Papers and Originals

Long-Term Corticosteroid Treatment of Asthma

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This report deals with 170 hospital patients suffering from severe bronchial asthma treated with long-term steroids. The first admissions to this survey were in April 1952 and the last in April 1962. The periods of observation ranged from 2 to 13 years. The patients were seen weekly or monthly at first and then at gradually longer intervals, with the exception of five who were followed-up by postal questionnaire at least twice each year. One patient was lost. All were under the care of two of us (J. L. L. and R. S. B. P.), and only those whose treatment with long-term corticosteroids was initiated by us are included in this study. Assessments were made by one of us (K. M.), who had access to all records and interviewed the patients individually.

In defining asthma we used the functional criterion of attacks of dyspnoea due to widespread airways obstruction which alternated with more or less normal breathing; more severe cases had evidence of obstruction between attacks. These fluctuations in respiratory function were measured by simple physiological tests when the patients visited hospital. The major factors known to precipitate attacks, acting singly or in combination, were allergic or infective. Other conditions which played a major or minor part included emotional disturbances and nasal abnormalities—polypi, infected antra (24). In some cases there was no clue to the cause, and they were labelled "idiopathic" or non-specific. All patients with chronic bronchitis who developed attacks of wheezing as a secondary phenomenon were excluded.

Patients who were thought to need steroid treatment were usually admitted to hospital for investigation. Many were subject to recurrent attacks of status asthmaticus, and treatment was often begun after emergency admission for this condition.

The assessment of severity was based mainly on the length of time lost from work and the response to treatment, as follows:

Group 5.—Unable to work for six months during the previous year because of asthma (32 patients).

Group 4.—Off work for more than four weeks but less than six months a year with poor response to orthodox treatment or because of admission to hospital in status asthmaticus (116 cases).

Group 3.—Occasional attacks requiring only odd days off work (22 patients). In no case in this group were more than 28 days lost each year, and most lost a few days only.

Group 2.—No loss of time from work; attacks easily controlled by simple remedies. No patient of this severity was put on long-term steroids, but 95 patients reached this stage at the end of the observation period.

Group 1 indicates freedom from symptoms.

Examination included: naked-eye examination of fresh sputum if available, as well as bacteriology and cytology; skin tests with pollen, moulds, house dust, and other household

inhalants; examinations of the upper respiratory tract; x-ray examination of chest and sinuses; and measurement of vital capacity and/or peak flow. If the patients failed to improve markedly after a period of inpatient treatment with conventional methods, they were put on moderately large doses of prednisone or prednisolone (40-60 mg. daily) for a few days with or without antibiotics. If the response was good as judged by clinical symptoms and signs, cessation of sputum, and pronounced improvement in respiratory function tests, the dosage of steroids was reduced slowly and a maintenance level (usually equivalent to 5-15 mg. of prednisone or an equivalent dose of other corticosteroids) established. Those who continued on the treatment for six months or more were regarded as having been treated on a long-term basis and are included in this survey.

Each patient was issued with a steroid card and instructed on no account to stop taking steroids without consulting his doctor. The latter was advised to double or treble the dose of steroids temporarily at the onset of infection or if asthma appeared to be deteriorating: after a few days the increased dose was brought back over 7 to 10 days to the maintenance level. Many patients learnt to do this for themselves, thereby preventing severe recurrences. Antibiotics were given concurrently if infection developed. The doctor was advised to arrange admission to hospital in the event of a relapse which was not responding to increased steroid treatment after 24 hours.

The main drugs used were prednisone or prednisolone given in 5-mg. and 1-mg. tablets, labelled as such to avoid errors by the patient when adjusting the dose. Methylprednisolone and triamcinolone, as well as betamethasone, were given in a few cases. Patients treated with corticotrophin only were not included, but one patient received it once or twice weekly in addition to prednisolone. We did not include patients who emigrated (2), who died from incidental causes (6), or who died in status asthmaticus before the initial period of six months on steroid treatment was completed (2).

