Incidence of serious complications of corticosteroid therapy in respiratory disease

A retrospective survey of patients in the Brompton Hospital

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A retrospectively controlled study is described of mortality and serious morbidity in 550 patients treated with corticosteroids and 499 controls. The overall incidence of side-effects was similar in both groups, but gastro-intestinal bleeding, diabetes, and mental disturbance early in treatment occurred more frequently in the corticosteroid group. Other individual side-effects did not occur significantly more often than in the controls, but there was an overall increased frequency of complications with increased dose, and also an increased mortality with increase in the mainten-ance dose. Gastro-intestinal bleeding was not related to a past or present chronic peptic ulcer, and was not commoner in treated patients. Reactivation of tuberculosis and exacerbation of mental disturbance did not occur. Weight gain occurred in 29% of patients, but appeared to be related closely to a satisfactory response to treatment. Hypertension occurred in 4% of the treated group. Overall mortality in the two groups was similar. Mortality due specifically to corticosteroids was difficult to assess: two patients died of haematemesis and three died with severe asthma during withdrawal of treatment, but there was no increase in mortality following physical stress in the treated series. Sudden death in asthmatics was not more frequent in cortico-steroid-treated patients. All seven control patients who died suddenly with asthma were middle-aged. Increase in duration of treatment was not associated with increased risk. Indeed the long-term, low-dose group had a lower incidence of complications than the rest and a mortality similar to that of the controls. A trial of corticosteroids for less than one month carried no risk in 41 patients.

A knowledge of the frequency with which serious complications arise during treatment with cortico-steroids should foster a rational approach to their use (Nicholson, 1965; Thorn, 1966). Pre-vious estimates of this risk, often a by-product of the main work, have varied considerably. Many factors contribute to this variability—bias due to selection inherent in 'personal series', different diseases treated, the protean nature of complica-tions, and failure to use controls. We have tried to allow for these factors in the present study by surveying 550 National Health Service patients who started treatment with corticosteroids in Brompton Hospital between December 1956 and December 1961, together with 499 similar patients not so treated. The overall incidence of possible side-effects was similar in corticosteroid-treated patients and 'controls'. Therefore, it seemed un-profitable to express an overall rate of these com-plications. Rather we have studied individual complications in an attempt to determine those due to corticosteroid treatment in our series of patients with respiratory diseases, mostly on a low maintenance dose.

SELECTION OF SERIES

We looked at the case-notes of all corticosteroid-treated patients admitted to the Brompton Hos-pital between December 1956 and December 1961, and the following groups of patients were excluded:

(*a*) those already receiving corticosteroids at the time of admission or during the preceding year;

(*b*) those whose corticosteroid treatment was solely intravenous hydrocortisone as a resuscita-tive measure;

(*c*) 42 patients with asthma under the care of one physician who was concurrently conducting a similar study for the Asthma Research Council. We were able to make our own analysis of these patients in order to assess how their exclusion

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affected our results. In fact their inclusion would have increased the incidence of crushed vertebra and underlined the direct relationship between frequency of complications and increased dose of corticosteroid ;

(*d*) 41 patients treated with corticosteroids for less than one month. These were studied separately after a preliminary analysis of all the remainder. In all these patients the treatment was stopped because of failure to respond, and never because of side-effects. In most instances the physician in charge intended a 'trial of corticosteroids'.

After these exclusions 550 patients were left in the 'treated' series, and relevant data were transferred from the case-notes to mechanically sorted punch cards via a proforma. Initial sorting of the cards yielded information concerning the 'treated' series which was used as a pattern for the 'control' series.

Four hundred and ninety-nine controls were obtained from N.H.S. patients admitted to the Brompton Hospital who had not received corticosteroids for at least one year previously and never continuously for more than one month. They were matched as far as possible with 'treated' patients for disease, age in decades, sex, and year of entry to hospital. If more controls were available than treated patients in any disease group, selection depended on the reverse order of the hospital number. If too few controls were obtained patients were recruited from adjacent years of entry, including 1962, but even then these were insufficient to match some groups such as middle-aged female asthmatics, and hence there were only 499 controls for 550 patients.

DATA RECORDED

The same information was extracted from the notes of the controls (by C. K. C.) as from the treated (by H. C. S.). The main diagnosis was recorded as the one for which the patient received treatment. Subsidiary diagnoses were also noted, but where asthma and bronchitis were diagnosed asthma was recorded by us as the primary diagnosis.

The type of corticosteroid given was noted together with the dose on which the patient was usually maintained. This amount was fairly constant over a long period for each patient. It was expressed in terms of prednisone using the usually accepted pharmaceutical equivalent dosages.

'Low dose' refers to patients maintained on 10 mg. prednisone per day or less, and 353 of our

550 patients were in this category (Table VII). 'High dose' refers to patients on more than 10 mg. daily. 'Short term' refers to patients treated for less than two years. 'Long term' refers to patients treated continuously for more than two years.

Of clinical events which might be attributed to unwanted effects of corticosteroids, we selected those which would give rise to serious mental or physical morbidity or to death, as follows: excessive weight gain, *i.e.*, greater than 14 lb. (6 kg.) ; hypertension (a rise of more than 20 mm. Hg in diastolic pressure to give readings of 110 or more) ; diabetes mellitus (raised blood glucose) ; gastric or duodenal ulceration (radiographic or operative evidence) ; gastro-intestinal bleeding ; perforation of abdominal viscus ; mental illness requiring a psychiatric opinion ; fractured bones ; sudden unexpected death ; other.

