

From Sagamihara National Hospital, Pediatric Department and
National Children's Hospital, Allergy Clinic, Sagamihara-City, Japan.

DISODIUM CROMOGLYCATE (INTAL) IN THE TREATMENT OF BRONCHIAL ASTHMA IN CHILDREN

By

H. SHIODA, J. MURANO, K. MISHIMA, Y. IIKURA,
F. TANAKA & M. IZEKI

Intal (Disodium cromoglycate, FPL 670) is one of a series of bichromones synthesized and studied in the research laboratories of Fisons Pharmaceuticals Limited. It has been shown by Cox (1967) that this drug interferes in some way with the release of pharmacologically active substances such as histamine, following the union of antigen and reaginic antibody in sensitised tissue cells, but does not antagonise any of the known mediators of the anaphylactic reaction.

Howell & Altounyan (1967) first reported the therapeutic value of this drug and demonstrated its clinical benefit and safety in the treatment of allergic bronchial asthma. Smith & Devey (1968) described the beneficial effect of disodium cromoglycate in a double-blind cross-over trial on 44 children with asthma. Recently we had an opportunity to use Intal—supplied to us in Japan by Fujisawa Pharmaceutical Company Limited—for the evaluation of the effects of disodium cromoglycate in children with bronchial asthma.

We attempted to evaluate the drug by examining the following points:—

1. Protective effect against antigen challenge.
2. Clinical effectiveness.

3. Influence of treatment, if any, on reaginic antibody titre.

PATIENTS AND METHODS

Fifty-three children attending the allergy clinic at the Sagami-hara National Hospital and the National Children's Hospital were investigated. Of these, 41 were boys and 12 girls. Age ranged from 6–15 years, average 10.4 years. The children were diagnosed as allergic bronchial asthmatics according to their history and the result of skin tests. Seven of the children had been admitted to hospital because the severity of their asthma required the use of corticosteroids, either continuously or intermittently, for more than one year.

1. Protective Effect of DSCG against Antigen Challenge Experimental Design of Antigen Provocation Test

Thirteen children of primary school age with known hypersensitivity to the inhalation of house dust extract were selected for study. The provocation tests were performed when all these patients were free from symptoms and had no anti-allergic drugs for at least 7 days before tested. Each patient was challenged by house dust aerosol 30 minutes after inhalation of a placebo (Spincap containing 35 mg lactose and 5 mg sodium sulphate). The same test was repeated one week later using active drug (Intal Spincap containing 20 mg disodium cromoglycate and 20 mg lactose).

FVC and FEV₁ were measured before each antigen provocation test and from this the FEV₁% was calculated. Then 0.5 ml of saline was inhaled through a nebulizer (Vaponephrine type) and the FEV₁ was again recorded to provide a base line value. Intal or placebo was then administered by Spinhaler (inhaler device) and FEV₁ measurements were recorded at 5, 12 and 20 minutes after inhalation of house dust extract. If there was no response to a 1:100 dilution of house dust extract, a 1:10 dilution was given.

TABLE 1

Inhibitory Effects of Placebo on Provocation Tests (H. D.).

Name	Sex	Age	FEV ₁	FVC	FEV ₁ FVC $\times 100$	Reduction rate	Symp- tom
Y. H.	♀	13	2800	3420	82.0	22.6	+
K. M.	♂	13	2100	2750	75.5	35.0	+
O. R.	♀	13	2290	2610	87.7	32.0	+
N. H.	♂	11	1930	2320	82.7	11.5	±
O. E.	♀	11	1385	1860	77.8	9.7	+
T. K.	♂	12	2040	2510	80.5	8.5	+
M. Y.	♀	10	1540	1810	85.0	17.0	+
H. M.	♂	8	1490	1970	75.5	24.0	+
N. R.	♂	13	2870	3450	83.3	12.3	+
O. A.	♂	10	1990	2660	75.0	12.5	±
K. E.	♀	13	2450	2690	91.0	13.6	+
M. Y.	♀	9	1695	1925	88.0	10.5	±
K. T.	♀	12	2200	2660	83.0	21.5	+

Results of Antigen Provocation Tests

Table 1 shows the percentage fall in FEV₁ following antigen challenge giving the placebo as premedication. Eleven of the 13 children responded to challenge with a fall in FEV₁ of > 10 per cent (average reduction 17.75) and all developed wheezing symptoms shortly after inhalation of the antigen.

