striking finding at necropsy. This impression was confirmed when the weights of the kidneys of treated and untreated cases were compared, normal values being taken from the hospital necropsy records and allowance being made for age. Kidneys of more than double the expected weights were found in 18 out of 24 treated cases (75%) as opposed to 5 out of 19 untreated cases (26%). The possibility of such a finding occurring by chance is remote ($P = <0.02$). The degree of renal enlargement did not appear to vary with the antileukaemic agent used or with the degree of associated enlargement of liver or spleen. Microscopically, the enlargement was found to be due to extensive leukaemic infiltration. This infiltration, which was never severe enough to produce uraemia, was presumably related in some way to the effects of treatment. It cannot be explained on the grounds of increased survival time, as treated patients with enlarged kidneys usually succumbed quite early—an observation also made by Pierce (1957).

Discussion

Remission treatment has become almost a standard practice for acute leukaemia, because it offers a high expectation of clinical improvement and the risks of toxicity with modern methods are small. Since remissions alone, and never cures, have been obtainable by use of the present antileukaemic drugs, a more fundamental form of treatment is needed urgently. One possibility follows upon the animal work of

Medawar (1958) on homografts with tissue cells, following which grafts of foetal haemopoietic tissue after total body *x*-irradiation have been tried (Thomas *et al.*, 1959). The hope of ultimate success from this or other methods gives a further measure of justification for the interim use of the agents capable of inducing remissions.

In the present series clinical improvement occurred in 76% of the cases, usually without discomfort to the patient, and the duration of stay in hospital was kept to a minimum. Some of the children were able to return temporarily to school. The true prognosis of leukaemia was always given to the parents, and treatment was carried out only after full explanation and if it was desired.

The question arises as to the place which is most appropriate for supervision of patients under treatment for acute leukaemia. Using a pre-planned regimen, Farber (1958) was able to report that 10% of a consecutive series of 900 leukaemic children were still surviving two and a half years after the onset of the disease. Such a result suggests that, in spite of the distance and discomfort sometimes involved, there is some advantage to be gained by over-all supervision in a special centre. When the appropriate therapy has been instituted and a remission obtained the patient can return home until a relapse occurs, follow-up blood counts being arranged at the nearest convenient laboratory.

Now that a choice of antileukaemic agents is available, their order of administration has to be decided. In the present series the three drugs used were usually given in sequence, because we found no evidence of synergic effect, nor was resistance to individual components prevented by combinations of drugs.

Steroids were found to be the most effective and rapidly acting drugs, particularly for the acute stages with thrombocytopenia and anaemia. In other cases they were usually held in reserve for the time when both aminopterin and 6-mercaptopurine had failed. This series gave information with respect to treatment with cortisone rather than the newer analogues. A dosage of cortisone smaller than 200 mg. daily for two weeks failed to give a good remission rate. For rapid action steroids were given intravenously in the form of hydrocortisone or corticotrophin. After a patient had become apparently resistant to cortisone, a further remission was sometimes obtained by an increase in dosage to 300–400 mg. daily or by a change in preparation to one of the newer analogues or to corticotrophin. Experience in the present cases suggested that it is reasonable to combine an antimetabolite with cortisone in certain cases in the acute stage—namely, when there is leucocytosis, polymorphonuclear predominance in the peripheral count, or a very short clinical history. The results also suggested that administration of antimetabolites should be started in acute cases treated with steroids when the initial fever fails to resolve within three days of beginning therapy. Otherwise it was unusual for aminopterin or 6-mercaptopurine to give a successful remission in cases which had failed to respond initially to steroids, but the adjuvant value of including them in the regimen raised the survival time considerably over that of cases treated with steroids alone.

When a remission is obtained the question arises whether to continue on a maintenance dose of the drug. Our relatively small data showed no advantage from maintenance steroid therapy, while vertebral collapse occurred in two cases. It was our definite impression that maintenance treatment with 6-mercaptopurine was useful in prolonging remissions, but overlap with other agents made quantitative assessment impossible.

Summary

Observations are presented on 100 consecutive patients seen at the Hospital for Sick Children, Great Ormond Street, with leukaemia (acute undifferentiated, 92; acute monoblastic, 5; chronic myeloid, 2; and plasma-cell, 1).

