prolonged treatment secondary changes such as fluid retention may necessitate increments in the daily dose in resistant cases.

It has been suggested that a combination of hypotensive agents given in low dose is a useful way to reduce high blood pressure.¹⁶ Nevertheless, the response to D was related to its plasma concentration. A poor response was associated with extensive metabolism of the drug and was overcome by increasing the dose rather than by adding other hypotensive agents to the therapeutic regimen. This is important since compliance may fall as a result of using several drugs.¹⁷

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References

¹ Buhler, F R, *et al*, *New England Journal of Medicine*, 1972, **278**, 1209.

- ² Louis, W J, Doyle, A E, and Anavekar, S, *New England Journal of Medicine*, 1973, **288**, 599.
³ Sjoerdsma, A, *Circulation Research*, 1967, **21**, suppl No 3, p 119.
⁴ Morgan, T D, *et al*, *British Journal of Clinical Pharmacology*, 1975, **2**, 159.
⁵ Angelo, M, *et al*, *British Journal of Pharmacology*, 1975, **55**, 264.
⁶ Lennard, M S, *et al*, *Journal of Chromatography*, 1977, **133**, 161.
⁷ Malcolm, S L, and Marten, T R, *Analytical Chemistry*, 1976, **48**, 807.
⁸ Cohen, E L, *Journal of Laboratory and Clinical Medicine*, 1971, **77**, 1205.
⁹ Townshend, M M, and Smith, A J, *Clinical Science and Molecular Medicine*, 1973, **44**, 253.
¹⁰ Angelo, M, *et al*, *Biochemical Society Transactions*, 1976, **4**, 704.
¹¹ Kitchen, A H, and Turner, R W D, *British Medical Journal*, 1966, **2**, 728.
¹² Allen, J G, *et al*, *Drug Metabolism and Disposition*, 1975, **3**, 332.
¹³ Allen, J G, Brown, A N, and Marten, T R, *Xenobiotica*, 1976, **6**, 405.
¹⁴ Dunstan, H P, Tarazi, R C, and Bravo, E L, *New England Journal of Medicine*, 1972, **286**, 861.
¹⁵ Sandler, G, Leishman, A W D, and Humberstone, P J, *Circulation*, 1968, **38**, 542.
¹⁶ Petrie, J C, *et al*, *British Medical Journal*, 1976, **3**, 137.
¹⁷ Weintraub, M, Au, W, and Lasagna, L, *Journal of the American Medical Association*, 1973, **224**, 481.

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Recurrent breast cancer treated with the antioestrogen tamoxifen: correlation between hormonal changes and clinical course

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Summary

Forty-five post-menopausal women with recurrent breast cancer were treated with the antioestrogen, tamoxifen, 20 mg twice daily. Clinical assessment after 12 weeks indicated that 18 (40%) showed some remission. Gonadotrophins were suppressed within two weeks to relatively constant concentrations within the post-menopausal range, responses to luteinising hormone-releasing hormone (LH-RH) did not change, and androgen concentrations remained within the normal range in all patients. Oestradiol concentrations rose steadily only in women in whom treatment failed. Serum prolactin concentrations were raised in 18 out of the 44 (41%) patients in whom they were measured; 13 of these did not respond to treatment. Treatment did not change the average prolactin concentration when this was within the normal range, but it significantly reduced prolactin concentrations in hyperprolactinaemic patients—within two

weeks ($P < 0.01$) in those who responded well and by six weeks ($P < 0.05$) in those who showed no remission. Among patients with normal prolactin values the release of prolactin after thyrotrophin-releasing hormone was significantly greater in those with no remission than in those who responded to tamoxifen. Responses in those with hyperprolactinaemia were reduced to about half the control values, and again this change occurred faster in those who were successfully treated. Patients therefore seem to have a better chance of responding to antioestrogen treatment if prolactin secretion is low.

