Adverse reactions in patients with rheumatic diseases

Retrospective analysis of causes of admission and out-patient attendance in a specialist centre

P. LEE, S. McCUSKER, A. ALLISON, AND G. NUKI

From the Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow

It is now widely understood that the use of any therapeutic agent is inevitably associated with some risk of adverse effect. A rapidly expanding literature dealing with the manifestations of drug-induced disease testifies to an increasing awareness and concern about the wide spectrum of adverse effects that can accompany drug therapy, especially with newer and more potent pharmacological agents (Moser, 1969; Goodman and Gilman, 1970; Meyler and Herxheimer, 1968; D'Arcy and Griffin, 1972). By comparison there are relatively few published reports dealing with the prevalence or incidence of drug-induced iatrogenic disease. Such epidemiological studies as have been undertaken have established that adverse reactions to drugs are important causes of admission to general hospital medical wards and also of morbidity and mortality in patients admitted to hospital (Barr, 1955; Schimmel, 1964; Seidl, Thornton, Smith, and Cluff, 1966; Borda, Slone, and Jick, 1968; Hoddinott, Gowdey, Coulter, and Parker, 1967; Hurwitz and Wade, 1969), but there have been no systematic studies dealing with the incidence of iatrogenic illness in patients with chronic rheumatic diseases. Patients suffering from this group of diseases are frequently treated with multiple drugs over long periods of time so that it would be surprising if they did not suffer an appreciable incidence of drug side-effects.

In this paper, the first of a series of ongoing studies dealing with adverse drug reactions in patients with rheumatic diseases, we present a retrospective analysis of the reasons for admission and out-patient attendance of 500 consecutive patients referred to a regional rheumatic diseases unit in Scotland.

Material and methods

The case records of 500 consecutive patients first attending the Centre for Rheumatic Diseases in Glasgow between July 29, 1968, and April 21, 1969, were carefully scrutinized. The Centre is the only specialist unit dealing with rheumatic diseases in the Glasgow and west of Scotland area, comprising a population of approximately three million persons. The majority of patient referrals are from other hospital consultants in the region, though some patients are referred directly from general practice and a few from outside the nominal catchment area.

DEFINITIONS AND INFORMATION RECORDED

Proformas were completed for all out-patient attendances and hospital admissions where the primary reason for consultation or admission was related to the adverse effect of drugs. Adverse effects were defined as any noxious and unintended effects of a drug or drugs occurring at doses normally used for the prophylaxis, diagnosis, or therapy of disease in man (Royall, 1971). The severity of the adverse effect was classified following the scheme of Schimmel (1964):

- Severe:* Fatal or life-threatening.
Moderate: Requiring admission to hospital and/or administration of antidote.
Mild: Incidental requiring no antidote.

The type of reaction was categorized using a slight modification of the classification developed by Brown (1955), Rosenheim and Moulter (1958), Rosenheim (1962), and Hurwitz and Wade (1969).

- (1) *Excessive effect* Excessive pharmacological action with therapeutic dose: (a) Toxic extension of action, or (b) Conditioned intolerance.
(2) *Side-effect* Unwanted predictable pharmacological action not related to therapeutic effect and not due to overdose.

(3) *Hypersensitivity* Allergic sensitization by previous exposure to drug or related chemical. Mediated by antigen-antibody reaction.

(4) *Idiosyncrasy* Unrelated to known pharmacological action of drug and not mediated by immunological reaction.

Details of the adverse reactions were recorded. A record was made of the number of times and reasons for out-patient consultation related to adverse drug effects and whether consultations were primary referrals or return appointments. A note was made of any previous exposure to the drug as well as previous adverse reactions to the same or any other drug. Evidence for adverse drug reactions resulting from drug interaction were sought. Details of the clinical and administrative sequelae of the drug reaction were recorded: whether the patient required hospital admission, routine or close out-patient surveillance, and whether the drug was required to be discontinued or continued at a reduced dose. If the patient required hospitalization the length of the stay in hospital was recorded. Details of drug dosage and duration of therapy were recorded together with a list of other drugs being taken concurrently. A record was also made of the patient's age, sex, and diagnosis.

Results

IN-PATIENTS

Out of 500 consecutive referrals to the Centre for Rheumatic Diseases, 162 patients were admitted to hospital—a total of 205 separate admissions. Fifteen of these admissions (7.3 per cent.) in thirteen patients (8 per cent.) were primarily due to adverse reactions to drugs.