On admission the commonest symptoms were pallor, limb pain, and bruising, and the commonest signs were fever, lymphadenopathy, and hepatosplenomegaly. The total white-cell count was normal in nearly one-half; 25% had leucopenia and 30% leucocytosis. Abnormal white cells were present at the initial peripheral blood count in 58%. Radiological bone changes occurred in two-thirds of those *x*-rayed; the tibia and femur were the most frequent sites of involvement, and were rarely normal when bone changes were present elsewhere.

Of 63 patients receiving one or more courses of steroid, aminopterin, or 6-mercaptopurine, 34 (54%) had one or more complete clinical remissions of up to seven months in duration. A further 14 (22%) had partial remissions, giving improvement in a total of 76%. In those treated with all three drugs (later in the series) the average survival time was 13.3 months, as opposed to three months in untreated cases. The longest survival in the series was 2½ years.

Steroids proved the most frequently effective of the remedies used: the earliest sign of remission was a prompt return of the temperature to normal; further leucopenia and a fall in haemoglobin level were frequently seen at the onset of remissions; leucocytosis and neutrophil predominance were relatively unfavourable to the development of a steroid remission.

Present-day therapy not only prolongs the course of leukaemia, but also influences the manifestations. Mention is made of meningeal and renal involvement.

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REFERENCES

Burchenal, J. H., Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, T. C., Leone, L. A., Karnofsky, D. A., Craver, L. F., Dargeon, H. W., and Rhoads, C. P. (1953). *Blood*, **8**, 965.
Farber, S. (1958). *Proc. roy. Soc. Med.*, **51**, 410.
—— Diamond, L. K., Mercer, R. D., Sylvester, R. F., and Wolff, J. A. (1948). *New Engl. J. Med.*, **238**, 787.
Hewitt, D. (1955). *Brit. J. prev. soc. Med.*, **9**, 81.
Medawar, P. B. (1958). *Proc. roy. Soc. B*, **149**, 145.
Pierce, M. I. (1957). *Pediat. Clin. N. Amer.*, **4**, 497.
Registrar-General's Statistical Review of England and Wales for the Years 1938–1957. H.M.S.O., London.
Stewart, A., Webb, J., and Hewitt, D. (1958). *Brit. med. J.*, **1**, 1495.
Sullivan, M. P. (1957). *Pediatrics*, **20**, 757.
Thomas, E. D., Lochte, H. L., jun., and Ferrebee, J. W. (1959). *Blood*, **14**, 1.

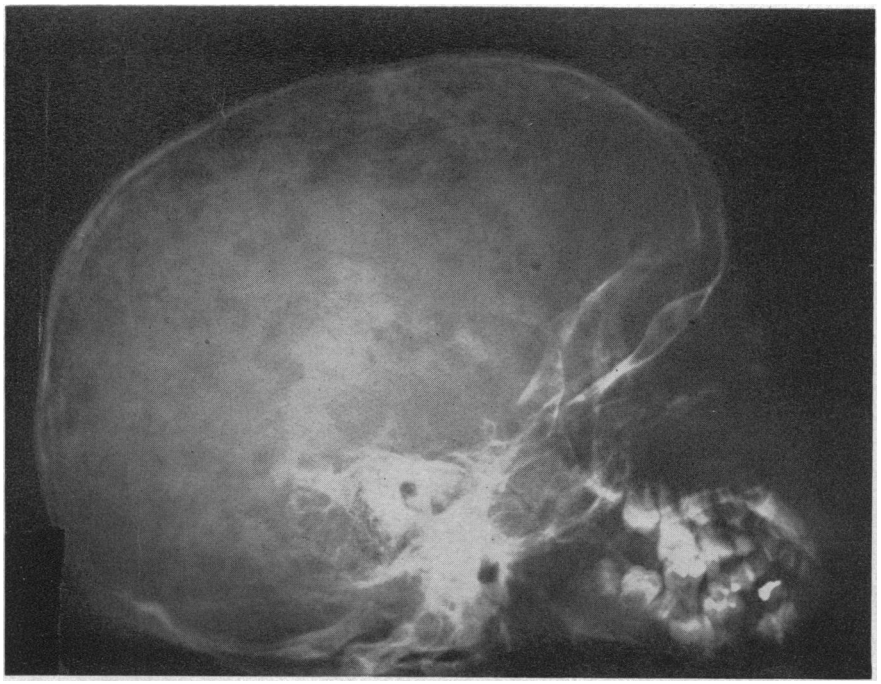

FIG. 1.—Radiograph of skull, showing extensive round translucent areas.

