Substitution of inhaled beclomethasone dipropionate for ingested prednisone in steroid-dependent asthmatics

A.T. KERIGAN, MB, FRCP[C]; S.O. PUGSLEY, MD, FRCP[C]; D.W. COCKCROFT,* MD, FRCP[C]; F.E. HARGREAVE, MD, FRCP[C]

The effect of inhaled beclomethasone dipropionate (dose, 400 μg daily) was investigated in 31 prednisone-dependent asthmatics. In a double-blind noncrossover study of 25 patients dependent on a daily prednisone dose of 17.5 mg or less, the dose of ingested prednisone was significantly diminished through the use of beclomethasone as compared with placebo ($P < 0.001$). In a subsequent single-blind study of the 12 patients who had received placebo, a similar decrease in prednisone dose was possible when these patients received beclomethasone. In all 25 patients the effect of beclomethasone was maintained for 2 years; 9 came to require less beclomethasone and 1 required more. In an additional single-blind study of six patients with severe asthma, dependent on prednisone in a dose of 20 to 25 mg/d, the response to beclomethasone was more variable and less significant ($P < 0.01$). However, at 2 years there was no significant benefit ($P > 0.05$) and there were two treatment failures.

In patients in whom reduction of dose or discontinuation of prednisone was possible plasma cortisol values before and after corticotropin administration increased significantly ($P < 0.001$). Prednisone reduction was associated with the appearance of mild musculoskeletal steroid-withdrawal symptoms of short duration in 15 patients, and recurrence of symptoms of rhinitis in 15 patients. Side effects of beclomethasone included episodes of hoarseness in 6 and easily treated oropharyngeal *Candida albicans* infection in 14.

L'effet du dipropionate de béclométhasone en inhalation (à la dose quotidienne de 400 μg) a été étudié chez 31 asthmatiques requérant de la prednisone. Dans une étude à double-insu sans chassé-croisé chez 25 patients nécessitant une dose quotidienne de prednisone de 17.5 mg ou moins, cette dose a diminué significativement à l'emploi de la béclométhasone par comparaison au placebo ($P < 0.001$). Dans une deuxième étude à simple-insu chez 12 patients qui avaient reçu un placebo, on a constaté une diminution semblable de la dose de prednisone lorsque ces patients ont reçu de la béclométhasone. Chez les 25 patients, l'effet de la béclométhasone s'est maintenu pendant 2 ans; 9 en vinrent à nécessiter moins de béclométhasone et 1 dut augmenter la dose. Dans une autre étude à simple-insu chez six patients souffrant d'asthme grave et dépendant de la prednisone à la dose de 20 à 25 mg/j, la réponse à la béclométhasone a été plus variable et moins significative ($P < 0.01$). Toutefois, après 2 ans il ne restait aucune amélioration significative ($P > 0.05$) et on avait enregistré deux échecs thérapeutiques.

Chez les patients où il fut possible de diminuer la dose ou d'interrompre le traitement à la prednisone, les teneurs plasmatiques en cortisol après administration de corticotropine ont augmenté significativement ($P < 0.001$). La diminution de la dose de prednisone a été associée à l'apparition chez 15 patients d'un syndrome de sevrage stéroïdien qui s'est manifesté par de légers symptômes musculosquelettiques de courte durée, et à une récidive des symptômes de rhinite chez 15 patients. Les effets secondaires de la béclométhasone ont compris des épisodes d'enrouement chez 6 et des infections buccopharyngées à *Candida albicans*, de traitement facile, chez 14.

The treatment of "corticosteroid-dependent" asthma has recently been greatly improved by the introduction of aerosols of triamcinolone-16, 17-acetonide; betamethasone-17-valerate; and beclomethasone-17, 21-dipropionate.[1-3] These adrenocorticosteroids have potent local effects — beclomethasone, for example, has a topical potency 500 times that of dexamethasone.[4] The swallowed absorbed portion is rapidly inactivated by metabolic processes[5] and, as a result, asthma may be controlled by doses that do not induce systemic effects.