Note was made of any of the above occurring before treatment. We did not record acne or moon face, as we felt these could not be regarded as serious complications in the treatment of potentially fatal or disabling disease. Weight gain and hypertension were not analysed in the controls because this information was scanty compared with the treated series. We anticipated difficulty in making a fair assessment of the frequency of respiratory infection in bronchitis and of episodes of ischaemic heart disease. If either of these proved to be a significant complication we hoped that this would be revealed in the mortality figures. Exposure to stress, such as fever, accident or operation with anaesthetic, was noted.

The fate of the patient was then recorded as alive, dead from disease, dead from corticosteroid treatment, or dead from other cause. Sudden death was put down as death due to corticosteroids plus the main disease or the other cause of death. Apart from this instance only single causes of death were recorded. The fate of controls was similarly analysed as if they had received corticosteroids. For example, 'death due to corticosteroids' was recorded in those controls who died of causes which would have been attributable to corticosteroid treatment had this been given, though no control patient received corticosteroids at any time during the period of survey.

FOLLOW-UP

Corticosteroid-treated patients were followed from the first day of treatment and controls from the day of admission to hospital. Where information was lacking postal enquiry was made from the

general practitioner, the patient, other hospitals, Executive Councils, and, in a few, the General Registry Office. The precise length of follow-up depended on the date on which the patient's notes were studied. Records complete to within three months were accepted. The work on treated patients was spread over one year, the median date of which was 31 December 1963, and so the subsequent analysis of controls was continued until that date. On the few occasions when a control admitted in 1962 was matched to a treated patient from 1961, the last date of follow-up was extended to 31 December 1964.

A few patients from both series were accepted as lost to follow-up on 31 December 1965. Where the cause of this was known, e.g., emigration, the patient was recorded as 'alive, lost to follow-up, cause known', his duration of follow-up being up to his last visit. Where the patient was lost without trace he is recorded as 'lost'.

RESULTS

Table I gives the age, sex, disease, and fate of the 550 treated patients and 499 controls. *

Matching each treated patient with a control did not prove possible. In all but five of the large disease–age–sex groups 75% representation in the control group was attained ; it was less than 50% in only three groups:

(1) Female asthmatics, sixth decade: 48 treated, 22 controls ;

(2) Female asthmatics, seventh decade: 27 treated, 12 controls.

(3) Male asthmatics, sixth decade: 44 treated, 13 controls.

We assume that the deficiency of controls for female asthmatics in the sixth and seventh decades is due to the frequent necessity for corticosteroid treatment in these groups. There were no controls for some diseases rarely seen at the Brompton Hospital. The excess of controls among the bronchitics was due to the late withdrawal of the 'trial of corticosteroids' group from the treated series.

Follow-up was good, better for the treated patients than for the controls. Table II shows the follow-up period for the two groups. The potential period of follow-up was only 18 months for a few treated patients, but more than two years for most, and for all controls. Four (0·7%) treated patients and 26 (5·2%) controls were lost from the series for an unknown cause. In addition, three (0·5%) treated patients were lost for known causes, and in 14 patients (2·6%) in whom treatment had been stopped no attempt was made to trace them though they had not been seen for more than a year before the investigation.

INCIDENCE OF COMPLICATIONS IN CORTICOSTEROID-TREATED AND CONTROL PATIENTS   Table III gives a crude comparison of the frequency of complications in the two series. Excluding obesity and hypertension, there were 62 instances in 550 treated patients and 50 in 499 controls. This is an insignificant difference.

We have compared the frequency and time of onset of each complication in the treated series

TABLE I

COMPOSITION AND FATE OF SERIES (CONTROLS IN PARENTHESES)

Disease	Grand Total	Alive M	Alive F	Dead from: Disease M	Disease F	Steroid M	Steroid F	Other M	Other F	Unknown M	Unknown F	Lost M	Lost F	Total M	Total F
Asthma	410	113	168	8	14	4	5	1	2			1	2	123	187
	(240)	(86)	(116)	(4)	(7)	(3)	(7)	(7)	(1)	(2)	(1)	(5)	(8)	(105)	(135)
Bronchitis	94	45	14	28	2	2	1	1	1					76	18
	(131)	(58)	(19)	(29)	(1)			(15)	(2)	(2)		(1)	(2)	(107)	(24)
Tuberculosis	32	19	10	2	1									21	11
	(32)	(17)	(9)					(2)	(2)			(1)	(1)	(20)	(12)
Collagen disease ..	21	5	9	3	3							1		9	12
	(11)	(5)	(3)					(1)				(1)	(1)	(7)	(4)
Sarcoidosis	21	10	9	1	1							1		11	10
	(21)	(9)	(8)		(1)				(1)			(1)	(1)	(10)	(11)
Pulmonary fibrosis	27	9	7	8	3							1		17	10
	(25)	(9)	(3)	(4)	(5)			(1)	(2)			(1)		(15)	(10)
Cancer	34	1	1	22	10							1		23	11
	(34)	(1)	(1)	(18)	(8)			(2)	(1)			(1)		(23)	(11)
Other	11	8	2	1				(1)	(1)	(1)		(1)	(1)	8	3
	(5)	(1)	(1)					(1)	(1)		(1)	(1)		(4)	(1)
Total		210	220	72	35	6	6	2	3			2	2	288	262
		(186)	(160)	(55)	(22)	(8)	(8)	(29)	(8)	(5)	(1)	(12)	(14)	(291)	(208)
Grand total	550	430		107		12		5				4			
	(499)	(346)		(77)		(16)		(37)		(6)		(26)			