In contrast (Table 2), when premedicated with Intal, only one patient had a fall in FEV₁ of > 10 per cent (average reduction 3.5) and none developed wheezing.

*2. Clinical Effectiveness of DSCG**Design of Double-Blind Cross-Over Study*

Thirty four children with perennial asthma were selected to enter a clinical trial of eight weeks duration. During one 4-week period Intal was administered, and in the other placebo. The children were well trained in the correct use of the Spinhaler before starting the trial. Dosage was fixed at 4 SpinCaps daily—one on arising, one at noon, one at dinner

TABLE 2
Inhibitory Effects of INTAL on Provocation Tests (H. D.).

Name	Sex	Age	FEV ₁	FVC	$\frac{\text{FEV}_1}{\text{FVC}} \times 100$	Reduction rate	Symptom
Y. H.	♀	13	2840	3430	82.5	8.0	—
K. M.	♂	13	2550	2750	74.0	0	—
O. R.	♀	13	2080	2640	79.0	13.3	—
N. H.	♂	11	1995	2270	88.0	0	—
O. E.	♀	11	1725	2180	79.0	0	—
T. K.	♂	12	1925	2530	76.5	0	—
M. Y.	♀	10	1515	1720	88.0	6.5	—
H. M.	♂	8	1390	1670	83.5	3.0	—
N. R.	♂	13	2770	3180	87.0	3.3	—
O. A.	♂	10	2040	2680	76.5	2.0	—
K. E.	♀	13	2040	2740	74.5	4.0	—
M. Y.	♀	9	1590	1770	90.0	2.7	—
K. T.	♀	12	2090	2680	78.0	2.3	—

time, and one at bedtime. Order of treatment was selected at random and neither patient, parents nor clinician were aware of the contents of Spincaps during the period of the trial.

Clinical and Laboratory Assessment

All children and their parents, particularly the mothers, were instructed individually how to keep a daily record of the frequency and severity of asthma attacks, cough, wheeze, rhinitis, time off school, and the use of other drugs. These items were recorded in an asthma diary. The criteria used to grade intensity of asthma disability, and of cough, and the grading of response to therapy, are shown in Fig. 1.

Spirometry—At the end of each 4-week period, FVC and FEV₁ were recorded while patients were in no distress and from this data the FEV₁% was calculated. PFM measurements were made prior to entry into the trial and at intervals of one weeks thereafter.

No. of grade	Intensity	Asthma	Cough
1	Severe	Severe dyspnoea, disturbing daily living, occurring more than several times per month; or fairly severe dyspnoea, disturbing daily living, occurring almost everyday throughout a month.	Distressing cough most of the time.
2	Moderate	Severe dyspnoea, disturbing daily living, 1 to 2 times per month; or fairly severe dyspnoea, disturbing daily living, several times per month; or mild dyspnoea, not disturbing daily living, occurring almost everyday throughout a month.	Distressing cough in attacks only.
3	Mild	Fairly severe dyspnoea, disturbing daily living, 1 to 2 times per month; or mild dyspnoea, not disturbing daily living, occurring a few to several times per month.	Occasional cough, not distressing.
4	Well	No wheezing or dyspnoea.	No cough.

Effect of treatment on asthma disability and cough grades

Excellent	Became 4 during the active period from any lower category during the placebo period.
Good	Became 1 to 2 grades better during the active period as compared with those in the placebo period.
Poor	Remained on same grade during both periods.

Fig. 1.

Grades of intensities.