We report our experience with inhaled beclomethasone aerosol, based on a double-blind trial and a 2-year follow-up in 31 patients with steroid-dependent asthma. In this study the term "asthma" was used in conformity with accepted custom.[6]

From the respiratory unit, department of medicine, St. Joseph's Hospital and McMaster University, Hamilton

*Fellow of the Medical Research Council of Canada

Reprint requests to: Dr. F.E. Hargreave, St. Joseph's Hospital, 50 Charlton Ave. E, Hamilton, Ont. L8N 1Y4

Patients and methods

Patients and determination of maintenance dose

The study group comprised 31 patients with asthma from the chest/allergy clinic of St. Joseph's Hospital, Hamilton, Ont. Details of age, sex, atopic status, associated chest disease and forced expiratory volume in 1 second (FEV_1) are shown in Table I. The asthma could not previously be controlled by sodium cromoglycate or bronchodilators, or both. All patients had required additional prednisone daily for periods of 4 months to 12 years (mean, 2.7 years). Prednisone therapy had been initiated in a daily dose of 30 or 40 mg until symptoms had cleared or until symptoms and spirometry had indicated maximum improvement. The daily dose was then reduced, rapidly at first by 5 mg every 1 or 2 days to 15 mg and then more slowly by 2.5 mg at intervals of 1 week. When symptoms began to recur the daily dose was increased to 30 or 40 mg again until maximum improvement was achieved and then reduced rapidly to 2.5 mg above the dose at which symptoms had previously recurred. This dose was regarded as the smallest maintenance dose. In patients in whom there was exacerbation of symptoms at a daily dose of 15 mg, the dose was reduced gradually from 30 mg to identify the maintenance dose.

Study methods

The investigation comprised three studies.

Study 1: A double-blind noncrossover trial was conducted in 25 patients who required treatment with prednisone in a daily maintenance dose of 17.5 mg or less. In a random fashion 13 were selected to receive inhaled beclomethasone dipropionate in a dose of two puffs (100 μg) four times daily (group 1). The other 12 first received inhaled placebo, two puffs four times daily (group 2), before receiving beclomethasone.

On the initial visit vital capacity (VC), FEV_1, blood pressure and weight were measured. Leukocyte and total eosinophil counts were determined. Plasma cortisol concentrations were measured by the method of Keane and colleagues[9] before and 30 minutes after administration of synthetic β^{1-24}-corti-

Table I—Selected clinical, respiratory function and therapeutic data

Patient no.	Age (yr), sex	Forced expiratory volume in 1 second (*l*)		Prednisone therapy					Beclomethasone therapy
					Dose (mg)				
							After beclomethasone		
		Start of study	Past maximum	Duration (yr)	Start of study	After placebo	At end of: study 1 (group 1) study 2 (groups 2 and 3)	At 2 years: study 3	Dose (μg) after 2 yr
Group 1									
1	44, F	3.4	4.4	10	10	—	0	0	400
2	41, M	2.8	3.2	0.33	10	—	0	0	200
3*	77, M	1.5	1.6	2	7.5	—	0	2.5	400
4*	57, M	0.8	1.4	1	10	—	0	0	400
5	45, F	1.9	2.8	2	5	—	0	0	100
6†	34, F	1.9	2.1	1	5	—	0	0	200
7	47, M	2.1	2.9	0.5	7.5	—	0	0	400
8	29, M	3.2	3.2	0.33	12.5	—	0	0	400
9	58, M	2.0	2.3	2	2.5	—	0	0	100
10†	45, M	2.3	3.6	0.66	10	—	0	0	200
11	52, M	2.7	3.2	12	10	—	2.5	3.75	400
12	27, F	2.8	2.8	0.5	10	—	2.5	0	200
13	41, F	1.3	1.3	1	2.5	—	0	—	—
Mean ± SD					7.9±3.2		0.39±0.94‡	0.52	
Group 2									
14†§	44, F	0.4	0.8	7	15	15	12.5	3.75	600
15†	46, F	2.9	3.7	2	7.5	7.5	2.5	0	400
16*	42, F	1.4	1.4	6	15	12.5	5	5	300
17	35, F	2.8	2.8	0.59	7.5	7.5	0	0	400
18	47, M	2.6	2.8	0.5	15	12.5	7.5	0	400
19	29, F	2.8	3.4	0.5	7.5	7.5	0	0	400
20†	47, M	2.5	3.7	0.42	12.5	12.5	0	0	300
21	56, F	1.5	1.5	4	15	12.5	2.5	0	200
22†	30, F	1.5	1.8	8	17.5	17.5	7.5	2.5	400
23	27, F	2.6	3.1	0.33	10	10	0	0	400
24	66, M	1.4	1.7	3	7.5	7.5	2.5	5	400
25†	48, F	1.7	2.0	3	15	12.5	2.5	0	300
Mean ± SD					12.1±3.8	11.3±3.3	3.5±3.9¶	1.4	
Group 3									
26	54, M	1.8	2.2	1	25	—	15	17.5	400
27†	17, M	2.8	2.9	0.5	20	—	7.5	0	0
28†	40, M	2.7	3.9	1	20	—	20	20	0
29	38, M	3.4	4.4	1	20	—	7.5	15	600
30	47, M	1.5	1.5	4	20	—	7.5	5	800
31	46, F	1.8	1.8	6	25	—	15	25	0
Mean ± SD					21.7±2.6		12.1±5.3‖	13.8	