TABLE II

PERIOD OF OBSERVATION OF PATIENTS

	Period of Observation (months)											Total
	0–1	2–3	4–6	7–12	13–24	25–36	37–48	49–60	61–72	73–84	84	
Treated group												
No. of patients on corticosteroids	45	78	37	44	63	109	96	32	13	30	2	549[1]
No. of patients observed	5	21	16	27	62	160	138	61	16	42	2	550
Control group												
No. of patients observed	26	21	24	27	26	126	90	67	48	37	4	496[2]

[1] Duration of treatment unknown in one patient   [2] Three patients died at unknown time

TABLE III

FREQUENCY OF COMPLICATION.
TOTAL NUMBER OF EPISODES (DEATHS IN PARENTHESES)

Complication	Corticosteroid-treated (550 patients)	Control (499 patients)
Diabetes ..	9	2
Peptic ulcer	4	6
Acute gastro-intestinal bleeding	6 (2)	1 (1)
Perforated ulcer ..	0	0
Mental disturbance	10	16 (2)
Collapsed vertebra	3	1
Sudden death	8 (8)	10 (10)
Obesity ..	160	Not known
Hypertension ..	22	Not known
Other ..	22 (2)	14 (3)

FIG. 1.   See text.

with those of the controls. For valid comparison it was necessary to relate frequency to population at risk and duration of observation. We have calculated for each period shown in Table II the number of patient-months at risk. In the treated series patients were considered at risk only while on corticosteroids except where stated. Throughout the rest of this paper, the incidence of complications is expressed per 1,000 patient-months at risk.

Diabetes mellitus   The exacerbation and provocation of diabetes by corticosteroids have been more than adequately demonstrated in the past (Kirsner, Sklar, and Palmer, 1957; Lerner, Bianchi, Turkheimer, Singer, and Borman, 1964). The overall incidence of diabetes before treatment, 0·6%, was similar to that for the whole hospital. Our results show the expected trend in that nine patients became diabetic out of 550 treated, and only two in 499 controls (P=0·012). The time of onset in the treated is shown in Fig. 1 to be mainly in the first three months of treatment. Both controls developed diabetes late. Curiously, eight of the nine corticosteroid diabetics were males, a
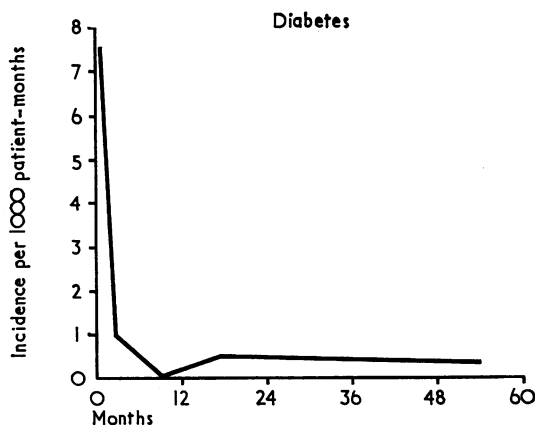
significant difference at P<0·05. No pretreatment glucose tolerance tests were performed.

Peptic ulcer and acute gastro-intestinal haemorrhage   The treated and control groups had a similar incidence of previous proved peptic ulceration (23 treated (4·2%) and 18 controls (3·6%)). None of the treated relapsed, but two controls with duodenal ulcer did so. New ulcers occurred in four treated patients (1 gastric ulcer) and six controls (3 gastric ulcers). Barium meal studies were performed only when indicated. Serious dyspepsia without radiographic evidence of ulcer was infrequent, being recorded in only three of the treated series. No instance of perforation complicated either series.

While we have no data on the effect of corticosteroids on active peptic ulcer it seems that they do not bring an increased risk of this complication either *de novo* or as a relapse in respiratory disease.

A review of the literature confirms that the risk is small or nil except in collagen diseases (Davis

and Zeller, 1952; Bulgrin, Dubois, and Jacobson, 1960; Hilbish and Black, 1958), where ulceration may be due to a combination of the underlying process and corticosteroid (Parker and Thomas, 1959) or aspirin (Roseman and Economou, 1965).

Acute gastro-intestinal haemorrhage occurred in six treated patients and in one control ($P=0.03$). Two of the six treated patients and the control died as a result. Four of the episodes in the treated patients occurred within three months of starting treatment. In no patient was there a history of previous ulcer nor any site of bleeding found at investigation or necropsy.

Mental disturbance This was recorded as present when serious enough to require psychiatric advice and treatment. The frequency of this degree of mental disturbance was 10 of 550 treated and 16 of 499 controls. There was a previous history of mental illness in 14 of the treated patients and in 13 controls, relapse occurring in three treated and in two controls. Two suicides occurred in controls without a previous history of mental disturbance. There was none among the treated.

Table IV and Fig. 2 show the time of onset of mental disturbance after the start of corticosteroids in the treated and after admission to hospital in the controls. Few patients were involved, and we cannot draw any firm conclusions. There is an increased incidence of mental illness at the start of treatment of doubtful significance: the incidence in controls was virtually constant throughout observation. As half of the mentally disturbed controls were middle-aged female asthmatics, and this group was inadequately represented in that series, the incidence of mental disturbance in the

FIG. 2. *See text.*

TABLE IV
MENTAL DISTURBANCE

	Time of Onset (mths)						
	0–1	2–3	4–6	7–12	13–24	25–36	37+
Treated							
No. of cases	4	1	—	—	3	1	1
Incidence per 1,000 patient-months	7·6	1·1	—	—	0·8	0·37	0·33
Controls							
No. of cases	1	1	1	1	4	3	5
Incidence per 1,000 patient-months	2·1	1·1	0·8	0·4	0·9	0·8	1·6

control series is an underestimate. This being so, there may be some reduction of continued risk of mental disturbance in the treated series.