TABLE
Results of 33 Asthmatics Treated

No.	Name	Sex	Age (yrs.)	Height (cm)	Weight (kg)	Duration of asthma (yrs.)	Family history of allergy	No. of times of hospital admissions and its total days require for control of asthma attacks during past years
1	T. I.	♂	15	146.6	35.5	2	+	7 (48)
2	S. K.	♂	9	132.0	38.0	7	+	0
3	N. T.	♂	9	130.8	23.5	5	+	0
4	I. T.	♂	12	144.0	32.0	10	—	0
5	M. K.	♂	13	159.8	45.5	12	+	0
6	S. O.	♂	11	136.3	39.0	10	—	0
7	M. S.	♂	7	100.4	16.5	6	+	2 (6)
8	K. K.	♀	12	132.3	24.0	9	+	1 (7)
9	K. S.	♂	7			3	+	0
10	T. K.	♂	8	118.0	19.5	6	+	2 (8)
11	M. M.	♂	12	141.5	30.0	8	—	0
12	S. I.	♂	9	130.6	22.0	7	+	5 (30)
13	E. H.	♂	13	142.4	27.5	10	—	20 (86)
14	M. K.	♂	14	146.5	29.0	11	—	5 (35)
15	H. K.	♂	10	129.0	35.0	9	+	2 (18)
16	T. Y.	♂	7	118.2	20.5	6	+	2 (14)
17	A. T.	♂	9	122.8	20.4	3	+	0
18	H. I.	♂	12	131.0	26.5	8	+	2 (12)
19	H. K.	♂	6	117.3	20.0	4	+	0
20	R. M.	♂	12	152.1	27.5	9	—	3 (21)
21	M. K.	♂	9	124.5	20.8	7	+	1 (10)
22	N. A.	♂	7	119.2	24.0	4	+	0
23	T. S.	♀	12	135.0	29.2	9	+	2 (6)
24	T. O.	♂	12	141.2	36.0	11	+	4 (28)
25	T. T.	♂	9	117.2	21.0	7	+	1 (5)
26	M. N.	♂	6	109.5	19.0	3	+	0
27	A. A.	♂	10	126.4	28.0	7	—	1 (7)
28	S. I.	♂	9	125.5	22.0	7	—	3 (9)
29	I. H.	♂	9	123.3	20.2	6	+	2 (15)
30	S. T.	♂	9	129.7	26.5	7	—	2 (6)
31	A. M.	♂	10	135.7	27.1	8	+	2 (12)
32	M. F.	♀	7	119.0	24.8	3	+	1 (7)
33	T. T.	♂	10	131.1	21.8	7	+	2 (9)
34	A. A.	♂	12	141.9	28.2	8	+	2 (8)

with Intal in Double-Blind Trial.

Total amount of Prednisone (mg/4 weeks)		Intensity of asthma		Intensity of cough		Absence from school because of asthma (4 weeks)		No. of occasions used Bronchodilator, mainly Neophyllin, Ephedrin, Isoprenaline (during last 2 weeks) (per os)	
Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
0	0	3	2	2	2	2	6	3	12
0	0	3	2	2	2	0	3	6	24
0	0	3	2	3	2	0	0	3	12
0	0	3	2	4	2	0	3	0	8
0	0	2	2	2	2	4	4	14	15
0	0	4	3	4	2	0	0	0	6
0	0	2	2	2	2	1	1	14	18
20	45	1	1	2	2	14	22	22	22
0	0	3	2	3	2	(inpatient)	0	0	10
0	0	3	2	3	2	0	3	0	19
0	25	2	2	2	2	(inpatient)	9	18	
0	50	4	1	4	2	(inpatient)	0	20	
0	37.5	2	1	3	2	(inpatient)	6	28	
70	70	1	1	2	2	(inpatient)	22	26	
0	8	3	2	4	3	2	12	2	23
0	0	4	3	4	3	0	1	3	20
0	0	3	2	3	3	0	2	33	52
0	0	4	3	4	3	0	0	4	15
0	16	1	1	2	2	7	20	6	15
0	0	4	2	4	3	0	10	8	25
0	0	4	3	4	4	0	0	0	5
0	160	3	2	3	2	(inpatient)	28	35	
112	176	1	1	2	2	4	11	26	39
0	0	4	3	4	3	0	1	0	4
0	0	3	2	3	3	0	0	6	18
0	0	4	3	4	3	0	0	0	6
0	0	3	2	3	3	0	1	10	25
0	0	4	2	4	3	0	2	0	15
0	0	4	3	4	4	0	0	4	7
0	0	4	3	4	4	0	0	0	6
0	0	4	3	4	4	0	0	0	4
0	0	3	3	3	2	0	0	4	16
0	0	3	2	3	2	0	1	1	9

TABLE 4

Results of 33 Children with Asthma Treated with INTAL in Double-Blind Cross-Over Trial.