Introduction

Breast cancer is the commonest malignancy to affect European and American women, and considerable efforts have been made to understand its pathogenesis and improve treatment. Hormonal manipulation has been tried for palliating inoperable disease. The endocrine glands have been surgically ablated,¹⁻³ and corticosteroids have been administered.⁴ Both methods may produce remissions in about a third of patients⁵⁻⁷ but there is no reliable way of predicting who will respond. Bulbrook,⁸ for example, derived a discriminant function but its predictive value is affected by many factors, including age, obesity, menopausal status, and drugs.^{9 10}

Specific oestrogen receptors have been recognised in some breast tumours.^{11 12} Since antioestrogens¹³ compete for binding with oestrogen at target sites¹⁴ a trial of such compounds in the treatment of breast cancer is indicated. The antioestrogen tamoxifen (Nolvadex)¹⁵ has been well tolerated by patients with inoperable breast cancer and has produced some clinical improvement.^{16 17}

There have been few studies of the hormonal changes produced by tamoxifen in patients with breast cancer.^{18 19} We determined its effects on pituitary and steroid hormones in postmenopausal patients with recurrent breast cancer and

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correlated any hormonal changes with the clinical course of the disease. In this way we hoped to define any hormonal differences between patients that would be useful in planning treatment.

Patients and methods

Forty-five post-menopausal women with recurrent breast cancer were investigated. They had received no treatment for three months before the trial, were taking no drugs likely to affect hormone concentrations, and had received no ablative endocrine treatment. The women were examined for evidence of local tumour as well as distant spread. The size of palpable tumour masses such as lymph nodes and skin nodules was measured in two planes at right angles, and the assessments were based on the product of these values.

Endocrine tests were then carried out. On the first day patients received luteinising hormone-releasing hormone (LH-RH; 100 µg)²⁰ at 0 minutes, and venous blood samples were taken at -15, 0, +30, and +60 minutes for hormone assays. Gonadotrophins released after LH-RH were expressed as the sum of the incremental values obtained by subtracting the basal value from concentrations at 30 and 60 minutes. On the second day thyrotrophin-releasing hormone (TRH; 200 µg) was administered at 0 minutes. Blood samples were obtained at -15, 0, +15, and +30 minutes for prolactin determinations. The response to TRH was expressed as the sum of the incremental values at 30 and 60 minutes.

When these investigations were completed the patients started tamoxifen 20 mg twice daily. Physical examinations and endocrine tests were then repeated after two, six, and 12 weeks of treatment. Treatment was considered a success when at least half the lesions reduced in size by 50% or more and no new lesions had occurred at 12 weeks. Patients whose disease progressed or remained static after 12 weeks were classified as treatment failures. When lesions advanced rapidly before 12 weeks tamoxifen was stopped and the patient was given other treatment. Thirty-six of the 45 patients completed the course.

LABORATORY METHODS

Immunoreactive LH and follicle-stimulating hormone (FSH) were determined in the serum samples by double antibody radioimmunoassays²⁰ and results were expressed in terms of units MRC 69/104.

Prolactin was determined by a double antibody radioimmunoassay.²¹ The antigen for labelling was NIH V-L-S 2 and the antibody was kindly provided by Dr G V Groom (Cardiff). Results were expressed as mU/l MRC 71/222. Because of pulsatile fluctuations and the possible effect of stress on prolactin secretion, determinations were made on two samples taken at 15-minute intervals from an indwelling catheter. Repeated estimations were made 24 hours later on 25 of the patients. The coefficient of variation for the pairs of results within the normal range was 10%. The lower result in each pair was used for analysis. The normal range was calculated from results obtained in 46 post-menopausal women aged 43-70 years who had no breast cancer and were taking no drugs. One was found to be hyperprolactinaemic (860 mU/l) and was excluded from the calculation of the normal

range. In the remaining 45 the mean ($\pm$ 2 SD) was 230 (90-370) mU/l, which is similar to the range reported by Vekemans and Robyn.²² Oestradiol and androgens (testosterone and androstenediol) were measured by radioimmunoassays as described.^{20, 23}

The results were analysed statistically by Student's *t* test, analysis of variance, and Wilcoxon's rank sum tests when appropriate. Basal values for most hormones were determined in each of the 45 patients. The effects of treatment were analysed from results obtained in the 36 patients who completed the 12-week course.

Results

Clinical assessment—At 12 weeks treatment was considered a success in 18 (40%) of the 45 patients.

Gonadotrophins—There were no significant differences in the mean pretreatment serum LH and FSH values between the patients who subsequently showed remission and those in whom treatment failed (table I). Treatment with tamoxifen significantly decreased ($P < 0.001$) both hormones by the second week, and this effect was maintained until the 12-week assessment. The effects were similar in the two groups of patients. Responses to LH-RH were similar in both groups of patients and treatment with tamoxifen produced no significant changes in response in either group (table I).