*Patient also had chronic obstructive bronchitis.[7]
†Patient manifested atopy (one positive wheal and flare response, or more, to prick tests with 17 common allergen extracts).
‡Significantly different from mean ± SD at start of study ($P < 0.001$).
§Patient also had allergic bronchopulmonary aspergillosis.[8]
¶Significantly different from mean ± SD after placebo ($P < 0.001$).
‖Significantly different from mean ± SD at start of study ($P < 0.01$).

cotropin (Cortrosyn), 0.25 mg intravenously. An increase in plasma cortisol concentration of 7 μg/dl or greater was considered normal[10] and an increase of 6 μg/dl or less was taken to be definitely below normal. The patients were then seen weekly. After 1 week of therapy the daily dose of prednisone was reduced by 2.5 mg/wk until there was an exacerbation of asthma or until the prednisone was discontinued. In some patients with adrenal suppression, as indicated by the corticotropin stimulation test, prednisone reduction was halted at a daily dose of 5 to 7.5 mg. Care was taken to check that the test inhalers were used correctly. No change was made in the dose of other drugs such as inhaled and oral bronchodilators that the patient was receiving. In the event of an exacerbation of asthma the daily dose of prednisone was increased to 30 or 40 mg until symptoms cleared, and then reduced rapidly to 2.5 mg above the flare-up dose. Study 1 was concluded when the degree of asthma had been stable for 4 weeks on the new treatment regimen.

Study 2: A subsequent single-blind trial was carried out in the 12 group 2 patients who had received placebo in study 1 and in 6 patients with severe asthma who were dependent on prednisone in a daily dose of 20 or 25 mg (group 3). These patients received inhaled beclomethasone at a dosage of two puffs (100 μg) four times daily, except for two in group 3 who received three puffs (150 μg) four times daily (Table I, nos. 29 and 30). Patients were followed up in the same fashion as outlined for study 1.

Study 3: Follow-up of the 31 patients over 2 years, in which the dose of beclomethasone was varied according to the needs of the patient, constituted study 3. The condition of all patients was reviewed at intervals of 1 to 3 months during this 2-year period. In those in whom prednisone therapy could be discontinued the daily beclomethasone dose was reduced by 100 μg every 1 or 2 weeks until symptoms recurred. Symptoms were then controlled by increasing the beclomethasone dose to 400 μg daily or by prednisone, as already described. The daily dose of beclomethasone was then maintained at 100 μg above the dose at which symp-

toms had recurred. In patients still taking prednisone a further attempt was made to reduce the daily dose by 2.5 mg each week; if this failed, the beclomethasone dose was increased up to 300 μg four times daily and the attempt at prednisone reduction was repeated. After 2 years the blood tests carried out at the start of the study were repeated at the same time of day.

Differences in doses for the three groups were considered for means and standard deviations.