Our incidence of mental disturbance was about the same as was found in other series, except in one of ulcerative colitis, where it was much higher (Kirsner, Palmer, Spencer, Bicks, and Johnson, 1959). We were unable to demonstrate that previous history helps to indicate patients at particular risk.

Fractured bones Only three of 550 treated patients and one of 499 controls were found to have crushed vertebrae which occurred without trauma. Although three further instances occurred in the 42 treated Asthma Research Council patients, their inclusion would still not make the difference between treated and controls significant. These numbers are too small to permit a firm conclusion to be drawn, especially as routine radiographs of the spine were not taken.

Crushed vertebra has been reported in previous studies of respiratory patients (Rees and Williams, 1962; Charpin, Payan, Luccioni, Lieutaud, Ohresser, and Nicolino, 1963). It seems that it occurs after long-term therapy (Rees and Williams, 1962; Demartini, Grokoest, and Ragan, 1952) and in the older age groups (Charpin et al., 1963). Our youngest patient was 49 years of age. One treated patient sustained a fractured metatarsal without adequate trauma and one control died following a fractured femur also virtually atraumatic. Four traumatic fractures occurred in the treated series.

Sudden death Sudden unexpected death occurred in eight of 550 patients and in 10 of 499 controls. All the treated patients and seven of the controls were asthmatics. In three of the treated patients reduction or withdrawal of corticosteroids was being undertaken at the time of death. Seven deaths in the controls occurred in middle-aged
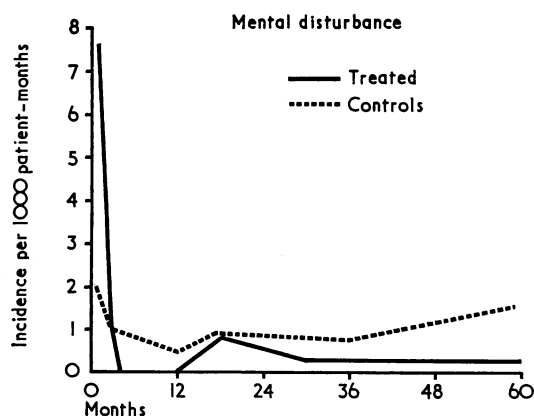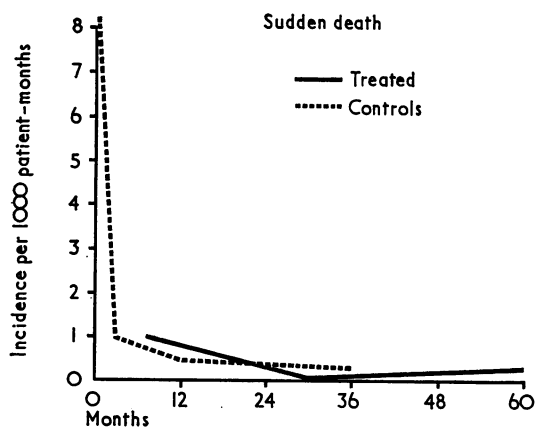
FIG. 3. *See text.*

asthmatics, a group which is 50% deficient in controls because insufficient were available. Allowance for this would make even more significant the trend shown in Figure 3. All sudden deaths in the treated patients occurred at least four months after the start of treatment, while half the sudden deaths in the controls, including those of four middle-aged asthmatics, occurred within the first four months of observation. This suggests that the middle-aged are at particular risk of sudden death when their asthma first requires treatment, and that corticosteroids protect against this risk. Later there may be an increased risk of sudden death during periods of reduction of therapy (Knowles, 1961; Medical Research Council, 1956; Pearson, Baylis, and Smellie, 1961).

Weight gain Weight gain was defined as a rise in weight to 14 lb. (6 kg.) above the weight before treatment. This occurred in 160 patients (29%). Insufficient information was available among the controls to make a comparison worth while. Electrolyte disturbance (Kirsner *et al.*, 1959; Riley and Scaglione, 1959) was not a problem. Gross oedema was rare and we do not think that weight gain should be regarded as a measure of fluid retention (Kirsner *et al.*, 1957; Elliott and Carbone, 1957).

In treated patients weight gain was commoner in males (31%) than in females (27%). It was inversely related to dose, occurring in 25·5% of the low-dose and in 19·8% of the high-dose groups (P<0·005). It never occurred after treatment was stopped, but was directly related to the period of therapy. A rise in weight, however, occurred early in treatment (Table V).

There is no significant difference in the time at which weight gain began in these patients on long-term corticosteroids as compared with those on short-term corticosteroids. Incidence of weight gain was significantly greater in those on long-term as opposed to those on short-term corticosteroids (see Table V). This direct relationship to the ultimate period of therapy and inverse relationship to dose suggests that weight gain is related to favourable response to treatment, as the low-dose, long-term group are those with the most satisfactory control of symptoms. Breathless patients frequently lose weight, so some of this weight gain represents weight regained after satisfactory treatment. It may be that the healthy person is better able to produce an anabolic response to corticosteroids (McCance, 1953).