Assessment of Results

Only 11 out of 170 patients were under 15 years of age at the beginning of treatment—the youngest was 10 years—58 were aged 15 to 39 years, and 101 were older, the oldest being 75. There were more females (101) than males (69). Assessment was made after the first year of observation when a suitable maintenance dose had been attained. During this initial period results were often uneven and at variance with subsequent progress. The basis for classification was as follows:

Good.—Improvement had been sustained throughout the period of observation, enabling the patient to lead a more active life, with little or no loss of time from asthma. Any relapses were mild and easily controlled. The patient continued on a maintenance dose,

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which was increased temporarily if necessary. In some cases the good result was maintained after withdrawal of steroids. This group includes three patients who relapsed severely during the early years of treatment, but were well controlled subsequently.

Moderate Results.—Improvement was moderate only or was marred by one or more severe relapses with status asthmaticus or periods of disability lasting for one month or more. Relapses after the withdrawal of steroids were excluded. Patients in this group were subjectively improved and able to lead more active lives.

Failures.—There was no change in severity. Some of these patients claimed to be subjectively improved, but this was not confirmed on questioning or by examination of their case records.

The following are examples:

Good Result.—The patient was a man aged 44. After the onset of asthma in the previous year he had had eight attacks of status asthmaticus (group 5). Long-term steroid therapy was initiated with a maintenance dose of 15 mg. daily; over three years this was gradually reduced to 5 mg. daily. From this time he had no further attacks of status asthmaticus and suffered from only mild intermittent wheezing during the six years of observation. No allergic factors were detected, but he had a well-marked depressive tendency for which he was given amphetamine sulphate 5 mg. b.d. The forced vital capacity (F.V.C.) averaged 4,200 ml., with a forced expiratory volume in one second (F.E.V.₁) of 3,000 ml. on 15 mg. of prednisolone, and 3,800 ml. with an F.E.V.₁ of 2,800 ml. on 5 mg.

Moderate Result.—The asthma of this woman aged 61 started at age 60 and was associated with perennial rhinitis of long standing. Though status asthmaticus was not recorded there was considerable disability with limited activity. During the first year of treatment she had one severe relapse, but apart from this was greatly improved. Improvement was maintained in the second year of treatment on a daily dose of 12.5 mg. of prednisone. During the third year there were two periods of incapacity, each persisting for one month. The steroids were raised to a maximum dose of 40 mg., with a weight increase of 15 lb. (6.8 kg.). During the fourth year she remained in good health, with little disability on the original maintenance of 12.5 mg.

Failure.—In this patient, a man aged 53, the onset of asthma at age 49 was associated with infection and depression. He was severely incapacitated and unable to work (group 5) on account of asthma. His mother suffered from asthma. He had summer hay-fever. On a maintenance dose of 15 mg. of prednisolone his average F.V.C. rose temporarily from 1,800 to 2,400 ml., but he continued to be short of breath on effort and to have nocturnal attacks of asthma. He retired from work and led a restricted life with periodic bouts of respiratory tract infection during six years of observation. Lung damage was suspected.

Precipitating Factors

The presence of an allergic factor was accepted if the patient gave a history indicating that attacks followed contact with specific sensitizing material such as animal hair or grass pollen, provided this was confirmed by skin testing. Food allergy was accepted on the history alone, as was allergy to aspirin (10 cases). Only eight patients were found to have an allergic factor as the sole precipitating cause of asthmatic attacks. In 70 patients allergic and infective factors were present. Infection was diagnosed partly on the history of infective episodes immediately preceding attacks, or when sputum containing pus (degenerated polymorphs) with or without eosinophils was present on one or more occasions. Pathogenic bacteria, including pneumococci, *Haemophilus influenzae*, and *Escherichia coli*, were cultured in some cases, but most commonly commensal organisms only were grown. In 75 patients infection was the only precipitating cause found. In 17 no cause could be discovered.

Table I shows the duration of treatment of 170 cases. Of these, 29 were successfully withdrawn; 10 died.