Ten of the thirteen patients (76.9 per cent.) were admitted directly to hospital, the other three being admitted after out-patient consultation. Thirteen admissions in eleven patients (84.6 per cent. of those admitted with adverse reactions to drugs) were attributable to side-effects of oral corticosteroids, one (7.7 per cent.) to Indomethacin, and one (7.7 per cent.) to Ibuprofen. More detailed analyses of the adverse reactions to corticosteroids and other drugs resulting in admission to hospital are summarized in Table I. All of the thirteen patients admitted suffered from rheumatoid arthritis. The mean age was 60.2 yrs ($\pm$ S.D. 9.1) and eleven out of thirteen (84.6 per cent.) were women. The mean age $\pm$ S.D. of the 149 patients admitted for other reasons was 55.9 $\pm$ 15.2 yrs; 60.4 per cent. suffered from rheumatoid arthritis and the female to male ratio was 2.4:1 (70.7 per cent. females). The differences in the mean ages and sex ratio of the two groups are not significant ($P > 0.15$ and $P > 0.10$ respectively), but the incidence of rheumatoid arthritis is significantly greater in the group admitted for adverse reactions ($P > 0.01$).

Type and severity of effect

All the adverse effects due to corticosteroids which resulted in admission to hospital (Table I) were classified as side-effects. One was graded as severe and twelve were of moderate severity; one patient died of congestive cardiac failure after admission to hospital. All showed the classical stigmata of iatrogenic Cushing's syndrome; weight gain, fluid retention, and truncal obesity being the cause of

Table I *Adverse side-effects requiring hospital admission, of oral corticosteroids in eleven patients and*

Case no.	Age (yrs)	Sex	Drug	Dose (mg.)†	Duration of therapy (mths)	Adverse effects
1	67	M	Triamcinolone	12 (15)	72	Exacerbation of arthritis after dose reduction
2	42	F	Synacthen depot	0.25	1	Acne, hirsutism, menstrual irregularity
3	76	F	Prednisolone	10	48	Obesity
4	44	F	Synacthen depot	0.5	24	Obesity, hypertension, bruising
5	61	F	Prednisolone	15	3	Obesity
6	69	F	Prednisolone	15	2	Diabetes mellitus
7*	61	F	Prednisolone	15	132	Obesity Obesity, capsular cataracts Osteoporosis, vertebral body collapse, hypertension, glaucoma
8	57	M	Prednisolone	15	111	Obesity, hypertension, osteoporosis
9	74	F	Methyl prednisolone	4 (5)	48	Hypertension, congestive cardiac failure
10	63	F	Betamethasone	1.5 (15)	24	Obesity, purpura
11	62	F	Triamcinolone	4 (5)	60	Obesity, skin atrophy, bruising, and striae
12	59	F	Indomethacin	100	—	Gastrointestinal bleeding (melaena)
13	57	F	Ibuprofen	600	6	Gastrointestinal bleeding (haematemesis)

* Three admissions of same patient, whose treatment was changed to synacthen depot after the first admission

† Dosage per day, except for Synacthen depot (Tetracosactrin depot) which was given twice a week. Amounts in () are dose equivalents of prednisolone

admission in eight out of thirteen (61.5 per cent.). However, significant hypertension (4), severe osteoporosis (2), vertebral body collapse (1), glaucoma (1), cataracts (1), overt diabetes mellitus (1), hirsutism and menstrual irregularity (1) were additional complications in others. The admission of one patient was precipitated primarily as a result of exacerbation of arthritis after reduction of corticosteroid therapy as an out-patient.

The adverse effects attributable to non-steroidal analgesic anti-inflammatory drugs which resulted in admission to hospital (Table I) were also classified as side-effects of moderate severity. Both patients, one receiving Indomethacin and one receiving Ibuprofen, suffered major gastrointestinal haemorrhage; the latter had a past history of gastric ulcer.

Clinical and administrative outcome

Excluding the single patient who died in hospital, the mean duration of hospital admission for all patients admitted as a result of adverse effects of drugs was 33.5 days $\pm$ S.D. 22.3 compared with a mean stay of 38.4 days $\pm$ 50.9 for the 190 patients admitted for other reasons. This difference is not significant ($P > 0.25$).

In five of the ten surviving patients admitted owing to adverse effects of corticosteroids, steroid therapy was discontinued, and in five the dose was reduced. Six of the ten required close out-patient supervision after discharge.

Indomethacin was discontinued in the one patient admitted with an adverse reaction to this drug, but Ibuprofen was continued in reduced dosage. Neither required close out-patient surveillance after discharge from hospital.

of other drugs in two patients, all with rheumatoid arthritis

Dosage, duration of treatment, and concomitant drug therapy

Expressed as mg./day prednisolone equivalent, the mean dose of oral corticosteroids being taken by nine patients admitted on account of adverse effects of steroid therapy was 12.2 mg. (range 5 to 15). Six out of nine (66.7 per cent.) were taking more than 10 mg. prednisolone or equivalent daily. The two patients receiving Synacthen depot (Tetracosactrin) received an average dose of 0.38 mg. twice weekly. The mean duration of steroid therapy was 47.8 mths (range 1 to 132). The patient admitted with a haematemesis whilst on Ibuprofen had been taking 600 mg. daily for 6 mths; the duration of Indomethacin administration in the patient admitted for side-effects to this drug was not known.