TABLE V

WEIGHT GAIN

| | Time taken to gain 14 lb. (6 kg.) (mths) | | | | | | |
	0–1	2–3	4–6	7–12	13–24	25+	Total
No. of cases:							
Long-term[1] ..	18	49	26	15	8	5	121
Short-term[2] ..	10	16	8	4	1	—	39
Total	28	65	34	19	9	5	160
Incidence[3] per 1,000 patient-months:							
Long-term[1] ..	66	103	43	14	3·9	—	
Short-term[2] ..	42	65	23	9·1	3·1	—	

[1]Should read "Long-term corticosteroids"
[2]Should read "Short-term corticosteroids"
[3]In calculating the incidence per 1,000 patient-months at risk it has been necessary to assume that, within the short-term group, the chance of gaining weight while at risk is not related to the ultimate period of therapy.

Hypertension Twenty-two patients had significant hypertension on corticosteroids. The retrospective nature of this survey makes it possible that some were missed, and the incidence quoted, 4%, is therefore a minimum value. It should be added that the blood pressure was recorded regularly in the majority of treated patients because hypertension was expected. This was not the case in the controls, so that the incidence in them could not be estimated. The relatively benign nature of hypertension complicating corticosteroids is reflected in the absence of mortality. Low or absent mortality from hypertension was found consistently in a review of the literature.

Other complications Other possible complications are listed in Table VI.

It will be noted that there were no eye complications. There were two normal pregnancies

TABLE VI

OTHER COMPLICATIONS (DEATHS IN PARENTHESES)

Complication	Treated	Control
Pneumothorax	2	4
Muscle disease	2	
Acute infection	3	1 (1)
Tuberculosis	1	2
Diverticulosis	1 (1)	
Peripheral vascular lesions	3 (1)	2
Abdominal pain, etc. ..	2	
Fractures	1	1 (1)
Back pain, osteoporosis ..		2
Gynaecomastia		1
Acute hypotension ..	4	1 (1)
Skin manifestations ..	2	
Withdrawal symptoms ..	1	

among the treated patients. We were unable to demonstrate any increase in pneumothorax (Olesen and Quaade, 1961 ; British Tuberculosis Association, 1961).

Corticosteroid myopathy was demonstrated by electromyography and increased creatine excretion. One of the patients was on prednisone and the other on triamcinolone (Walton, 1964).

Peripheral vascular lesions were equally common in the two groups, with one death among the treated from obscure arterial embolism that had started before treatment. Two control patients died from cerebrovascular accidents but were not recorded as possible 'complications'. One treated patient died in his twenties from myocardial infarction due to polyarteritis nodosa. There were no deaths among the other five treated patients who had myocardial infarctions, but six deaths in eight controls (P=0·016). The suggestion that corticosteroids may be of value in the treatment of myocardial infarction (Baroody and Baroody, 1965 ; Dall and Buchanan, 1962) has been disputed. Our results suggest that the hypercoagulability of blood reported in patients on corticosteroids (Ozsoylu, Strauss, and Diamond, 1962 ; Eisenmenger, Slater, and Bongiovanni, 1952) was not of clinical significance. Arteritis due to underlying disease may well have been blamed on corticosteroids in the past (Bywaters and Scott, 1963 ; Parker and Thomas, 1959).

Infection, regarded by some as a serious hazard of corticosteroid therapy (*Lancet*, 1951 ; *British Medical Journal*, 1954), did not emerge as an increased risk. Patients on corticosteroids with evidence of previous tuberculosis were not routinely given antituberculous cover. There was only one case of new tuberculosis in the treated patients and no instance of reactivation. There was one new case and one relapse of tuberculosis among the controls. The only instance of fungal infection

(Murray and Sladden, 1965) among the treated was in a patient with generalized aspergillosis at necropsy. She died following mesenteric infarction and had been treated with an inferior vena caval drip for 14 days.

Severe acute infection occurred three times (2 pneumonias in non-bronchitics and a pyosalpinx) among the treated patients but only once in the controls. Acute chest infection among the bronchitics was impossible to assess on the number of episodes, as these occurred so frequently in both groups and the evidence for infection was often equivocal. It was hoped to estimate the risk by comparing the mortality of the bronchitics in the two groups. The incidence of death from disease in the treated (32%) was higher than in the controls (23%) (P=0·005), but the overall death rates (37% and 39%) were similar. This might reflect some increased risk of infection among the treated. Equally, it may be due to the fact that the more advanced bronchitics were selected for corticosteroid treatment.

The steroid withdrawal syndrome (Amatruda, Hurst, and D'Esopo, 1965 ; Henneman, Wang, Irwin, and Burrage, 1955) was not frequent in these patients. One man developed a constitutional reaction associated with a raised E.S.R. which responded to restoration of treatment. He was then maintained on treatment until the end of the study. Steroid dependence (Vaughan, 1965) was difficult to assess since, when the physician was in any doubt about the return of symptoms, he usually continued long-term therapy.

Hypotensive episodes compatible with pituitary adrenal collapse (Andersson and Kjerulf, 1961 ; Meakin, Tantongco, Crabbé, Bayles, and Nelson, 1960) occurred in four treated patients, all long-term. The precipitating factors were fever, road accident, acute asthma, and cor pulmonale. Although there were no deaths among these four, it is possible that pituitary adrenal collapse contributed to some of the sudden asthmatic deaths. One control died with irreversible hypotension in cor pulmonale.

RELATION OF MAINTENANCE DOSE TO FREQUENCY OF COMPLICATIONS   Table VII shows an apparent increase of frequency of complication with increase of dose.