	Excellent	Good	Poor	Total
Severe	1	1	4	6
Moderate	2	12	3	17
Mild	9	0	1	10
Total	12	13	8	33
%	36.4	39.3	24.3	

Results of Double Blind Study

Of the 34 children admitted to the trial, one boy was withdrawn, (case No. 9—Table 3) because of moderately severe perioral dermatitis which developed in the first week on treatment. Clinical assessment of response to treatment during each period of the trial was made before breaking the code of the treatment.

Assessment was based on analysis of the data shown in Table 3. Particular attention was paid to the results obtained in the last two weeks of each 4-week period, to obviate any carry-over effect on crossover from active drug to placebo. The spirometric results were not known at the time of this assessment.

Analysis of Changes in Symptoms During Double Blind Trial

Asthma attacks. The results are summarised in Table 4. An excellent response was obtained in 12 patients (36.4 per cent) who were free from wheezing on active drug, but in whom 9 had mild, 2 had moderate, and 1 had severe symptoms during the placebo period.

A good response to active drug was obtained in 13 patients (39.3 per cent) in whom 12 had moderate, and 1 had severe symptoms during the placebo period.

A poor response was obtained in the remaining 8 patients

TABLE 5
Statistical Analysis of Results Shown in Table 3.

Index	Number of patients	Scores*		Probability† (one tailed)
		Placebo	Intal	
Prednisone dosage	9§	65.3 ± 61.3	22.4 ± 40.8	< 0.005
Intensity of asthma	33	2.1 ± 0.7	3.0 ± 1.0	< 0.005
Intensity of cough	33	2.5 ± 0.7	3.2 ± 0.8	< 0.005
Time off school	17**	6.1 ± 6.7	2.0 ± 3.7	< 0.005
Bronchodilator dosage	33	17.5 ± 10.7	7.1 ± 9.2	< 0.005

* Values are mean ± S.D.

† Based on Wilcoxon Matched-Pairs Signed Rank Test.

§ Only those patients who received prednisone during one or both treatment periods were included in the statistical analysis.

** Includes only those patients who were absent from school during one or both periods and who record the time off school as scores.

(24.3 per cent) in whom 1 had mild, 3 had moderate, and 4 had severe symptoms during the placebo period.

In sum, 25 patients (75.7 per cent) were regarded as responding in favour of the drug.

Cough. Assessment of response was graded as shown in Fig. 1. The results are shown in Table 3. Excluding 4 patients who were free from cough in both periods, of the 29 patients, 10 (34.5 per cent) had an excellent response, 7 (24.1 per cent) had a good response, and 12 (41.4 per cent) had a poor response.

In sum, 17 patients (58.6 per cent) were regarded as showing in favour of active drug.

Bronchodilator usage. Fourteen of the 33 children made regular use of oral bronchodilators. As shown in Table 3, during the period on active drug, 11 children discontinued use of bronchodilators, 15 children made less use (25 per cent-50 per cent of requirements during the placebo period), and 7 children made about equal use during either period.

In total, 26 out of the 33 cases were regarded as responding in favour of the drug.

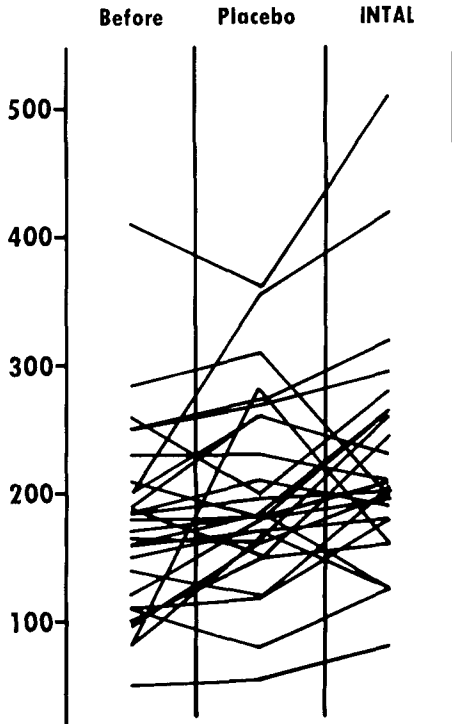


Fig. 2.
Variation of PFM.

School absence. The number of days off school due to asthma is shown in Table 3. During the placebo period 17 children were absent from school for a total period of 103 days. On active drug, 7 children were off school for a total of 34 days.