Oestradiol—Mean values before treatment were not significantly different in the two groups. Seven patients (three with remission and four without) had values above the normal range expected for the method (300 pmol/l (81.7 pg/ml)) before treatment but they fell to within the normal range after two weeks' treatment. There was no overall change in oestradiol values in the group with remission, but there was a highly significant linear increase with treatment in those who had no remission, and the value reached by 12 weeks (294 ± 45 pmol/l (80.1 ± 12.3 pg/ml)) was significantly higher than the basal value (193 ± 34 pmol/l (52.6 ± 9.3 pg/ml); $P < 0.01$) (table I).

Androgens—Before treatment basal androgen values were within the normal range for postmenopausal women and there were no significant differences between the treatment groups. Tamoxifen had no effect (table I).

Basal prolactin values—Eighteen of the 44 women in whom results were available had basal prolactin values above the normal post-menopausal range (table II). Only two women with tamoxifen-induced remission remained hyperprolactinaemic after six weeks' treatment

TABLE II—Incidence (%) of hyperprolactinaemia before and during treatment with tamoxifen. Figures in parentheses show how many patients had hyperprolactinaemia out of number studied

Treatment	Tamoxifen treatment			
	Before	2 Weeks	6 Weeks	12 Weeks
Successful	29 (5/17)	6 (1/17)	12 (2/17)	6 (1/17)
Unsuccessful	48 (13/27)	35 (9/26)	39 (9/23)	12 (2/17)*

*Five patients with continuing hyperprolactinaemia had been put on to other treatment before the 12-week assessment.

TABLE I—Mean hormonal values ($\pm$ SE of mean) during treatment with tamoxifen

	Total No of subjects	Basal value	Patients completing 12-week trial					Treatment: success or failure
			No of patients	Basal	2 Weeks	6 Weeks	12 Weeks	
Basal gonadotrophins:								
LH (U/l)	18	20.4 ± 1.6	18	20.4 ± 1.6	12.6 ± 1.3†	13.2 ± 1.6†	13.4 ± 1.7†	Success
	27	21.7 ± 2.6	18	22.4 ± 2.6	14.8 ± 1.9†	12.0 ± 1.6†	11.5 ± 1.6†	Failure
FSH (U/l)	17	57.0 ± 4.0	17	57.0 ± 4.0	38.8 ± 2.4†	41.2 ± 3.0†	36.6 ± 3.0†	Success
	26	61.0 ± 5.1	18	61.5 ± 6.6	47.5 ± 5.3†	43.1 ± 5.2†	37.4 ± 5.6†	Failure
LH-RH tests (total increments):								
LH (U/l)	18	82.8 ± 9.3	16	78.9 ± 9.4	75.1 ± 7.5	78.9 ± 7.5	81.4 ± 8.3	Success
	26	85.6 ± 6.9	17	91.6 ± 9.1	82.7 ± 8.7	76.9 ± 8.6	79.6 ± 7.9	Failure
FSH (U/l)	17	49.9 ± 7.6	14	45.5 ± 8.1	34.1 ± 6.9	40.5 ± 6.7	45.2 ± 7.1	Success
	26	46.3 ± 4.9	16	52.0 ± 5.7	44.2 ± 6.6	44.1 ± 7.8	41.0 ± 6.3	Failure
Basal gonadal steroids:								
Oestradiol (pmol/l)	18	211 ± 34	17	216 ± 34	210 ± 42	200 ± 39	246 ± 32	Success
	26	186 ± 26	18	193 ± 34	248 ± 30	249 ± 27	294 ± 45†	Failure
Androgens (nmol/l)	18	3.8 ± 0.35	17	3.9 ± 0.35	4.4 ± 0.52	4.2 ± 0.30	4.5 ± 0.50	Success
	26	3.2 ± 0.29	18	3.5 ± 0.39	4.0 ± 0.41	3.7 ± 0.31	4.3 ± 0.45	Failure

Significance of change from basal: † $P < 0.01$; ‡ $P < 0.001$.

Conversion: SI to traditional units—Oestradiol: 1 pmol/l $\approx$ 0.27 pg/ml. Androgens (testosterone and androstenediol): 1 nmol/l $\approx$ 0.29 ng/ml.