This relationship suggests that the possible complications we recorded were in fact due to corticosteroid treatment. On the other hand, a comparison with controls has indicated that some possible complications occurred incidentally, *e.g.*, peptic ulceration, mental illness, etc. The data

TABLE VII

COMPLICATION AND DOSE (WEIGHT GAIN EXCEPTED)

Dose (prednisone equivalent in mg.)	No. of Patients	No. of Complications	Incidence per 1,000 Patient-mths
−10	533	47	4·3
10–15	112	21	9·6
15–20	50	11	16
20–	31	4	16
Total ..	550[1]	84[2]	6·2

[1]Three patients on ACTH only; one dose not known
[2]ACTH rash not included in subtotals

expressed in Table VII were therefore divided into two: (1) complications occurring more frequently in the treated than in the controls, and (2) those occurring with equal or lower frequency. Both sub-groups showed the same relationship to dose as in the Table. This suggests that for group 2 our data were insufficient to demonstrate these as complications when considered individually, or that the higher incidence in the higher dose group was due to their poorer health.

COMPLICATIONS AND LENGTH OF CORTICOSTEROID TREATMENT Here again there are difficulties of interpretation. We have already shown that the incidence of many complications was greatest within six months of starting treatment. This and the possibility that some patients had their treatment stopped prematurely because of complications makes a direct comparison of long- and short-term treatment difficult.

Table VIII shows details of the complications occurring in 281 patients on long-term, continuous treatment and in controls observed for more than two years.

The complication rate (excluding hypertension) was not significantly greater than in the

TABLE VIII

LONG-TERM THERAPY (>2 YEARS)

Complication	Low Dose (221 pts.)	High Dose (60 pts.)	Total (281 pts.)		Controls (387 pts.)	
Ulcer	3	—	3		5	
				2%		2%
Haemorrhage ..	1	—	1		1	
Mental disturbance	2	2	4	2%	12	3%
Crushed vertebrae	1	—	1	½%	—	
Diabetes	3	—	5	2%	2	½%
Sudden death ..	—	1	1	½%	1	½%
Other	8	2	10	3%	11	3%
Total	18 8%	12 20%	25 8·9%		32 8·3%	
Hypertension ..	13	5	18 6%			
Total	31 14%	12 20%	43 15·4%			

The figures refer to the number of patients developing the complications

controls. The incidence of complications per 1,000 patient-months at risk has been calculated and was lower in the long-term group (3·5) than overall (6·2). Forty per cent of these complications are those of hypertension which arises throughout therapy and has proved to be benign. In assessing risk associated with continuous therapy for asthma it is of interest to note that our figures are closer to those of the intermittent group of Walsh and Grant (1966) than the higher one obtaining in their continuous group.

MORTALITY The overall mortality of the treated patients was 21% (8·7 per 1,000 patient-months at risk). This compares with a control mortality of 25%. The relative excess of bronchitics as opposed to asthmatics in the control series accounts for this difference in mortality. Life tables to three years were constructed and showed no significant difference in the overall mortality of the controls and treated patients (Cochran's criterion).

Prolonged therapy was not associated with increased mortality compared with the controls. The annual mortality rate in the third and subsequent years of treatment was 4·2%, and in the third and subsequent years of observation of controls it was 5·7%.

An increased dose of corticosteroid was associated with increased mortality (Table IX).

TABLE IX

PERCENTAGE OVERALL MORTALITY

Dose (prednisone equivalent in mg.)	All	Asthma	Bronchitis
−10	15.6	6·6	35
11–15	20·5	10·7	29
16–20	·40	} 18·5	} 67
21–	52		
Total	21	8·4	37
Control	25	10·4	39

A further exact comparison of the overall mortality of high- and low-dose groups within three years' observation, excluding patients with cancer, showed a mortality nearly twice as great with a high dose (Cochran's criterion P=0·01).

As the overall mortality was similar in the controls we suspect that greater severity of illness was an important factor in the high-dose group. The mortality from steroids was difficult to assess. As described in the section on method, 'death from steroids' was recorded in the treated, and

also in those controls in whom we felt that death might reasonably have been attributed to cortico-steroids had the patient been so treated. In the first analysis there is an excess of 'death from steroids' in the controls (16 deaths in controls; 12 in the treated series). The only deaths associated with conditions that appear to be side-effects of corticosteroids in our paper are those attributed to acute gastro-intestinal haemorrhage. This gives an overall mortality rate of 0.4% directly attributable to the side-effects of steroids. Steroid withdrawal may have contributed to death in three further cases, *i.e.*, 0.6%. This gives an overall mortality rate from steroid therapy of 0.9% (0.037 per 1,000 patient-months at risk), rather less than that reported by Allanby (1957).

There was no increase in mortality during various stressful situations not related to their illness among the treated group (Table X).

TABLE X
STRESS AND MORTALITY (DEATHS IN PARENTHESES)

Stress	All Treated	Long-term Low-dose	Control
Accident	7 (0)	2 (0)	7 (4)
Surgery	26 (1)	11 (0)	79 (5)
Fever	24 (4)	8 (0)	22 (3)
Other	5 (0)	1 (0)	8 (1)
Total	62 (5)	22 (0)	116 (13)
Mortality %	8	0	11

No significant difference

In particular there was no mortality in the long-term, low-dose treated patients. This probably reflects careful supervision with a temporary increase of corticosteroid at the time of such stresses as surgery or intercurrent fever. This care might not be possible at the time of accidents, but the four fatalities following accidents were all in the control group.