TABLE I.—Duration of Treatment in 170 Cases

Years	6/12	2	3	4	5	6	7	8	9+
No. of cases	19	11	19	24	27	16	17	13	24

The overall results are set out in Table II. It will be seen that the result of treatment is the same for each sex, with approximately 60% of good results for both. There is also no appreciable difference between those who were under 40 years at the start of treatment and those above this age. Three of the eight deaths in status asthmaticus took place within six months of withdrawal.

TABLE II.—Results by Age and Sex

	Total	Good		Moderate		Failed		Died*	
		No.	%	No.	%	No.	%	No.	%
Males { 10-39 years	29	18	62	7	24	2	7	2	7
{ 40-75 " "	40	22	55	11	28	6	15	1	2
Females { 10-39 " "	40	25	62	10	25	3	7	2	5
{ 40-75 " "	61	36	59	16	26	4	7	5	8
Total ..	170	101	59	44	26	15	9	10	6

* Eight deaths due to status asthmaticus, two to other respiratory disorders.

Table III shows the severity (groups 5-2) at the start of the observation period and during the last year of observation in each patient. In no case was there complete remission of symptoms (group 1).

TABLE III.—Severity at Beginning and End of Observation

	Total	Group 2	Group 3	Group 4	Group 5	Died
Initially ..	170	—	22	116	32	—
End of period ..	170	95*	34	28	3	10

* Includes 28 cases successfully withdrawn from long-term steroids.

Both these methods of assessment indicate a high rate of improvement.

Effect of Duration of Treatment.—It has been suggested that steroid treatment may become less effective when it is continued over a number of years. This was not found to be the case (Table IV). More deaths occurred in the first two years of

TABLE IV.—Results of Duration of Treatment

Duration of Treatment	Total	Good		Moderate		Failed		Died	
		No.	%	No.	%	No.	%	No.	%
Less than 6 years ..	100	61	61	19	19	12	12	8*	8
6 years or more ..	70	40	57	25	36	3	4	2	3

* Three deaths after withdrawal from long-term steroid therapy.

treatment than in the subsequent eight years: three of these took place after withdrawal. There was no evidence that the maintenance dose of steroid needed to be increased with the passage of time—rather the reverse. When once a satisfactory maintenance dose had been reached it was either kept constant or was reduced slightly as time progressed. Exceptions to this were few. The dose, however, was temporarily increased, usually for 7 to 14 days, to combat exacerbations or prophylactically during infective episodes.

Incidence of Status Asthmaticus.—Of the 170 patient 60 (35%) had a history of one or more attacks of status asthmaticus before treatment with long-term steroids: in only 31 were attacks recorded during treatment. Out of 52 patients whose steroids were withdrawn 11 had attacks of status asthmaticus shortly afterwards.

Duration of Asthma.—A comparison was made between those cases with a duration of asthma for five years or less at the

TABLE V.—Results by Duration of Asthma Before Treatment

Duration	Total	Good		Moderate		Failure		Died	
		No.	%	No.	%	No.	%	No.	%
5 years or less ..	58	31	53	19	33	4	7	4	7
More than 5 years ..	112	70	62	25	22	11	10	6	5

start of treatment (58) and those whose asthma had been present for more than five years (112) and showed a somewhat smaller proportion of good results in the former group (Table V).

Severity of Asthma.—As might be expected, patients whose asthma was judged to be less severe (group 3) at the onset of treatment reached group 2 more often than the more severe cases in group 5 and 4, and therefore show a higher proportion of "good" results (Table VI). Conversely, the most severe

TABLE VI.—Results by Severity at Onset of Treatment

Severity at Onset	Total		Good		Moderate		Failure		Died	
	No.	%	No.	%	No.	%	No.	%	No.	%
Group 5	32	15	47	11	34	4	12	2	6	
" 4	116	69	58	30	26	11	9	6	5	
" 3	22	17	77	3	14	0	—	2	9	

cases (group 5) have a lower proportion of good results. This observation is also confirmed by comparing the maintenance dose of steroid given with the results achieved, those receiving a low dose (2–5 mg.), obviously the less severe cases, had good results in 65%, but those who required a higher dose (11–20 mg.) had good results in only 32.5%.