Results

Reduced prednisone requirements (Table I)

Study 1: In all 13 patients who received beclomethasone (group 1) it was possible to reduce the daily maintenance dose of prednisone by 2.5 to 12.5 mg. The daily prednisone dose was reduced from a mean (± standard deviation) of 7.9 mg ± 3.2 to 0.39 mg ± 0.94, a decrease of 7.5 mg ± 3.1 ($P < 0.001$). In contrast, in the 12 patients who received placebo (group 2), only 4 were able to reduce their daily dose of prednisone, and then only by 2.5 mg each. The mean dose decreased from 12.1 mg ± 3.8 to 11.3 mg ± 3.3, a decrease (not significant) of 0.83 mg ± 1.2 ($P < 0.05$). The difference between the reductions achieved by the two groups is highly significant ($P < 0.001$).

Study 2: Among the 12 group 2 patients, who received inhaled beclomethasone, the prednisone reduction was halted in 3 at 5 to 7.5 mg because of an impaired response to synthetic corticotropin. The daily dose of prednisone was reduced from a mean of 11.3 mg ± 3.3 to 3.5 mg ± 3.9, a decrease of 7.7 mg ± 2.9 ($P < 0.001$). Among the six group 3 patients, in whom asthma was initially controlled by 20 or 25 mg of prednisone daily, beclomethasone inhalation permitted a decrease in daily prednisone dose in five patients by 10 to 12.5 mg daily. In three of the five, reduction of prednisone was arbitrarily halted at 7.5 mg daily because of adrenal suppression. The mean prednisone reduction was from 21.7 mg ± 2.6 to 12.1 mg ± 5.3, a decrease of 9.6 mg ± 4.9 ($P < 0.01$).

Study 3: In group 1, the mean reduction of prednisone was maintained at 7.8 mg ± 3.0; one patient was lost to follow-up so that the group numbered 12. In 6 of the 12 patients there was a reduction of the daily beclomethasone dose to between 100 and 200 μg. In group 2 the mean reduction of prednisone was even greater — 9.9 mg ± 3.5. Four patients required less beclomethasone (200 or 300 μg daily) and one needed more (600 μg daily). In group 3 the mean prednisone reduction was less — 7.9 mg ± 8.1 ($P > 0.05$). Two patients did well with reductions in the total daily prednisone dose of 15 and 20 mg (one required beclomethasone, 800 μg and one had discontinued both prednisone and beclomethasone), two patients were able to tolerate reductions of 5 and 7.5 mg (on beclomethasone, 600 and 400 μg, respectively) and two patients had no prednisone reduction even when the dose of beclomethasone was increased to 1200 μg daily. Beclomethasone was discontinued in the latter two patients.

Control of asthma

In patients who responded to treatment with beclomethasone, good subjective and objective control of the asthma was achieved. For example, sleep was not disturbed by symptoms and ordinary activities during the day were not limited. In addition the FEV_1 values at the end of each study were not significantly different from the values at the start ($P > 0.2$). During the 2-year follow-up, exacerbations of asthma, unrelated to further reductions of prednisone or beclomethasone dose, occurred in 12 of the 28 (43%) beclomethasone-responsive patients on a total of 27 occasions (once in each of 4 patients, twice in 3 patients and three to five times in 5 patients). These were controlled by temporary increases or reintroduction of ingested prednisone.

Reduced systemic steroid effects

At the end of study 3 the plasma cortisol values before and 30 minutes after corticotropin administration increased significantly ($P < 0.001$) (Table II). At 2 years there were 11 normal, 11 reduced and 3 borderline-reduced results of corticotropin stimulation tests.

Withdrawal of prednisone was associated with a recurrence of atopic dermatitis in 1 patient and of rhinitis in 15 patients. The rhinitis caused troublesome nasal obstruction and loss of smell or taste in 14 patients; 7 had nasal polyps and 3 required polypectomy. The total blood eosinophil count ($\times 10^6/l$) increased from 126 ± 164 at the start of the investigation to 378 ± 324 ($P < 0.01$) at 2 years. A decrease in blood pressure of at least 30 mm Hg systolic or at least 15 mm Hg diastolic, or both, was noted in eight patients. Weight reduction (> 5 kg) was achieved by four patients. Mild fatigue, muscle stiffness and arthralgia, which may have been the result of steroid-withdrawal,[11] occurred in 15 patients when the daily dose of prednisone was reduced to 5 mg or less.

Side effects of beclomethasone

Episodic hoarseness was a complaint made by 6 patients and oral *Candida albicans* infection occurred in 14 patients. The *C. albicans* infection usually affected the soft palate or tongue and responded in all cases to treatment with nystatin, 100 000 U three times daily, held briefly in the mouth and then swallowed.