TRIAL OF CORTICOSTEROIDS   The importance of objective assessment before and during a short trial period of corticosteroid therapy before embarking on long-term therapy has been emphasized by Nicholson (1965). We attempted to assess the risk in the 41 patients who had been subjected to a trial period of therapy which had proved ineffective.

Only one complication arose—recurrence of pain in a man with a previous peptic ulcer. This, though not the reason for stopping the corticosteroids, resolved after treatment. No patient gained weight during the trial. We were unable to demonstrate any risk from a short trial of corticosteroids, though our numbers are small.

VALIDITY OF OUR RESULTS   The accuracy of the incidence of the arbitrarily selected side-effects which we have reported depends on the success with which we were able to follow up the patients and extract the information from their records. Our interpretation of these side-effects depends largely on the extent to which the corticosteroid-treated patients were comparable with the control series.

The main error arising from such a retrospective survey would be omission of data either from the case-notes or subsequently. In this respect we feel that, for the treated patients, circumstances were in our favour. Follow-up was exceptionally good and the fear of complications induced the physician to see the patients frequently and look carefully for the known side-effects. When in doubt about the diagnosis we satisfied ourselves by obtaining detailed evidence.[1] Though inevitably some side-effects, particularly ones not previously reported, must have escaped our notice, we do not believe that many of those which we set out to find can have been missed. In particular, it is most unlikely that we have missed many deaths. Thus the crude incidence of side-effects in the treated group must be an underestimate, though almost certainly not a serious one. Follow-up of the controls was less complete than that of the treated patients. Control patients were not seen so frequently and were discharged from the care of the hospital more often, so that we had to rely more on postal reports. It is much more likely that morbidity and even mortality was missed in this group. This underestimate in the controls does not therefore invalidate our finding of a comparatively low incidence of complications and death in the treated series.

A further minor factor applies. Controls were followed up to a fixed date (31 December 1963), whereas treated patients were followed up to their last out-patient appointment, provided that it was within the previous three months. During the time that elapsed between the out-patient visit and perusal of the notes, the treated were at least partially under observation, because morbidity may well have led to an early return and mortality may have been reported. This small error results in a slight underestimate of the time the patients were at risk and so in an overestimate of the complication rate. Comparing the incidence of side-effects in patient-months on treatment (except in the case of sudden death) with patient-months

[1] This means that we compared the results of pathological investigations, radiographic findings, physiological studies, and necropsy findings to see whether our retrospective opinion agreed with that of the physician in charge of the patient at the time he was under observation

observation of controls again would have led to an overestimate of the complication rate in the treated patients if any risk of side-effects persisted after treatment was stopped.

The treated and control patients were independently studied by H. C. S. and C. K. C. respectively. Any difficulty in interpretation was discussed between the two authors. Although this arrangement had the disadvantage of possible differences in interpretation, it had the important advantage that C. K. C. was not biased by knowledge of the results of the treated series during the analysis of the controls.

The severity of the illness and the general health of the treated group might have differed from that of the controls, but the overall mortality was similar. The increased mortality in the controls from 'other causes' suggests that, although the general health of the control group was similar to that of the treated group, the controls were more heterogeneous so far as the disease process was concerned.

Tests of statistical significance have been applied where possible. Their validity was greatest in the case of mortality, where stratification was possible by disease, sex, and age. In comparing the incidence of complications it was only possible to test for differences in frequency without correction for differences in composition of the treated and control groups. Despite the size of the series, the numbers of complications were small, so that where differences occurred they were of borderline significance. Conclusions about complications in this paper are therefore offered as pointers rather than proved facts.

CONCLUSION

We have demonstrated that, taken overall, complications usually attributed to corticosteroids occurred to a similar extent in both treated and control patients. Overall mortality was also similar in the two groups. Death attributable to corticosteroids was probably less than 1%. Although corticosteroids may contribute to the occurrence of some of the complications investigated, only diabetes mellitus, acute gastrointestinal haemorrhage, and mental disturbance early in treatment emerged with a suggestive preponderance in the treated patients. On the other hand, corticosteroids failed to exacerbate preceding peptic ulcer, mental illness, and tuberculosis. There was some evidence that sudden death in asthma was prevented by corticosteroids, especially in the middle-aged. A trial of cortico-

steroids for less than one month in 41 patients produced no morbidity nor mortality.

Our conclusions are restricted to patients with chest diseases in whom the usual dose of corticosteroid was low and who were regularly supervised. In such patients where there was serious morbidity or risk of mortality we were unable to find justification for withholding corticosteroids for fear of side-effects.

REFERENCES

Allanby, K. D. (1957). Deaths associated with steroid-hormone therapy. An analysis of 18 cases. *Lancet*, 1, 1104.

Amatruda, T. T., Hurst, M. M., and D'Esopo, N. D. (1965). Certain endocrine and metabolic facets of the steroid withdrawal syndrome. *J. clin. Endocr.*, 25, 1207.

Andersson, E., and Kjerulf, K. (1961). Adrenal cortical function during steroid therapy. *Acta med. scand.*, 169, 577.

Baroody, N. B., and Baroody, W. G. (1965). Adrenocorticosteroids in acute myocardial infarction. *Amer. J. med. Sci.*, 250, 402.

British Medical Journal (1954). Editorial. Cortisone and infection. 1, 381.

British Tuberculosis Association (1961). A trial of corticotrophin and prednisone with chemotherapy in pulmonary tuberculosis. *Tubercle (Lond.)*, 42, 391.