Effect of Allergy.—When the results in patients with allergic precipitating factors are compared with those with infective precipitating factors only, and those with neither allergic nor infective precipitating factors, there is no appreciable difference between the three groups (Table VII). It must be remembered that in 70 of the 78 cases in the allergic group infective factors were also present.

TABLE VII.—Results of Treatment in 170 Patients With and Without Allergic Factors

	No.	Good		Moderate		Failure		Death			
		No.	%	No.	%	No.	%	S.A.		O.R.D.	
Allergic factors present*	78	44	57	20	26	10	13	4	6	0	—
Infective factors only	75	47	62	20	27	3	4	4	5	1	1
No allergic or infective factors	17	10	59	4	23	2	12	0		1	6

* In 70 cases infective factors were present in addition to allergic. S.A.: status asthmaticus. O.R.D.: other respiratory disease.

Withdrawal of Steroids.—Withdrawal was carried out in 52 cases in the present series, and those who were successfully withdrawn (29) were subsequently observed for periods of time varying from 22 months to seven years. One patient was withdrawn because of failure to respond to treatment and has been classified as a failure. Table VIII shows that withdrawal was

TABLE VIII.—Withdrawal of Steroids

	No. of Patients	Successful Withdrawal		Withdrawal followed by Severe Relapse*	
		No.	%	No.	%
Group 5	32	1	3	3	9
" 4	116	21	18	20	17
" 3	22	6	27	1	6
Maintenance dose:					
2–5 mg. prednisone	35	13	37	4	11
5 mg. and over ..	135	15	11	20	15
Duration of treatment:					
Six months to 6 years	100	21	37	10	10
More than 6 years	70	7	10	14	20
Allergic factor:					
Present	78	17	22	8	10
Absent	92	11	12	16	17

* Steroid therapy was re-established in this group except for three patients who died in status asthmaticus.

more likely to be successfully accomplished if the asthma was graded as less severe, the maintenance dose was small, treatment was of less than five years' duration, and allergic factors were present. Of the 24 cases whose asthma relapsed severely after withdrawal three died in status asthmaticus.

Deaths

Among the 170 cases eight deaths (4%) occurred from status asthmaticus. Six of these patients were women. Three died after withdrawal of steroids: the fatal attack took place at intervals of 10 weeks, nine weeks, and six months after cessation of treatment, which had been given for six, nine, and 12 months respectively. During her terminal attack one of these was admitted to a hospital where steroids were not administered during the first 48 hours of treatment. The second patient died at home. The third, a boy aged 13, was found at necropsy to have a cerebral abscess with meningitis in addition to "plugged" bronchi; he died in spite of large doses of steroids. Two of these three patients had had attacks of status asthmaticus before treatment with long-term steroids.

Four of the remaining five patients who died in status asthmaticus had had attacks of "status" before treatment; one of these died in the ambulance on the way to hospital and three at home. One developed status asthmaticus while in hospital for treatment of psoriasis and died after transfer to another hospital.

Two other patients died with chest infections: (1) A woman of 69 who had responded well to steroids but who probably failed to maintain regular therapy at home: death was recorded as due to bronchopneumonia; (2) a man of 49 who died after four years' treatment: death was certified as due to bronchitis and cor pulmonale.

In addition, two patients died in status asthmaticus who were treated for less than six months and therefore did not qualify for inclusion in the series: one (a man aged 28) died in status three days after stopping steroid treatment given for a period of two months; the other (a man aged 46), who was treated for five months, died two weeks after cessation of treatment.