None of the thirteen admissions could be attributed to previous sensitization to the offending drug or to a specific drug interaction.

OUT-PATIENTS

The 500 patients under survey made a total of 1,951 visits to the out-patient clinic. 29 (5.8 per cent.) were recorded as having attended on 34 occasions (1.2 per cent. of all visits) primarily on account of adverse effects of drugs. The mean number of out-patient attendances per patient for these 29 patients was 11.5 ± 9.8 (range 1 to 39) compared with 3.4 ± 3.0 (range 0 to 26) for the 471 patients who were not seen on account of adverse drug effects. The difference is statistically significant ($P < 0.0005$). Nine of these 29 out-patients (31.0 per cent.) had adverse reactions to steroid therapy (three to oral corticosteroids and six to intramuscular corticotrophin)

Severity	Duration of admission (days)	Outcome			Follow up		
		Clinical	Drug		Close	Routine	None
			Stopped	Dose reduced			
Moderate	4	Improved	+			+	
Moderate	2	Improved		+		+	
Moderate	60	Improved		+	+		
Moderate	60	Improved		+	+		
Moderate	30	Improved	+		+		
Moderate	60	Improved	+			+	
Moderate	30	Improved	*	+	+		
Moderate	14	Improved	*	+	+		
Moderate	72	Improved	*	+	+		
Moderate	47	Improved		+		+	
Severe	4	Died					
Moderate	30	Improved	+		+		
Moderate	30	Improved	+		+		
Moderate	30	Improved	+			+	
Moderate	30	Improved		+		+	

(Table II), ten (34.5 per cent.) to Indomethacin (Table II), six (20.7 per cent.) to aspirin (Table II), three (10.3 per cent.) to mefenamic acid, and one (3.5 per cent.) to paracetamol (Table II). Two patients (Cases 2 and 7) attended on more than one occasion for adverse effects from corticosteroids and accounted for a total of seven out-patient visits.

Of the 29 patients, 27 (93.1 per cent.) suffered from rheumatoid arthritis; one patient with muzziness and headache due to Indomethacin (Case 13) had osteoarthritis, and one with the nail patellar syndrome (Case 29) receiving paracetamol suffered dyspepsia. The mean age was 53.8 yrs $\pm$ 13.5 (range 25 to 74) and 26 of the 29 patients (89.7 per cent.) were women.

Table II Out-patient attendances due to adverse effects of therapy on 29 patients

Case no.	Diagnosis	Age (yrs)	Sex	Drug	Dose† (mg.)	Duration of therapy (mths)	Adverse effects	Type
1	R.A.	49	M	Synacthen depot	0.5	7	Obesity, glycosuria, macular oedema + pigmentation	Side-effect
2*	R.A.	44	F	Synacthen depot	0.5 alt. days	1	Oedema (fluid retention)	Side-effect
				Synacthen depot	0.5 twice weekly	12	Fluid retention, hypertension	Side-effect
				Synacthen depot	0.25 twice weekly	6	Fluid retention, hypertension	Side-effect
3	R.A.	52	F	Synacthen depot	0.5 twice weekly	1	Fluid retention, intertrigo	Side-effect
4	R.A.	67	F	Prednisolone	15	18	Obesity, hypertension	Side-effect
5	R.A.	46	F	Prednisolone	5	15	Gastric ulceration	Side-effect
6	R.A.	74	F	Methyl-prednisolone	4	48	Hypertension, congestive cardiac failure	Side-effect
7	R.A.	40	F*	ACTH	20 U.daily	0.25	Vomiting	Hypersensitivity
				Synacthen depot	0.25 thrice weekly	1	Glycosuria	Side-effect
				Synacthen depot	0.25 twice weekly	20	Blurred vision	Hypersensitivity
8	R.A.	73	F	Synacthen depot	0.25 thrice weekly	23	Glycosuria, polyuria, polydipsia	Side-effect
				Synacthen depot	0.25 thrice weekly	23	Glycosuria, polyuria, polydipsia	Side-effect
9	R.Z.	57	F	Synacthen depot	0.25 alt. days	17	Hypertension, glycosuria	Side-effect
10	R.A.	25	F	Indomethacin	75	4	Rash, urticarial	Hypersensitivity
11	S.S.	68	F		75	3	Gastric ulceration	Side-effect
12	R.A.	56	F		75	1	Nausea	Side-effect
13	O.A.	61	F		75	1	Headaches, muzziness	Side-effect
14	R.A.	49	F		75	1	Headaches	Side-effect
15	R.A.	55	F		100	4	Headaches, nausea	Side-effect
16	R.A.	37	M		100 (suppositories)	6	Rectal bleeding (piles)	Side-effect
17	D.U.	51	F		75	3	Haematemesis‡	Side-effect
18	R.A.	61	F		100	5	Vomiting	Side-effect
19	R.A.	61	F		100	5	Giddiness	Side-effect
20	R.A.	54	F	Aspirin	4,000	2	Dyspepsia	Side-effect
21	R.A.	73	F		4,000	10	Deafness, tinnitus	Excessive effect
22	R.A.	61	M		4,000	1	Hyperhydrosis, drowsiness	Side-effect and excessive effect
23	R.A.	30	F		4,500	?	Nausea, tinnitus	Excessive effect
24	R.A.	40	F		?	12	Haematemesis‡	Side-effect
25	R.A.	59	F		3,500	9	Melaena	Side-effect
26	R.A.	39	F	Mefenamic acid	?	?	Skin rash	Hypersensitivity
27	R.A.	37	F		?	?	Diarrhoea	Side-effect
28	R.A.	71	F		1,000	8	Diarrhoea	Side-effect
29	Nail patellar Syndrome	69	F	Paracetamol	4,000	3	Epigastric pain	Side-effect