Bulgrin, J. G., Dubois, E. L., and Jacobson, G. (1960). Peptic ulcer associated with corticosteroid therapy: serial roentgenographic studies. *Radiology*, 75, 712.

Bywaters, E. G. L., and Scott, J. T. (1963). The natural history of vascular lesions in rheumatoid arthritis. *J. chron. Dis.*, 16, 905.

Charpin, J., Payan, N., Luccioni, R., Lieutaud, R., Ohresser, Rh., and Nicolino, J. (1963). Essai d'evaluation du risque osseux chez les asthmatiques soumis au traitement cortisonique au long cours. *Sem. Hôp. Paris*, 39, 2129.

Dall, J. G. C., and Buchanan, J. (1962). Steroid therapy in heart block following myocardial infarction. *Lancet*, 2, 8.

Davis, T. A., and Zeller, M. (1952). Multiple peptic ulcers with massive hemorrhage during oral cortisone therapy; report of a case. *J. Amer. med. Ass.*, 150, 31.

Demartini, F., Grokoest, A. W., and Ragan, C. (1952). Pathological fractures in patients with rheumatoid arthritis treated with cortisone. *Ibid.*, 149, 750.

Eisenmenger, W. J., Slater, R. J., and Bongiovanni, A. M. (1952). Hypercoagulability of the blood of patients with hepatic cirrhosis following administration of ACTH. *Amer. J. Med.*, 13, 27.

Elliott, J. M. and Carbone, J. V. (1957). The long-term treatment of ulcerative colitis with hydrocortisone, prednisone and prednisolone. *Gastroenterology*, 33, 423.

Henneman, P. H., Wang, D. M. K., Irwin, J. W., and Burrage, W. S. (1955). Syndrome following abrupt cessation of prolonged cortisone therapy. *J. Amer. med. Ass.*, 158, 384.

Hilbish, T. F., and Black, R. L. (1958). X-ray manifestations of peptic ulceration during corticosteroid therapy of rheumatoid arthritis. *Arch. intern. Med.*, 101, 932.

Kirsner, J. B., Palmer, W. L., Spencer, J. A., Bicks, R. O., and Johnson, C. F. (1959). Corticotrophin (ACTH) and the adrenal steroids in the management of ulcerative colitis: observation in 240 patients. *Ann. intern. Med.*, 50, 891.

—— Sklar, M., and Palmer, W. L. (1957). The use of ACTH, cortisone, hydrocortisone and related compounds in the management of ulcerative colitis. *Amer. J. Med.*, 22, 264.

Knowles, J. P. (1961). Difficulties in weaning in steroid treatment of asthma. *Brit. med. J.*, 2, 1396.

Lancet (1951). Editorial. 1, 381.

Lerner, L. J., Bianchi, A., Turkheimer, A. R., Singer, F. M., and Borman, A. (1964). Anti-inflammatory steroids: potency, duration and modification of activities. *Ann. N.Y. Acad. Sci.*, 116, 1071.

McCance, R. A. (1953). Overnutrition and undernutrition. I. Causes. *Lancet*, 2, 685.

Meakin, J. W., Tantongco, M. S., Crabbé, J., Bayles, T. B., and Nelson, D. H. (1960). Pituitary-adrenal function following long-term steroid therapy. *Amer. J. Med.*, 29, 459.

Medical Research Council (1956). Controlled trial of effects of cortisone acetate in chronic asthma. *Lancet*, 2, 798.

Murray, P. J. S., and Sladden, R. A. (196ᶜ). Disseminated histoplasmosis following long-term steroid therapy for reticulosarcoma. *Brit. med. J.*, 2, 631.

Nicholson, H. (1965). The management of asthma. *Practitioner*, 195, 742.

Olesen, K. H., and Quaade, F. (1961). Pneumothorax accompanying staphylococcal pneumonia in patients treated with steroids. *Lancet*, 1, 535.

Ozsoylu, S., Strauss, H. S., and Diamond, L. K. (1962). Effects of corticosteroids on coagulation of the blood. *Nature (Lond.)*, 195, 1214.

Parker, R. A., and Thomas, P. M. (1959). Intestinal perforation and widespread arteritis in rheumatoid arthritis during treatment with cortisone. *Brit. med. J.*, 1, 540.

Pearson, R. S. Bruce, Baylis, J. H., and Smellie, H. C. (1961). Treatment of chronic asthma with prednisolone and the newer steroids. *Ibid.*, 1, 315.

Rees, H. A., and Williams, D. A. (1962). Long-term steroid therapy in chronic intractable asthma. A study of 317 adult asthmatics on continuous steroid therapy for an average period of 2½ years. *Ibid.*, 1, 1575.

Riley, C. M., and Scaglione, P. R. (1959). Current management of nephrosis. *Pediatrics*, 23, 561.

Roseman, D. L., and Economou, S. G. (1965). Treatment of complications of gastroduodenal "steroid ulcers". *Arch. Surg.*, 90, 488.

Thorn, G. W. (1966). Clinical considerations in the use of corticosteroids. *New Engl. J. Med.*, 274, 775.

Vaughan, V. C. (1965). Diagnosis and treatment: Use of steroids in asthma in children. *Pediatrics*, 35, 113.

Walsh, S. D., and Grant, I. W. B. (1966). Corticosteroids in the treatment of chronic asthma. *Brit. med. J.*, 2, 796.

Walton, J. N. (1964). Some diseases of muscle. *Lancet*, 1, 447.