TABLE IX.—Deaths from Status Asthmaticus and Other Respiratory Disease

Sex	Age at Onset	Age at Death	Years of Therapy	Group	Previous Status	Details of Death
Deaths from Status Asthmaticus during Long-term Steroid Therapy						
F	47	55	2 10/12	1	Yes	Died in ambulance. Coroner's P.M.
F	25	32	1 6/12	3	No	Died at home. No P.M.
F	20	59	1 1/12	2	Yes	
F	22	55	7	2	"	Died in hospital. No P.M.
M	15	38	5 1/12	3	"	Died at home. Coroner's P.M.
Deaths from Status Asthmaticus after Withdrawal from Long-term-steroid Therapy						
F	5	52	6/12	1	Yes	At home 10 weeks after withdrawal
F	2	26	9/12	2	"	In hospital 9 weeks after withdrawal. P.M.
M	1	13	1	3	No	In hospital 6 months after withdrawal. Cerebral abscess found. P.M.
Deaths from Other Respiratory Diseases during Long-term-Steroid Therapy						
F	66	69	2	2	Yes	Died in hospital. P.M. Bronchopneumonia
M	49	53	4 2/12	2	No	Died at home. Bronchitis with heart failure. No P.M.

Side-effects

Thirty-four patients (20%) had side-effects, and 16 of them had more than one. Weight increase of more than 14 lb. (6.4 kg.) occurred in 12 patients, but some of these were underweight at the start of treatment; two gained over 45 lb. (20.4 kg.), both on large doses of prednisone. Five patients showed a rise in blood pressure to a level of more than 200/100; all were mildly hypertensive (B.P. above 160/90 before treatment) and four were adequately controlled by reserpine with continuance of long-term steroids. Two other cases with hypertension before steroid therapy showed no deterioration. Four patients had vertebral collapse, and two of these also had rib fractures; the diagnosis was made in three

of these after radiological examination for pain and in one during a routine examination of 64 patients who had had treatment for more than five years. Treatment with anabolic steroids and calcium was given to these four cases, and long-term steroids were continued in one case for a further five years without further deterioration. Peptic ulcer was diagnosed in six patients, one of whom had a haematemesis; all were treated medically with recovery, and treatment was continued with keratin-coated prednisolone in five. Two were taken off steroids because of severe side-effects, in one case due to duodenal ulcer and in the other to gross increase in weight (46 lb.; 20.9 kg.) with other Cushingoid features.

In addition, two cases had myopathy and one a reactivation of pulmonary tuberculosis which was satisfactorily treated during therapy. Twenty-six cases were examined by Mr. R. A. Owen for ocular tension and outflow: three showed a borderline raised tension in one eye and borderline outflow; one case developed glaucoma. These cases are more fully reported elsewhere (Paterson and Owen, 1966). Cataract occurred in four patients, but in one of these it was attributed to severe atopic eczema. Striae and bruises were recorded in some patients and mooning of the face in 10 (severe in two). Table X shows the relation of side-effects to maintenance dosage.

TABLE X.—*Relation of Side-effects to Dosage*

Daily Maintenance Dosage of Prednisone*	Total	Side-effects Absent		Side-effects Present	
		No.	%	No.	%
2-5 mg.	35	31	89	4	11
6-10 „	92	78	85	14	15
11-20 „	43	27	63	16	37
Total	170	136	80	34	20

* Intermittent higher dosage was given to eight patients.

It is evident that the incidence of side-effects rises steeply with the higher doses. Though side-effects were usually diagnosed after several years of treatment, in six cases they were recorded within two years, including one patient with vertebral collapse: this patient had, however, received 50-60 mg. of prednisone for three months. Weight increase, hypertension, myopathy, and cataract were also recorded in the first two years of treatment.

Discussion

There has been general agreement that in carefully selected cases long-term steroid therapy may revolutionize the life of the disabled chronic asthmatic. With the use of varying methods of assessment satisfactory results have been claimed in from 70 to 85% of cases. Thus Pearson, Bayliss, and Smellie (1961) and Livingstone and Davies (1961) showed that long-term steroid treatment of severe chronic asthma in 36 and 71 cases for periods of up to five years was effective in the majority of cases. Rees and Williams (1962) reported the results of treatment of 317 cases for an average period of two and a half years with approximately similar results: 96 of these cases received corticotrophin as well as adrenal steroids. Walsh and Grant (1966) treated 273 patients with chronic asthma for periods of 1 to 10 years, using regular intermittent treatment in 180 adults and 17 children with equally good results. Anderson (1960) and Morrison Smith (1965) reported beneficial results in children (39 and 56) treated for a period of one year or more; Morrison Smith recorded satisfactory withdrawal of treatment in nearly half his patients.