D.U. = duodenal ulcer S.S. = Sjögren's syndrome

* Multiple attendances of same patient corticosteroids 2 and 7

† Daily dose unless otherwise specified

‡ Referred from General Medical Ward

The mean age of 471 patients who were not seen on account of adverse drug effects was $52.3 \text{ yrs} \pm 14.2$ (range 21 to 83), 49.5 per cent. suffered from rheumatoid arthritis, and the female to male ratio was 2:1 (67 per cent. females). The difference in the mean age of the two groups is not statistically significant ($P > 0.30$), but the differences in the sex ratio and

incidence of rheumatoid arthritis are significant ($P < 0.01$ and $P < 0.0005$ respectively).

Type and severity of effect

All but two of the adverse effects due to steroid therapy which occasioned out-patient consultation were classified as side-effects (Table II). One was

Severity	Pre- vious expo- sure	Pre- vious reac- tion	Result		Drug			Follow up	
			Hospital admission	Clinical	Continued	Stopped	Dose reduced	Close	Rou- tine
Moderate	—	—	+	Improved			+		+
Mild	—	—		Improved			+	+	
Mild	—	—		Unchanged			+	+	
Moderate	—	—	+	Improved			+	+	
Mild	—	—		Improved			+	+	
Mild	—	—		Improved			+	+	
Mild	—	—		Lost to follow up			+		
Severe	—	—	+	Died	—	—	—		None
Mild	—	—		Improved	+			+	
Mild	—	—		Improved			+	+	
Mild	—	—		Improved	+			+	
Mild	—	—		Improved			+	+	
Mild	—	—		Improved			+		+
Moderate	—	—		Improved	Plus chlor- propamide		+	+	
Mild	—	—				+		+	
Mild	—	—			+	+			+
Mild	—	—					+		None
Mild	—	—				+			+
Mild	+	+				+			+
Mild	+	—				+			+
Moderate	—	—				+		+	
Mild	—	—				+			+
Mild	—	—				+			+
Mild	+	Dys- pepsia			+				+
Mild	—	—				+		+	
Mild	—	—				+			+
Mild	?	—				+			+
Moderate	—	—				+			+
Moderate	?	—				+			+
Mild	—	—				+		+	
Mild	—	—				+		+	
Mild	—	—				+		+	
Mild	—	—				+		+	

severe, three moderate, and ten mild in severity. Three required admission to hospital. One patient (Case 6) died as a result of congestive cardiac failure after admission. Weight gain, fluid retention, and truncal obesity alone resulted in out-patient attendance in six instances. However diabetes mellitus (5), hypertension (5), blurring of vision (2), vomiting (1), monilial intertrigo (1), and gastric ulceration (1) were additional complications in others. The adverse effects attributable to Indomethacin which led to out-patient attendance are detailed in Table II, nine classified as side-effects and one as hypersensitivity. None was severe, one moderate, and nine mild in severity.

The four adverse effects of mefenamic acid and paracetamol were all mild in severity. All were gastrointestinal side-effects, apart from a single skin rash resulting from hypersensitivity to mefenamic acid.

Clinical and administrative outcome

After eleven out-patient attendances for adverse effects of corticosteroid therapy in nine patients not requiring hospital admission, therapy was continued in reduced dosage in nine instances and in two the dose was unchanged. Control of the iatrogenic diabetes mellitus in Case 9 (Table II) required the administration of chlorpropamide in addition to a reduction in dosage of Tetracosactrin.