Steroid requirements. Nine of the 33 children were receiving corticosteroids during the period of the double-blind study. The total requirements are shown in Table 3. On active drug, 6 patients discontinued steroids, 2 patients were able to reduce their dosage, and 1 patient remained on the same dose.

Statistical analysis of results on these items was shown in Table 5.

TABLE 6

Evaluation of Reaginic Antibody Levels to House Dust Extract in Sera Kept for 3 to 6 Months at Various Temperatures Using Passive Transfer Procedures.

Patients	Temp.	Dilution of serum						
		1:5	1:10	1:20	1:40	1:80	1:160	1:320
K. M.	-70° C	+++	+++	++	++	+	+	—
	-20° C	+++	+++	++	+	+	—	—
	-4° C	+++	++	+	+	+	—	—
I. S.	-70° C	++	+	+	+	—	—	—
	-20° C	++	+	+	+	—	—	—
	-4° C	+	+	+	+	—	—	—
H. E.	-70° C	++	++	+	+	—	—	—
	-20° C	++	++	+	+	—	—	—
	-4° C	++	+	+	—	—	—	—

House dust extract P. N. = 0.18 $\mu\text{g/ml}$. Vanselow's criteria used to intradermal tests were adopted.

Spirometry. Overall no significant difference was found between active and placebo periods when comparing weekly PFM readings taken throughout the trial. Fig. 2 gives an indication of the scatter of results obtained. It is perhaps not altogether surprising that since the FEV₁% were almost within normal limits for all patients admitted to the trial and that FVC and FEV₁ measurements were taken at intervals of 1 month that no significant change in spirometry was seen.

Further studies. The effect of long-term treatment with Intal was investigated in 10 patients in open trial (Table 8). These patients were treated for at least 10 weeks. All patients had been admitted to hospital due to severe asthma and had been treated with corticosteroids, either continuously or intermittently, for at least 1 year.

Results. In 3 of the 10 patients, steroids were withdrawn after 4 weeks treatment with Intal.

Of the other 7 patients, steroid dosage was markedly reduced in 4 cases, but not in the remaining 3 cases. Changes in the other parameters measured are as shown in Table 8.

Side effects. Three patients (nos. 9, 23 and 28) developed

TABLE 7
*Evaluation of the Influence of INT-AL on the Reaginic Antibody Response to
 House Dust Extract by Passive Transfer Procedure.*

Patients	Dilution of serum													
	Before*							After†						
	1:5	1:10	1:20	1:40	1:80	1:160	1:320	1:640						
A. T.	+	+	+	+	+	+	+	+						
T. N.	+	+	+	+	+	+	+	+						
H. T.	+	+	+	+	+	+	+	+						
S. N.	+	+	+	+	+	+	+	+						
T. H.	+	+	+	+	+	+	+	+						
K. E.	+	+	+	+	+	+	+	+						
H. E.	+	+	+	+	+	+	+	+						
K. M.	+	+	+	+	+	+	+	+						
I. S.	+	+	+	+	+	+	+	+						
M. M.	+	+	+	+	+	+	+	+						

House dust extract: P. N. = 0.18 µg/ml

* Sera were kept at -20° C for 3 to 6 months.

† Sera were kept at -20° C for 10 to 30 days.

Vanselow's criteria used to read intradermal tests were adopted.

perioral contact dermatitis. One patient (no. 23) complained of headache. In all but one case (no. 9), these side effects were transient and mild and did not necessitate withdrawal from the study. All these side effects developed during active period. No similar reactions occurring during placebo period. No abnormal hematologic, renal or hepatic laboratory findings were noted on these 3 patients.

3. Influence of Treatment on Reaginic Antibody Titre

From the viewpoint of management of allergic asthma, it was considered of interest to attempt to assess the influence of Intal on reaginic antibody titre.

Passive transfer tests. Reaginic sera was obtained from 3 asthmatic children with hypersensitivity to house dust. Six ml of serum was taken from each patient and this was divided under sterile conditions into aliquots of 2 ml. Two aliquots were frozen immediately after withdrawal of blood and then stored at a temperature of -70°C and -20°C respectively until thawed for use. The remaining aliquot was stored at -4°C in an ordinary refrigerator until use.

Another set of reaginic sera was obtained from 10 asthmatic children with house dust sensitivity who were selected at random from the children who took part in the double-blind study. These sera were frozen immediately on withdrawal and stored at -20°C until thawed for use.