TABLE III—Serum prolactin (mean $\pm$ SE of mean) and response to TRH (mean sum of increments $\pm$ SE of mean) during tamoxifen treatment

	Patients who responded to treatment					Patients who did not respond to treatment				
	No of patients	Basal	2 Weeks	6 Weeks	12 Weeks	No of patients	Basal	2 Weeks	6 Weeks	12 Weeks
<i>Basal prolactin</i>										
Normal basal values	12	249 $\pm$ 25	278 $\pm$ 31	231 $\pm$ 20	232 $\pm$ 26	10	259 $\pm$ 17	255 $\pm$ 21	225 $\pm$ 15	223 $\pm$ 31
Hyperprolactinaemia	5	608 $\pm$ 167	280 $\pm$ 48 [†]	398 $\pm$ 93	190 $\pm$ 39 [‡]	7	699 $\pm$ 121	634 $\pm$ 121	470 $\pm$ 65*	233 $\pm$ 43 [‡]
<i>Response to TRH</i>										
Normal basal prolactin	12	2410 $\pm$ 226	1846 $\pm$ 170 [†]	1844 $\pm$ 184 [†]	1858 $\pm$ 184 [†]	10	2907 $\pm$ 330	2354 $\pm$ 342	2420 $\pm$ 411	2958 $\pm$ 790
Hyperprolactinaemia	5	4366 $\pm$ 1179	2286 $\pm$ 367 [†]	2410 $\pm$ 131	2330 $\pm$ 156 [†]	7	5839 $\pm$ 567	4447 $\pm$ 790	3566 $\pm$ 428	2650 $\pm$ 211 [‡]

Significance of change from basal: *P < 0.05; [†]P < 0.01; [‡]P < 0.001.

and only one after 12 weeks. There was a significant reduction in the mean value by the second week ($P < 0.01$; table III). Nine of the 13 in whom treatment failed, however, remained hyperprolactinaemic until the sixth week, when the first significant reduction in the mean value occurred ($P < 0.05$; table III). Treatment was changed before the 12th week because the condition of five of these patients had deteriorated. Two of those who continued treatment until the 12th week remained hyperprolactinaemic. Treatment had no significant effect on the average amount of prolactin secreted in patients of either group who had normal basal values (table III).

Prolactin response to TRH—There was a positive correlation between the amount of prolactin released and the basal levels of prolactin ($r = 0.59$; $P < 0.001$). The TRH responses to patients with normal basal prolactin values and responses in those with hyperprolactinaemia were therefore considered separately (table III). The TRH responses among patients with normal prolactin values were greater in those who did not respond to tamoxifen than in those who did respond to tamoxifen throughout the 12 weeks ($P < 0.001$). There was a significant reduction ($P < 0.01$; 23%) in the average response by two weeks, and this was maintained until the end of treatment in those who achieved remission but not in those without remission. The responses of the hyperprolactinaemic patients in both treatment groups were significantly ($P < 0.001$) greater than the responses of those with normal values. In successfully treated patients tamoxifen reduced the responses to about half the pretreatment values by two weeks ($P < 0.01$) and this suppression was maintained until 12 weeks. In unsuccessfully treated patients the response was also suppressed but more gradually, and the reduction became significant only after six weeks ($P < 0.05$).

Discussion

These trials have shown that tamoxifen produced certain significant changes in hormone production. Except for prolactin and oestradiol values, however, the basal values and the changes produced by treatment were similar irrespective of whether treatment succeeded or failed.

The reduction in gonadotrophin secretion was unexpected because the drug is considered to act as an antioestrogen rather than as an oestrogen. Similar results have been reported, however, in normal postmenopausal women treated with clomiphene.²⁴ These drugs oppose the negative feedback effect of oestrogen in young women, thereby provoking the release of gonadotrophins, but in older women oestrogen secretion is low and presumably there are no sites on the receptors controlling gonadotrophin secretion for the drugs to exert their anti-oestrogenic effects. In our trial there was no evidence that tamoxifen acted by suppressing pituitary responsiveness since the responses to LH-RH did not change throughout the course of treatment.

Androgens remained relatively constant within the normal menopausal range throughout the trial, but oestradiol concentrations showed more variation and gradually increased in the treatment failure group. By 12 weeks those without remission were producing on average significantly more oestradiol than those who were successfully treated. Since the patients were menopausal increased ovarian production seemed unlikely. Some breast carcinomas can synthesise oestradiol²⁵ and those in whom treatment failed may have had a larger mass of tumour, which

produced oestrogen, possibly by conversion from androgen.