Ten (77 per cent.) required close out-patient surveillance and two were followed up routinely. One patient (Case 5) was lost to follow-up.

Indomethacin had to be discontinued in eight of the ten patients presenting with adverse reactions. The drug was continued in reduced dosage in one patient and without dose reduction in another. Only two patients were put under close out-patient surveillance as a result of their adverse response to Indomethacin.

Five of the six patients presenting with adverse reactions to aspirin (88 per cent.) discontinued the drug; the other patient continuing to take aspirin without change in dosage. Only one was followed up with close out-patient supervision.

All four patients seen as out-patients on account of adverse reactions to mefenamic acid or paracetamol discontinued the offending medication and none required special out-patient surveillance.

Dosage, duration of treatment, and concomitant drug therapy

Six (66.7 per cent.) of the nine patients attending the out-patient clinic for adverse effects of corticosteroid therapy, were receiving intramuscular Tetracosactrin (Synacthen depot), the mean duration of therapy being 18.7 mths (range 1 to 44). One patient had previously attended for adverse effects due to 'natural' ACTH therapy. The dose of Tetracosactrin

varied considerably (Table II), ranging from 0.25 mg. per week to 0.5 mg. daily.

The mean dose of corticosteroid being taken by the three patients presenting as out-patients with adverse reactions to oral corticosteroid drugs was 8.3 mg./day prednisolone equivalent. One out of the three was taking more than 10 mg./day prednisolone or equivalent. The mean duration of steroid therapy was 27.0 mths (range 15 to 48). The patients presenting with adverse reactions to 'natural' ACTH had been receiving 20 u. per day for one week. The out-patients presenting with adverse reactions to Indomethacin were taking 84.4 mg./day (range 75 to 100) for 3.4 mths (range 1 to 6); those with aspirin side-effects 4.0 g./day (range 3.5 to 4.5) for 6.8 mths (range 1 to 12). Except in one case, the dose and duration of mefenamic acid therapy were not documented. The single patient with paracetamol dyspepsia had been taking 4 g. daily for 3 months.

Discussion

By intensive monitoring of patients in hospital, several independent groups of investigators have demonstrated that 8 to 18 per cent. of patients in General Medical Wards suffer adverse reactions to drugs (Seidl and others, 1966; Ogilvie and Ruedy, 1968; Hoddinott and others, 1967; Hurwitz and Wade, 1969). A lower incidence of 1 to 10 per cent. has generally been found where the study relied on completion of adverse drug reaction report cards (MacDonald and MacKay, 1964; Schimmel, 1964; Reidenberg, 1968). Nevertheless, using intensive monitoring methods, an incidence as low as 1.54 per cent. was found in a survey of an entire Veterans Administration Hospital (Wang and Terry, 1971) and as high as 35 per cent. in a survey of a medical ward for the chronically sick (Borda and others, 1968). Hurwitz and Wade (1969) found that the number of patients suffering adverse drug reactions varied from 2 and 3 per cent. in Psychiatric and Surgical Wards to 8 and 16 per cent. in Dermatological and Medical Wards. In a comprehensive hospital in-patient survey, Smidt and McQueen (1972) found an overall incidence of adverse drug reactions of 3 per cent. with the highest rate in Adult Medical Wards (6.4 per cent.) and the lowest in Ear, Nose and Throat and Ophthalmic Wards (0.3 per cent.). It was considered that 2.7 per cent. of hospital deaths were contributed to by an adverse drug reaction. Adverse reactions are listed as the eighth most important cause of hospital admissions in the International Classification of Diseases (Cluff, 1965), 2 to 6 per cent. of all admissions to General Medical Wards and 0.3 per cent. of all admissions to a General Hospital being primarily the result of an adverse drug

effect (Seidl and others, 1966; Ogilvie and Ruedy, 1968; Hurwitz, 1969; Royall, 1971; Smidt and McQueen, 1972). 28 per cent. of patients gave a history of previous adverse reactions to drugs and 30 per cent. or more suffered further drug reactions on admission to hospital (Ogilvie and Ruedy, 1968; Smidt and McQueen, 1972). The duration of stay in hospital of patients suffering adverse reactions is markedly increased (Schimmel, 1964; Seidl and others, 1966; Ogilvie and Ruedy, 1968). The cost of hospital care in the United States for patients with iatrogenic disease has been estimated at 3 billion dollars (United States Department of Health, Education, and Welfare, 1969).