None of the sera was preserved chemically. All sera were passed through a sterilising filter before tests. Twelve healthy young student nurses acted as volunteers. The upper arms were used to provide a skin surface for sensitizing sites, each of which was prepared by injecting intradermally 0.10 ml of serum in various dilutions. Twenty-four hours later, 0.02 ml of house dust extract was injected intradermally into the previously sensitised sites and into non-sensitised sites.

Results. As shown in Table 6, no significant reduction of reaginic antibody levels of the sera was detected under the different storage temperatures chosen over a period of 3 to 6

No.	Name	Sex	Age (yrs.)	Height (cm)	Weight (kg)	Duration of asthma (yrs.)	Fam- hist- of aller-
1	S. M.	♀	12	138.0	33.0	5	-
2	Y. I.	♀	14	149.0	41.0	12	+
3	T. M.	♂	15	152.4	40.0	11	+
4	T. S.	♂	6	110.0	17.0	5	+
5	T. T.	♂	13	134.4	26.0	12	+
6	H. N.	♂	6	102.0	15.0	3	-
7	S. I.	♂	9	125.5	22.0	7	+
8	E. H.	♂	13	142.4	27.5	10	-
9	M. K.	♂	14	146.5	29.0	11	-
10	H. K.	♂	10	129.0	35.0	9	+

months. Therefore, sera was stored thereafter at -20°C . Our experience confirms that of *Perlman & Layton* (1967) who reported that freezing of reaginic sera and storage at -20°C had little effect on the sera.

Although the passive transfer test is a relatively crude system for measurement of reaginic activity, no reduction of reaginic antibody level was observed following treatment with Intal over a period of 4 weeks (Table 7). The immediate effects of Intal inhalation on the results of intradermal skin tests with specific allergen in asthmatic children is being investigated.

CONCLUSION

In 13 asthmatic children sensitive to house dust by provocation tests Intal showed a significant protective effect against reduction of FEV₁ and/or development of wheezing, as compared with placebo medication.

In our double-blind study of the effect of disodium cromoglycate (Intal), 25 (75.7 per cent) of 33 children with

Severe Asthmatics in Open Trial.

No. of times of hospital admissions and its total days required for control of asthma attacks during past years	Steroid administration after Intal (Prednisone mg)		Intensity of asthma	Intensity of cough	Absence from school because of asthma (days/month)
	First 4 weeks	Following 6 weeks			
5 (15)	60	0	1 → 3	2 → 3	10 → 3
5 (35)	72	65	1 → 2	2 → 2	15 → 10
2 (6)	32	32	1 → 2	2 → 3	15 → 13
3 (21)	40	30	1 → 1	2 → 2	inpatient
4 (20)	45	6	1 → 2	2 → 3	20 → 10
3 (15)	70	0	2 → 4	2 → 4	(Kindergarden)
5 (30)	32.5	10	2 → 3	2 → 2	inpatient
20 (86)	105	35	1 → 2	2 → 2	inpatient
5 (35)	127.5	32.5	1 → 2	2 → 2	inpatient
2 (18)	35	0	1 → 4	2 → 3	inpatient

asthma, improved while on treatment with active drug. Twenty-three of the children had moderate to severe asthma. In this group improvement was found in 16 (69.5 per cent) cases, hence the drug gave better results in children with mild to moderate asthma.

Of 9 children treated with corticosteroids, steroids were discontinued in 6 cases, and reduced in 2 cases.

In a subsequent open trial in 10 steroid-treated patients with severe asthma, steroids were discontinued in 3 cases and reduced in 4 cases, following treatment with Intal over a period of 10 weeks.

REFERENCES

- Altounyan, R. E. C.*: Acta Allergol. 22, 487, 1967.
Cox, J. S. G.: Nature, Lond. 216, 1328, 1967.
Howell, J. B. L. & Altounyan, R. E. C.: Lancet, 2, 539, 1967.
Pepys, J., Hargreave, F. E., Chan Moira & McCarthy, D. S.: Lancet, 2, 134, 1968.
Perlman, F. & Layton, L. L.: J. Allergy, 39, 205, 1967.
Smith, J. M. & Dacey, G. E.: Brit. med. J. 2, 340, 1968.