Eighteen of the 44 patients (41%) in whom basal prolactin was measured had values above the normal range for postmenopausal women, and in 13 of these tamoxifen had no success. The incidence of hyperprolactinaemia seems to be higher than has been reported elsewhere: Cole *et al.*²⁶ found raised values in the follicular phase of younger women with breast cancer, and Wilson *et al.*²⁷ reported that values were raised in older women but that the increase was not significant. Ohgo *et al.*,²⁸ however, reported that six patients (three of whom were postmenopausal) out of 29 were hyperprolactinaemic.

Like Golder *et al.*,¹⁸ we found that prolactin secretion was not changed by treatment in those patients with normal basal levels. The hyperprolactinaemic patients, however, showed considerable changes: those with tamoxifen-induced remission showed a significant reduction of more than half in the average concentration by the second week, and by the 12th week only one of the five patients originally hyperprolactinaemic remained so. The effect on those in whom treatment failed was smaller, and by the sixth week nine patients remained hyperprolactinaemic.

Differences between the treatment groups were also apparent in the TRH stimulation tests. The responses in patients with normal prolactin values who had no remission were significantly greater ($P < 0.01$) than those in patients who had remission throughout the 12 weeks. Furthermore, although the response was reduced by two weeks in the successfully treated group there was no significant change in the unsuccessfully treated group. In the hyperprolactinaemic group tamoxifen reduced the response to about half the control value by two weeks in those with remission and by 12 weeks in those without.

The changes in prolactin secretion during treatment conform with an antioestrogenic effect of tamoxifen at the central site for modulating the secretion of this hormone. Robyn and Vekemans²⁹ showed that treatment of postmenopausal women with oestrogen increased serum prolactin concentrations, and oestrogen enhanced the prolactin response to TRH.³⁰ The suppression noted in our trial shows the converse effect.

The treatment resulted in a remission rate of 40%, which compares favourably with that in other series. Cole *et al.*¹⁶ and Ward,¹⁷ using the same criteria, reported remission rates of 22% and 36% respectively using a dose of 10 mg twice a day. Ward¹⁷ subsequently used 20 mg twice daily and obtained remissions in 40% of women.

Our clinical impressions conform with those generally expressed about tamoxifen—namely, that it is an effective palliative in some cases of breast cancer and its lack of toxicity makes it especially acceptable to patients. Prolactin concentrations and the responses to TRH appear to offer indices that may be of some predictive value in selecting patients for treatment. Treatment will probably succeed if the prolactin concentration is within the normal range and the response to TRH not excessive.

It seems reasonable to suggest that treatment with tamoxifen may be more effective if prolactin production is controlled at the same time by treatment with a drug such as bromocriptine. Although tamoxifen may block oestrogen receptors in breast tumours, remission may also be related to the fall in serum

prolactin concentrations during treatment, and trials are under way to test this hypothesis.

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References

¹ Beatson, G T, *Lancet*, 1896, **2**, 104.
² Lett, H, *Lancet*, 1905, **1**, 227.
³ Huggins, C, and Bergenstal, D M, *Cancer Research*, 1952, **12**, 134.
⁴ Stoll, B A, *Hormonal Management in Breast Cancer*. London, Pitmans Medical, 1969.
⁵ Pearson, O H, and Ray, B S, *Cancer*, 1959, **12**, 85.
⁶ Atkins, H J B, *et al*, *Lancet*, 1960, **1**, 1148.
⁷ MacDonald, I, *Journal of the American Medical Association*, 1961, **175**, 787.
⁸ Bulbrook, R D, *et al*, *Lancet*, 1960, **1**, 1154.
⁹ Atkins, H J B, *et al*, *Lancet*, 1968, **2**, 1261.
¹⁰ Metcalf, M A, *Journal of Endocrinology*, 1974, **63**, 263.
¹¹ Jensen, E V, and Jacobson, H I, *Recent Progress in Hormone Research*, 1962, **18**, 387.