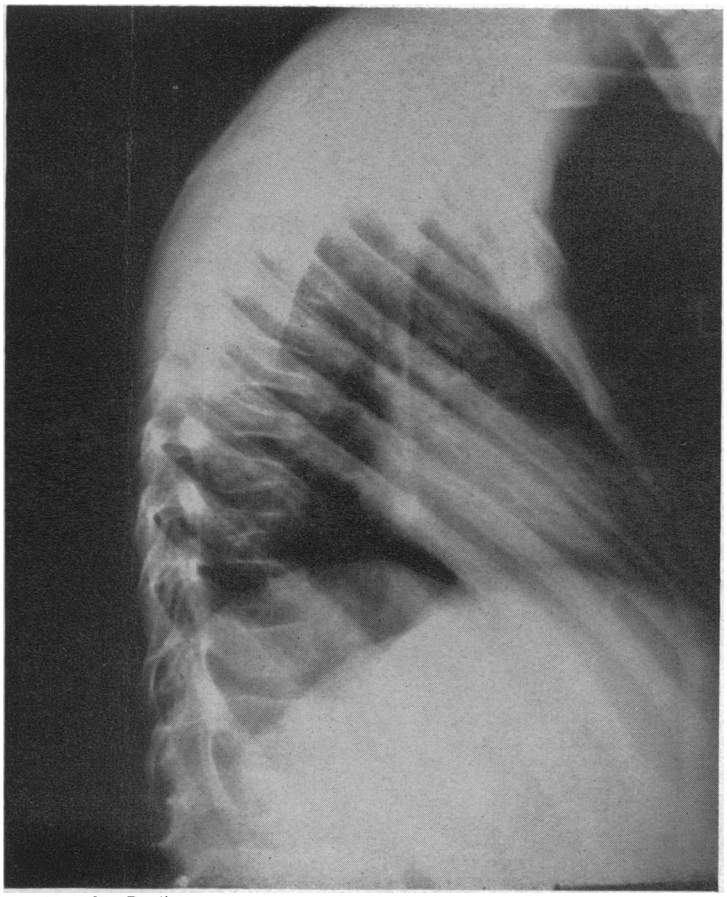

FIG. 2.—Radiograph of spine, showing collapse of vertebral bodies.

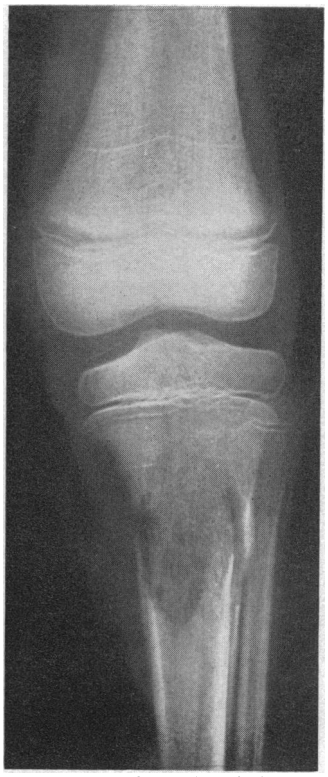

FIG. 3.—Radiograph of lower end of femur and upper end of tibia, showing translucent zones at metaphyses, large round area of translucency in tibia, spontaneous fracture, and periosteal double contour.

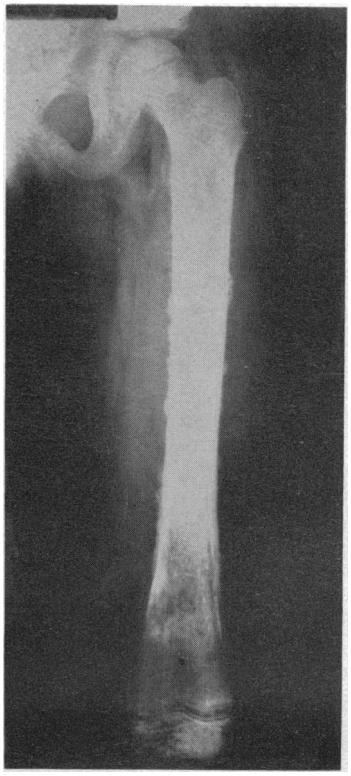

FIG. 4.—Radiograph of femur, showing periosteal irregularity and subperiosteal calcification.