A number of cases in this series had already been included in previous reports (Livingstone and Davies, 1961; Pearson *et al.*, 1961), but have now been observed over a longer period of time. Two of the deaths referred to in this paper were also included in previous publications. A number of fresh points have emerged.

It has been shown that there is no tendency for the effect of steroids to diminish with prolonged treatment; rather the reverse, since the maintenance dose of steroids was in many cases reduced by 5 mg., and in some cases by more with the passage of time. Increased maintenance dosage was rarely necessary except temporarily. Side-effects occurred in 34 cases (20%); in these patients attempts were made to reduce the maintenance dose if this was high, or in some cases the steroid was altered—for example, from prednisone to methylprednisolone or triamcinolone. In patients with peptic ulcer or dyspepsia without proved ulcer the use of keratin-coated prednisolone in addition to medical measures for the treatment of ulcer has proved useful. The one case of pulmonary tuberculosis was adequately treated while remaining on long-term steroids. Side-effects have clearly been shown to be related to steroid dosage, but their relation to length of treatment has not been proved. Increase in weight was seen to occur early, usually becoming stabilized within a year or so; restriction of calorie intake when necessary had no harmful effect. In adjusting the maintenance dose of steroids we have aimed to keep it to a level at which the life of the patients was not unduly handicapped by their asthma, rather than to attempt to render them symptom-free.

Though weaning from steroid therapy was successfully achieved in 29 cases, this was associated with considerable risk, since after withdrawal 11 out of 52 cases had attacks of status asthmaticus in which three died. These attacks sometimes developed suddenly, and it cannot be stressed too strongly that in such patients the resumption of steroid therapy in doses of 20-40 mg. daily should be begun as soon as the attack does not respond to simple oral bronchodilator drugs. If a satisfactory response then occurs the dose can be reduced over one to two weeks; but if it continues for 24 hours, or the patient's condition gives rise to anxiety at any stage, emergency admission to hospital should be arranged, with subsequent administration of large doses of prednisolone (60-120 mg. orally or hydrocortisone hemisuccinate 300-1,000 mg. intravenously in 24 hours). It must be remembered that steroids, whether given orally or intravenously, may take up to 36 hours before their effect is apparent; during this interval the patient may die directly from his asthma, or possibly, as has recently been suggested (Greenberg and Pines, 1967; Kerr, 1967; Exon, 1967), as the result of excessive use of isoprenaline or adrenaline aerosols. The use of aminophylline intravenously, oxygen, and, if necessary, aided respiration must not be overlooked.

There seems to be little doubt that asthmatic patients are particularly at risk for a variable period after withdrawal of steroids which have been given regularly for more than a few weeks, while those similarly treated for other forms of chronic disease such as rheumatoid arthritis are not so affected. In this condition rebound symptoms take the form of increased pain which is disabling, whereas the severe bronchial constriction of asthma may be fatal. It is usually assumed that such severe relapses are related to failure of the pituitary-adrenal axis to react to stress. Bayliss (1960) reported that after steroid therapy there was considerable variation in the speed with which the adrenal response to corticotrophin returned to normal, and that even when the response was normal "it does not follow that the patient's own pituitary will secrete more corticotrophin in a stressful situation." Cope (1966) also comments that after steroid therapy for a year or more "the pituitary-adrenal axis continues to be subdued for up to five months after weaning, though its activity is usually adequate for ordinary purposes." Further confirmation of the individual variation in the rate of recovery of the pituitary as shown by the response to insulin-induced hypoglycaemia has been presented by Livanou, Ferriman, and James (1967); they show that in some cases the suppressive effect of corticosteroid therapy may persist for up to one year.