Discussion

In this study the use of beclomethasone dipropionate aerosol, 100 μg four times daily, in steroid-dependent asthmatics usually allowed a reduction in the previous prednisone maintenance dose of 10 to 15 mg daily. In patients who were able to discontinue prednisone therapy a reduction in the beclomethasone dose was often possible. In patients unable to discontinue prednisone therapy an increase in the dose of beclomethasone to 800 μg daily sometimes made possible a further decrease in prednisone dose. Beclomethasone was ineffective in only two patients, who required prednisone, 20 to 25 mg daily. No tolerance was observed during the 2-year follow-up.

Others[12-15] have made similar observations. A number of reasons have

Table II—Plasma cortisol values after stimulation with β^{1-24}-corticotropin in 25 patients with reduced prednisone requirements at 2 years

	Plasma cortisol, μg/dl (mean ± SD)			No. and direction of test results*		
	Baseline	30 min after corticotropin	Response to corticotropin	Reduced	Borderline	Normal
Before trial	1.41 ± 1.19	4.84 ± 3.05	3.43 ± 2.64	20	1	4
Follow-up at 2 years	6.29 ± 4.91	13.01 ± 5.33	6.75 ± 3.55	11†	3‡	11
Change over 2 years	4.85 ± 4.62	8.18 ± 4.72	3.32 ± 3.68	—	—	—
Significance	$P < 0.001$	$P < 0.001$	$P < 0.001$			

*Increase in plasma cortisol value (μg/dl) < 6 was considered a reduced response; that of 6 to 7, borderline; and >7, normal.
†Recorded in six patients (nos. 11, 14, 16, 24, 30 and 36) who continued to require prednisone regularly, two (nos. 1 and 15) who required prednisone for a recent asthmatic exacerbation and three (nos. 9, 10 and 12) who had not used prednisone for at least 5 months.
‡In one patient (no. 3) still on maintenance prednisone and two (nos. 21 and 25) on none.

been put forward to explain individual variability in response. These include incorrect use of the inhaler,[16] severe reduction in FEV_1[16] and sputum production.[17] Brown, Storey and George[3] have also pointed out that poor control of asthma at the time of introduction of the inhaler may be another factor, which is overcome through better control with a temporary increase in prednisone dose. None of these considerations appeared to be responsible for the two treatment failures in our study, which occurred in relatively steroid-resistant patients.

Exacerbations of asthma may occur in patients well controlled by a maintenance dose of beclomethasone, just as they may do in patients taking prednisone. In this study they were controlled by temporary reintroduction or increase in the dose of ingested prednisone. Godfrey[15] has tried doubling or tripling the daily dose of beclomethasone to a maximum of 800 μg early when exacerbation occurs; he has, however, emphasized that ingested steroid is required if an increase in dose of aerosol does not control the symptoms rapidly.

The high incidence of musculoskeletal steroid-withdrawal side effects in this study suggests that prednisone should be withdrawn more slowly. Adrenal function is impaired by as small a dose of prednisone as 6 mg daily[18] and is minimally inhibited by prednisone on alternate days.[19] Therefore the dose of prednisone should preferably be reduced initially by changing the dose to an alternate-day regimen.

The persistence of a diminished adrenal response to corticotropin at the end of the study draws attention to another danger of steroid withdrawal. Slow recovery of adrenal function was also observed by Maberly, Gibson and Butler[20] in six asthmatics who required up to 15 mg of prednisone daily, in whom therapy was changed to inhaled beclomethasone. The response to synthetic corticotropin had returned to normal at 1 month in four patients, at 2 months in the fifth, and was still abnormal at 4 months in the sixth. There is, therefore, a risk of adrenal insufficiency developing at times of extra stress; then systemic steroid therapy would be required, probably for several years. One death in an episode of shock has been attributed to failure to reinstitute oral administration of corticosteroid to treat an exacerbation of asthma.[14]

The withdrawal of prednisone may be associated with recurrence of troublesome rhinitis and nasal polyps. The patients in this study did not respond to treatment with regular antihistamines, ingested decongestants and intranasal sodium cromoglycate. Intranasal beclomethasone may be useful but was not available during the study.[21]