This preliminary retrospective survey has served to show that adverse reactions to drugs used in the management of chronic rheumatic diseases are responsible for a significant proportion of the workload of a regional rheumatic diseases centre. Approximately 7 per cent. of all admissions were primarily the result of adverse drug reactions and 5.8 per cent. of 500 consecutive referrals were recorded as having attended an out-patient clinic on at least one occasion as a result of adverse drug effects. This degree of morbidity must represent a considerable economic burden when one considers that the cost of one in-patient day at the Centre is of the order of £10.00 (Brooks, 1969). The adverse reactions were all the result of corticosteroids or non-steroidal analgesic and anti-inflammatory drugs used in the management of patients with chronic rheumatic diseases. Analgesics account for less than 4 per cent. of reactions in surveys of adverse drug effects in general hospital medical wards (Ogilvie and Ruedy 1968), where digitalis preparations, diuretics, insulin, bronchodilators, antibiotics, tranquillizers, and antidepressants are most often implicated (MacDonald and MacKay, 1964; Ogilvie and Ruedy, 1968; Borda and others, 1964; Hurwitz, 1969; Hurwitz and Wade, 1969; Smidt and McQueen 1972). The limitations of this study must, however, be clearly stated. Hospital data of this kind is subject to the limitations of all Type L 'within hospital' epidemiological surveys (Masi, 1965). The numerator is represented by the patients presenting as out-patients or admitted to hospital primarily as a consequence of adverse drug effects, while the denominator is represented by the population of patients at risk. To carry any true epidemiological credence, such studies rely heavily on the enumeration of the mandatory referrals of all patients with the condition and on a careful definition of the population at risk. In the present study there is no way of determining what percentage of patients with chronic rheumatic diseases in the target population who have suffered adverse drug reactions are in fact being referred to the regional rheumatic diseases centre. Nor is there any information regarding the number of drug-patient

exposures in either the 500 patients surveyed or the population at risk. The retrospective nature of the study is unlikely to have influenced the ascertainment of cases admitted to hospital but may well have underestimated the number of clinic visits attributable to adverse effects, as it is well documented that there is always a discrepancy between sought-after and casually-recorded drug reactions (O'Brien, 1967). A direct comparison of spontaneous reporting with intensive surveillance suggested that 65 to 75 per cent. of adverse reactions in hospital were not spontaneously reported (Koch-Weser, Sidel, Sweet, Kanarek, and Eaton, 1969). The high preponderance of corticosteroid side-effects may well reflect a referral bias due to a longstanding interest of this centre in various aspects of corticosteroid therapy, while the absence of adverse reactions to drugs such as phenylbutazone, gold salts, antimalarials, and immunosuppressive agents cannot be interpreted as an indication of the safety of these agents, but is more likely to represent the relative rarity of their usage in the population under study. Adequate assessment of the true incidence of adverse drug reactions to various agents used in the management of the chronic rheumatic diseases must await the results of prospective studies in which adverse effects are related to drug consumption as well as to the number of patients at risk.

By definition, all the adverse effects which resulted in admission to hospital were severe or moderately severe. All were classified as side-effects, there being no instances of hypersensitivity reactions or idiosyncrasy. In a high proportion of the corticosteroid-treated patients (67 per cent. in-patients, 33 per cent. out-patients), the daily intake exceeded 10 mg. prednisolone or equivalent, often considered to be the maximum acceptable dose for the long-term management of rheumatoid arthritis. These were considered as side-effects rather than overdoses, as they were given with therapeutic intent. Although side-effects could be predicted, the anti-inflammatory pharmacological effect intended was not being exceeded. Unlike studies in General Medical Wards, the duration of hospitalization was not increased in patients admitted on account of adverse drug reactions when compared with patients admitted for other reasons (Schimmel, 1964; Seidl and others, 1966; Ogilvie and Ruedy, 1968). A high proportion of those presenting with adverse reactions to corticosteroids required close out-patient surveillance, but this was not generally the case for patients suffering adverse reactions to non-steroidal analgesic anti-inflammatory drugs. Apart from the single patient who died after admission to hospital, the adverse drug effects improved in all cases. Corticosteroid therapy was discontinued in 43 per cent. of the patients admitted to hospital, and was reduced in the remainder and in 79 per cent. of the patients seen as