During long-term steroid treatment the need for the temporary increase of steroids during exacerbations was repeatedly

observed, and was often best supplied when the decision to increase the dose was left to the patient: this must, however, depend on an assessment of each individual's personality. Antibiotics given early during infections of the upper respiratory tract also appeared to reduce the risk of serious relapse.

We reiterate the view that long-term steroid therapy is a valuable form of treatment, but it must be used circumspectly, with adequate supervision and full collaboration between the hospital consultant and the family physician. Though steroids often enable patients to lead a more active and useful life, attacks of severe asthma may still occur, and need urgent and thorough treatment.

Summary

One hundred and seventy patients treated with long-term steroids have been followed for up to 13 years. There was no evidence that steroid therapy lost its effect with the progress of time. Side-effects were not significantly related to length of treatment but to the average dose of steroid used. Treatment with steroids, though reducing the number of attacks of status asthmaticus, in no way alters the need for urgent treatment if these develop. Severe attacks of asthma are particularly apt

to follow "weaning" from long-term treatment, and in such cases steroid therapy should at once be resumed.

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Isolation of Cytomegalovirus and Clinical Manifestations of Infection at Different Ages

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Cytomegalovirus was long regarded as a rare cause of disease, affecting mainly newborn babies. It is in fact an important pathogen. Infection is common in both children and adults (Rowe *et al.*, 1956; Stern and Elek, 1965; Carlström, 1965). Young children excrete the virus for long periods, and often show evidence of liver damage (Rowe *et al.*, 1958; Hanshaw *et al.*, 1965), while adults may develop an atypical, Paul-Bunnell-negative form of infectious mononucleosis (Klemola and Kääriäinen, 1965; Anderson and Stern, 1966; Klemola *et al.*, 1967a). This latter syndrome, which also occurs as a common complication of operations requiring large transfusions of fresh blood (Kääriäinen *et al.*, 1966a), can present with hepatitis and jaundice (Lamb and Stern, 1966; Toghill *et al.*, 1967) or with polyneuritis or pericarditis (Klemola *et al.*, 1967b; Ironside and Tobin, 1967; Räsänen and Saikku, 1967). The neonatal disease is neither rare nor invariably fatal, but survivors are usually mentally retarded and microcephalic (Weller and Hanshaw, 1962; Medearis, 1964). Finally, cytomegalovirus infection is a serious and fatal hazard of the intensive immunosuppressive therapy of leukaemia and Hodgkin's disease and of renal homotransplantation (Hill *et al.*, 1964; Rifkind, 1965; Bodey *et al.*, 1965; Cangir and Sullivan, 1966).

The present paper reports an epidemiological study of cytomegalovirus infection in London, with an assessment of its clinical significance. Two associated studies are also described of cytomegalovirus infection in unexplained neonatal hepatitis and liver disease in children, and in Paul-Bunnell-negative glandular fever.

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Virological Methods

Urine and throat washings were collected into virus transport medium and inoculated within two hours into diploid human embryonic fibroblasts. Cytomegalovirus complement-fixing antibodies were estimated by the microtitre technique, using cell-associated antigen prepared from the Rawles strain of virus. The virus isolation and serological techniques have been described in previous papers (Stern *et al.*, 1963; Stern and Elek, 1965).

Prevalence of Cytomegalovirus Excretion in London

Urine was collected routinely from babies on the first or second day after birth, in the maternity units of St. George's Hospital and the Hillingdon Hospital. Urine and a throat washing or swab were taken from unselected admissions to the acute medical, surgical, and paediatric wards of St. George's

TABLE 1.—*Excretion of Cytomegalovirus in Unselected Neonates and Hospital Admissions in London*

Age Groups	No. Positive		% Positive
	No. Tested		
Neonates	3/118	2.5	
2-5 months	3/32	9	
6 months-4 years	10/104	10	
5-9 years	1/101	1	
10-14 "	0/72	—	
15-24 "	0/102	—	
25-34 "	0/100	—	
35-59 "	0/100	—	
60+ "	0/100	—	