¹² Toft, D, and Gorski, J, *Proceedings of the National Academy of Sciences of the United States of America*, 1966, **55**, 1574.
¹³ Lunan, C B, and Klopper, A, *Clinical Endocrinology*, 1975, **4**, 551.
¹⁴ Jensen, E V, *et al*, *National Cancer Institute Monographs*, 1971, **34**, 55.
¹⁵ Harper, M J K, and Walpole, A L, *Nature*, 1966, **212**, 87.
¹⁶ Cole, M P, *et al*, *British Journal of Cancer*, 1971, **25**, 270.
¹⁷ Ward, H W C, *British Medical Journal*, 1973, **1**, 13.
¹⁸ Golder, M P, *et al*, *European Journal of Cancer*, 1976, **12**, 719.
¹⁹ Willis, K J, *Journal of Endocrinology*, 1976, **61**, 51P.
²⁰ Shaw, R W, *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1974, **81**, 632.
²¹ Glass, M, *et al*, *British Journal of Obstetrics and Gynaecology*, 1976, **83**, 495.
²² Vekemans, M, and Robyn, C, *British Medical Journal*, 1975, **4**, 738.
²³ Duignan, N M, *et al*, *Clinical Endocrinology*, 1975, **4**, 287.
²⁴ Czygan, P-J, and Schulz, K D, *Gynecologic Investigation*, 1972, **3**, 126.
²⁵ Miller, W R, and Forrest, A P M, *Lancet*, 1974, **2**, 866.
²⁶ Cole, E N, *et al*, *Journal of Endocrinology*, 1976, **69**, 49P.
²⁷ Wilson, R G, *et al*, *Cancer*, 1974, **33**, 1325.
²⁸ Ohgo, S, *et al*, *Cancer*, 1976, **37**, 1412.
²⁹ Robyn, C, and Vekemans, M, *Acta endocrinologica*, (København), 1976, **83**, 9.
³⁰ Jacobs, L S, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1973, **36**, 1069.

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SHORT REPORTS

Steroid cards: patient compliance

Long-term oral corticosteroid treatment is associated with secondary adrenocortical atrophy. For this reason, each patient on steroids is issued with a card which indicates the nature and dosage of treatment. We have investigated the extent of patient compliance in carrying notification of steroid drug use.

Patients, methods, and results

One hundred patients, receiving corticosteroid drugs for rheumatoid arthritis, were interviewed. Each patient was asked (1) Do you have a steroid card? (2) Were you ever issued with a card? (3) Can you produce your card? (4) Do you know why you should always carry your card? The answers to the first three questions were scored on a "Yes" or "No" basis. Evaluation of a correct or incorrect answer to question (4) was made by the interviewer. Eighty-seven patients said that they had cards and 88 agreed that a card had been issued. Seventy-six could produce their cards, while 77 knew why they should be carried. The reasons for the discrepancies in the figures are shown in the table. In 43 cases the dose of drug currently being taken was compared with the dose on the card. Agreement was found on 29 occasions (67%) and discordance in 14 instances (33%). The mean discrepancy was 2.46 mg prednisolone equivalent (standard deviation 1.42 mg).

Breakdown of patients' replies to questioning

Do you know why you should always carry your card?							
Yes (n = 77)				No (n = 23)			
Card produced	Card not produced			Card produced	Card not produced		
	Never issued	At home	Lost		Never issued	At home	Lost
65	4	8	0	11	8	3	1

Discussion

In this survey almost a quarter of patients could not produce notification that they were taking steroid treatment. They must therefore be considered to be at risk of receiving inadequate treatment in an emergency. Half of them claimed that a card had never been issued. It was impossible to verify this. With one exception, the remainder claimed that the cards were at home, although most of them were aware of the necessity to carry the card at all times. Some four subjects

who had never received a card appeared to know why they should have one. Overall, only 65 patients could both show a card and explain why it should be carried. The discrepancy between recorded and actual doses in one-third of cases is of more academic than practical importance, since emergency "steroid cover" is an all-or-none phenomenon unrelated to daily dosage. Nevertheless, along with the failure of the patients to produce a card, for whatever reason, it points to a lack of close supervision of potentially hazardous treatment.

During the survey cards were issued to all subjects who were unable to produce one; dosage was updated when necessary; and a full explanation given to each patient about the potential hazards of steroid treatment.

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Simple method for diagnosing protein-losing enteropathies

Excessive loss of plasma proteins into the gastrointestinal tract occurs in several disorders. Methods currently available for detecting this loss are cumbersome, imprecise, and expensive and entail administering radioactive isotopes and collecting faeces over several days.¹

α_1 -Antitrypsin, a glycoprotein present in normal serum at a concentration of 1.9-5.0 g/l, has been measured in meconium from healthy infants and from those with cystic fibrosis.² This protease inhibitor itself appears to be resistant to degradation by gut proteases.

We present evidence that the measurement of α_1 -antitrypsin in a random faecal sample may be used to diagnose protein-losing enteropathy.