out-patients as a result of steroid side-effects. In a previous study of corticosteroid withdrawal in 47 patients with rheumatoid arthritis, it was found that half the patients with normal tests of hypothalamo-pituitary-adrenal axis function and a quarter of these with impaired function were still receiving steroid therapy 1 year after withdrawal (Nuki, Downie, Whaley, Dick, Freeman, and Buchanan, 1970). Adverse reactions to non-steroidal drugs were numerically more important as a cause of out-patient attendance than as a cause of admission. They were predominantly mild or moderate in severity and, apart from two instances of skin rashes due to hypersensitivity, all were classified as side-effects. The study gave no support to the suggestion that systemic lupus erythematosus (Harvey, Shulman, Tumulty, Conley, and Schoenrich, 1954) and Sjögren's syndrome (Bloch, Buchanan, Wohl, and Bunim, 1965; Williams, St. Onge, Young, Nuki, Dick, and Whaley, 1969) predispose to hypersensitivity reactions. In a study of clinical factors influencing susceptibility to adverse drug reactions, Smith, Seidl, and Cluff (1966) found a striking increase in hypersensitivity reactions in patients with gastrointestinal disease but none in patients with connective tissue disorders. The high proportion of patients with rheumatoid arthritis who were admitted or seen as out-patients as a result of adverse drug reactions can be largely explained by the overwhelming proportion of corticosteroid side-effects. The excess of women in both the in-patient and out-patient groups appears, however, to require another explanation. Seidl and others (1966) found that adverse drug reactions in hospital were more common in women, but the sex difference disappeared when minor gastrointestinal side-effects were excluded. Similarly, there was little difference between the sexes in the frequency of adverse reactions in the study of Smidt and McQueen (1972). Adverse drug reactions resulting in admission to hospital or out-patient attendances were not related to age in this study, and other workers have found that age did not affect the incidence of adverse reactions in patients admitted to medical wards (Smith and others, 1966; Ogilvie and Ruedy, 1968).

The majority of side-effects precipitating out-patient attendance or admission were dose-related for both corticosteroid and non-steroidal drugs. Prospective studies, in which efficacy and adverse effects are monitored together and related to drug dosage and consumption, should help to establish whether overall morbidity can be significantly reduced. No evidence for side-effects resulting from drug interaction were detected. Borda and others (1968)

found that 22 per cent. of adverse drug reactions experienced by patients in a chronic medical ward resulted from drug interactions, but oral analgesics seldom gave rise to adverse drug effects. Indomethacin and dextropropoxyphene was the only combination of analgesic and anti-inflammatory drugs identified as causing adverse effects in the study of Smith and others (1966).

Rheumatologists have long been enjoined to weigh carefully the risks to their patients which are involved in their 'pharmaceutical operations' (Hollander, 1965). There is little doubt, however, that meaningful interpretation of adverse drug reactions can best be achieved within the framework of a comprehensive drug surveillance programme (Borda and others, 1968). The establishment of such a programme with record-linkage in general practice and specialist centres in addition to general hospitals (Coull, Marron, Weir, and Crooks, 1968) should help considerably in evaluating various treatment regimes and should provide an earlier warning of adverse reactions to new drugs or drug interactions.

Summary

The case records of 500 consecutive patients attending a regional rheumatic disease unit were reviewed. Adverse drug reactions to anti-inflammatory and analgesic drugs were the primary cause of out-patient attendance on at least one occasion in 5.8 per cent. and the reason for hospital admission in thirteen out of 203 patients (6.4 per cent.). Corticosteroids were implicated as the major offending agents and much of the drug-induced morbidity was attributable to excessive dosage. There was one death, but the remaining patients improved when the drug was stopped or the dosage reduced. No instances of drug interaction were identified. The majority of the patients were women with rheumatoid arthritis.

Adverse drug reactions appear to be responsible for a significant proportion of the work-load of a regional rheumatic disease centre. Prospective studies of drug-induced morbidity in the chronic rheumatic diseases are indicated and these are at present under way.

The authors wish to thank Prof. W. Watson Buchanan for helpful criticism and advice in the preparation of this paper.

Peter Lee holds a Merck, Sharp and Dohme Clinical Research Fellowship. George Nuki was in receipt of a Ciba Clinical Research Fellowship and is at present a Merck Company Foundation International Fellow in Clinical Pharmacology at the Department of Medicine, University of California, La Jolla, California 92037.

References

- BARR, D. P. (1955) *J. Amer. med. Ass.*, **159**, 1452 (Hazards of modern diagnosis and therapy—The price we pay)
 BLOCH, K. J., BUCHANAN, W. W., WOHL, M. J., AND BUNIM, J. J. (1965) (*Medicine Baltimore*), **44**, 187 (Sjögren's syndrome. A clinical, pathological, and serological study of 62 cases)