Observed side effects of beclomethasone were episodic hoarseness and oral candidiasis, neither of which was troublesome. The cause of hoarseness is not known. Candidiasis tends to affect the soft palate and pharynx at areas of concentrated deposition of beclomethasone, and usually occurs above the oropharynx;[22] we observed it on the larynx, however, during bronchoscopy in one patient who was hoarse. Candidiasis seems to be related to the dose of beclomethasone and to occur especially with daily doses of 400 μg or more.[17,23] It usually responds to treatment with nystatin. It has been suggested, but not confirmed, that its occurrence may be reduced by rinsing the mouth and gargling with water after each beclomethasone inhalation.

Our experience has led us to use beclomethasone aerosol in steroid-dependent asthmatics in the following way. Meticulous care is first taken to ensure that the patient uses the aerosol correctly. Beclomethasone therapy is started in a dose of 100 μg four times daily when the asthma is under good control. After 1 week the frequency of prednisone administration is changed so that it is given on alternate days; the alternate-day dose is reduced by 5 mg/wk until the patient is receiving 10 to 20 mg on alternate days. A corticotropin stimulation test is then carried out, as described previously. If the result is normal, reduction of the alternate-day dose of prednisone is continued by 2.5 mg/wk. If the response to corticotropin is subnormal, the test is repeated at intervals until the response has returned to normal, after which reduction in prednisone dose is resumed. If the patient is able to discontinue taking prednisone the dose of beclomethasone is reduced slowly at weekly intervals to identify the lowest dose that is required. Bronchodilators are used regularly in addition to the beclomethasone.

If an exacerbation of asthma occurs the dose of beclomethasone is promptly doubled (or increased to at least 400 μg daily if this is larger), to a dose of 800 μg daily; if the condition does not improve rapidly, prednisone is introduced in a daily dose of 30 to 40 mg until symptoms have cleared (or improved to the previous best) and then rapidly reduced to zero. If an exacerbation of asthma occurs while the patient is still receiving prednisone, the attack is controlled with a higher dose of prednisone in the same way, and the dose of prednisone is reduced to 2.5 mg above that at which the exacerbation occurred. The dose of beclomethasone is then increased to 800 to 1200 μg daily and further attempts to reduce the dose of prednisone are made. Steroid systemic effects are not observed at a dose of 1200 μg but they are at 1600 μg.[13]

The patient must understand various aspects of beclomethasone therapy. The patient needs to know that beclomethasone is not a bronchodilator; that it must be used regularly even if he or she is feeling well; that, following reduction of prednisone dose rhinitis or steroid-withdrawal effects may develop; that prednisone may be required to treat a flare-up of asthma or to cover stress situations like an operation, accident or other severe illness; and that, if prednisone is required, it is dangerous to delay using it and its use will only be temporary.

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Physical and psychological complications after intestinal bypass for obesity

R.C. BOWEN,* MD, CM, FRCP[C]; L. SHEPEL,† PH D

Cognitive changes, depression, arthralgia and dermatitis developed in a 33-year-old woman 5 years after a jejunoileal shunt for massive obesity. The dermatitis and low serum carotene and vitamin C values suggested vitamin deficiencies. The serum magnesium concentration also was low. Vitamin and mineral replacement led to amelioration of the physical and psychological symptoms; the improvement has been maintained at 18-month follow-up. The favourable changes were documented with the Wechsler Adult Intelligence Scale, the Minnesota Multiphasic Personality Inventory and test performance ratings. It is concluded that the surgical procedure caused vitamin and magnesium deficiencies and that these resulted in the patient's symptoms.

Des troubles de la mémoire et de la concentration, de la dépression, de l'arthralgie et une dermatite sont apparus chez une femme de 33 ans, 5 ans après une opération de pontage jéjunoiléale pour obésité massive. La dermatite et les faibles teneurs sériques en carotène et en vitamine C ont indiqué la possibilité d'une carence vitaminique. On a aussi enregistré une faible concentration sérique en magnésium. Un traitement d'appoint composé de vitamines et de minéraux a amené une amélioration des symptômes physiques et psychologiques; en post-observation, cette amélioration continuait de se maintenir après 18 mois. Ces changements favorables ont pu être confirmés sur l'échelle Wechsler de quotient intellectuel pour adulte (Wechsler Adult Intelligence Scale), l'inventaire Minnesota de la personnalité (Minnesota Multiphasic Personality Inventory) et l'épreuve de mesure de la performance (test performance ratings). On conclut que l'intervention chirurgicale a causé des carences en vitamines et en magnésium qui ont entraîné les symptômes observés chez cette patiente.