- BORDA, I. T., SLONE, D., AND JICK, H. (1968) *J. Amer. med. Ass.*, **205**, 645 (Assessment of adverse reactions within a drug surveillance program)
- BROOKS, R. G. (1969) *Ann. rheum. Dis.*, **28**, 655 (Cost-benefit analysis of patients treated at a rheumatism centre)
- BROWN, E. A. (1955) *J. Amer. med. Ass.*, **157**, 814 (Problems of drug allergy)
- CLUFF, L. E. (1965) *Ibid.*, **191**, no. 3 (Medical News), p. 33 (Higher incidence of adverse drug reactions noted in women than in men)
- COULL, D. C. MARRON, A. C., WEIR, R. D., AND CROOKS, J. (1968) *Hlth Bull. Scot. Home Hlth Dept.*, **26**, no. 3, p. 38 (Drug monitoring systems in the health services)
- D'ARCY, P. F., AND GRIFFIN, J. P. (1972) 'Idiogenic Diseases'. Oxford University Press, London
- GOODMAN, L. S., AND GILMAN, A. Z. (1970) 'The Pharmacological Basis of Therapeutics', 4th ed. MacMillan, London and New York
- HARVEY, A. M., SHULMAN, L. E., TUMULTY, P. A., CONLEY, L. E., AND SCHOENRICH, E. H. (1954) *Medicine (Baltimore)*, **33**, 291 (Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases)
- HODDINOTT, B. C., GOWDEY, C. W., COULTER, W. K., AND PARKER, J. M. (1967) *Canad. med. Ass. J.*, **97**, 1001 (Drug reactions and errors in administration on a medical ward)
- HOLLANDER, J. L. (1965) *Ann. intern. Med.*, **62**, 1062 (The calculated risk of arthritis treatment)
- HURWITZ, N. (1969) *Brit. med. J.*, **1**, 539 (Admission to hospital due to drugs)
- AND WADE, O. L. (1969) *Ibid.*, **1**, 531 (Intensive hospital monitoring of adverse reactions to drugs)
- KOCH-WESER, J., SIDEL, V. W., SWEET, R. H., KANAREK, P., AND EATON, A. E. (1969) *New Engl. J. Med.*, **280**, 20 (Factors determining physician reporting of adverse drug reactions)
- MACDONALD, M. G., AND MACKAY, B. R. (1964) *J. Amer. med. Ass.*, **190**, 1071 (Adverse drug reactions)
- MASI, A. T. (1965) *Amer. J. publ. Hlth*, **55**, 658 (Potential uses and limitations of hospital data in epidemiologic research)
- MEYLER, L., AND HERXHEIMER, A. (1968) 'Side Effects of Drugs', vol. 6. Excerpta Medica, Amsterdam
- MOSE, R. H. (1969) 'Diseases of Medical Progress', 3rd ed. Thomas, Springfield, Ill.
- NUKI, G., DOWNIE, W. W., WHALEY, K., DICK, W. C., FREEMAN, P. A., AND BUCHANAN, W. W. (1970) *Ann. rheum. Dis.*, **29**, 60
- O'BRIEN, W. M. (1967) *Clin. Pharmacol. Ther.*, **9**, 94 (Indomethacin: A survey of clinical trials)
- OGILVIE, R. I., AND RUEDY, J. (1968) *Canad. med. Ass. J.*, **97**, 1450 (Adverse drug reactions during hospitalization)
- REIDENBERG, M. M. (1968) *J. Amer. med. Ass.*, **203**, 31 (Registry of Adverse drug reactions)
- ROSENHEIM, M. L. (1962) *Proc. roy. Soc. Med.*, **55**, 7 (Symposium on drug sensitization)
- AND MOULTER, R. (1958) 'Sensitivity Reactions to Drugs—A symposium'. Blackwell, Oxford
- ROYALL, B. W. (1971) *Biometrics*, **27**, 689 (International aspects of the study of adverse reactions to drugs)
- SCHIMMEL, E. M. (1964) *Ann. intern. Med.*, **60**, 100 (The hazards of hospitalization)
- SEIDL, L. G., THORNTON, G. F., SMITH, J. W., AND CLUFF, L. E. (1966) *Bull. Johns Hopk. Hosp.*, **119**, 299 (Studies on the epidemiology of adverse drug reactions. III. Reactions in patients on a general medical service)
- SMIDT, N. A., AND MCQUEEN, E. G. (1972) *N.Z. med. J.*, **76**, 397 (Adverse reactions to drugs: a comprehensive hospital in-patient survey)
- SMITH, J. W., SEIDL, L. G., AND CLUFF, L. E. (1966) *Ann. intern. Med.*, **65**, 629 (Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility)
- United States Department of Health, Education and Welfare (1969) Task Force on Prescription Drugs, Final Report. Government Printing Office, Washington, D.C.
- WANG, R. I. H., AND TERRY, L. CASS (1971) *J. clin. Pharmacol.*, **11**, 14 (Adverse drug reactions in a Veterans Administration Hospital)
- WILLIAMS, B. O., ST. ONGE, R. A., YOUNG, A., NUKI, G., DICK, W. C., AND WHALEY, K. (1969) *Ann. rheum. Dis.*, **28**, 607 (Penicillin allergy in rheumatoid arthritis with special reference to Sjögren's syndrome)