There have been numerous reports on the treatment of superobese patients by intestinal bypass operations.[1] Jejunocecal anastomoses were first used but reports of serious physical complications[2,3] led to the substitution of the jejunoileal anastomosis[4] and, most recently, to the end-to-end jejunoileal anastomosis with anastomosis of the distal ileum to the colon.[5,6] There have been reports of physical complications.[7-11] Psychiatric follow-up reports have been generally positive[6,12-15] but several authors[16-18] mention the development of psychiatric illness after bypass surgery.

We report a case of psychiatric disorder in a patient who had undergone bypass surgery because it appears to be the first detailed report of major psychiatric complications from jejunoileal anastomosis for obesity, because the follow-up period has been 6 years (complications first occurring 2 years after operation raise the issue of long-term follow-up for thousands of patients) and because the psychiatric and physical symptoms improved with replacement therapy.

Case report

Clinical features and course

A 33-year-old woman was admitted to hospital with complaints of general malaise, headaches, poor memory, depression, aching and stiffness in her joints, and a burning sensation in the gums and teeth. She also complained of occasional diarrhea. Anti-inflammatory agents prescribed before admission had not helped. The psychiatric symptoms had appeared 2 years previously, the polyarthralgia, 3 months previously. There was no family history of psychiatric problems. The patient's personal circumstances had not changed appreciably.

Approximately 4½ years previously she had undergone jejunoileostomy and ileocolostomy for intractable obesity; she had weighed 142 kg. At operation 40 cm of jejunum and 4 to 6 cm of ileum had been preserved as functional small bowel. Preoperatively results of all laboratory investigations had been within normal limits and a psychiatric assessment indicated that she was a pleasant, stable person with mild neurotic social fears and concerns about her obesity.

Examination after admission on the present occasion revealed that she was lethargic and had difficulty with concentration and memory; for example, she could not remember the details of her admission. Her weight was 82 kg. She complained of pains in her shoulders, elbows, wrists, hips, knees, the small joints of her hands, feet and neck, and of a temporal band-like headache that had been present for 3 months. She could not abduct her arms because of weakness. There was synovial thickening of the left wrist and small joints of both hands. The extensor surface of her forearms was hyperpigmented and the skin on her feet was hyperkeratotic, scaling and cracking.

A joint survey revealed slight demineralization of the joints of her hands and feet. A skeletal scan showed increased activity in the shoulders and hips, with increased relative activity about the sacroiliac joints.

The usual hematologic indices were low-normal except the erythrocyte count, which was 3.9 x 10^{12}/l and the erythrocyte sedimentation rate (ESR), which was 89 mm/h (Westergren). The sulfobromophthalein excretion was 11% in 45 minutes. The serum magnesium value was 1.4 mg/dl (normal, 1.7 to 2.26 mg/dl); other serum electrolyte, uric acid and alkaline phosphatase values were normal. The serum cholesterol value was 86 mg/dl (normal, 180 to 240 mg/dl) and that for triglycerides, 81 mg/dl (normal, 10 to 150 mg/dl). The serum ascorbic acid value was 0.4 mg/dl (normal, 0.8 to 1.4 mg/dl), that for vitamin B_{12}, 350 pg/ml (normal, 120 to 900 pg/ml), that for folate, 2.9 ng/ml (normal, > 2 ng/ml), and that for carotene, 25 mg/dl (normal, 50 to 300 mg/dl). The total fatty acid content of the stool was 12.7 g/24 h (normal, < 7.0). The serum iron value, iron-binding

From the department of psychiatry, University of Saskatchewan, Saskatoon

*Assistant professor, department of psychiatry
†Assistant professor, departments of psychiatry and psychology

Reprint requests to: Dr. R.C. Bowen, University Hospital, Saskatoon, Sask S7N 0W8