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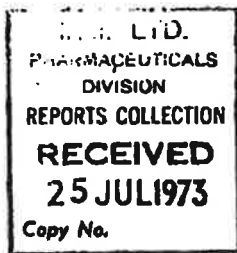
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IMPERIAL CHEMICAL INDUSTRIES LIMITED

PHARMACEUTICALS DIVISION

Title: A Summary of Clinical Results of the Phosphodiesterase  
Inhibitor ICI 63,197 in a Variety of Disease States.

Author: P.F.C. Bayliss

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A SUMMARY OF CLINICAL RESULTS OF THE PHOSPHODIESTERASE  
INHIBITOR ICI 63,197 IN A VARIETY OF DISEASE STATES

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I N D E X

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INTRODUCTION

ICI 63,197 was initially selected to go to clinical trial upon the basis of its anti-bronchoconstrictor effect in animals. Further work revealed that it had a variety of effects in animals suggestive of a possible central nervous system action. Clinical trials were begun in a variety of disease states in addition to studies in normal volunteers. At an early stage it became obvious that the agent had a variety of unpleasant side effects (nausea, vomiting, dizziness, flushing) at low doses (1 - 4 mg.) which made clinical trials difficult to conduct. At a later stage the agent appeared to induce angina pectoris in two patients with no previous history of the complaint. Because of this, and the fact that no beneficial effect had been seen in pilot studies, it was decided that no further work should be done with the agent and that existing trials with the agent should be wound up.

This report summarises the results seen in various areas of medicine. The appendix contains a brief description of each trial carried out, together with what results we possess. It will be appreciated that because of the severe side effects, lack of beneficial effect and difficulty in predicting a target disease state in which ICI 63,197 might be effective it was only possible to study small numbers of patients, most trials being stopped or abandoned rather than reaching completion.

SUMMARY OF RESULTS

1. Respiratory system

No evidence of protection against histamine induced bronchospasm (aerosol or i/v histamine) could be shown. No potentiation of the bronchodilator effects of isoprenaline or salbutamol were shown.

## 2. Cardiovascular system

No consistent effect was seen upon the blood pressure of either normotensive or hypertensive subjects. No consistent effect on pulse rate was seen. No evidence of potentiation of the effects of isoprenaline on heart rate were shown. Angina pectoris seems to have been induced in 2 subjects.

## 3. Psychiatric disorders

No beneficial effect was seen in patients with anxiety, depression or schizophrenia. In depression there was a suggestion that there was a worsening of the depressed mood.

## 4. The endocrine system

ICI 63,197 did not produce any effect in thyroid or adreno-cortical function. In one female subject there was a surge in LH levels. No consistent effect was produced upon a standard intravenous glucose tolerance test. There was a suggestion that ICI 63,197 suppressed the rise in insulin levels following an oral glucose load.

## 5. Obesity

No effect on body weight was shown.

## 6. Pharmacokinetics

The half-life of ICI 63,197 was between 1½ and 3½ hours.

## 7. Side effects

Nausea, vomiting and dizziness were commonly seen with ICI 63,197 at 1 mg. unit doses and above. Angina pectoris appeared on chronic dosing of 2 mg. TDS in 2 patients after 4 and 6 weeks respectively. Capillary fragility with a positive Hess's test was seen in one subject.

A P P E N D I X

Summaries of all clinical trials



CLINICAL PHARMACOLOGICAL STUDY OF ICI 63,197 IN NORMAL VOLUNTEERS  
(PROFESSOR J. CROOKS, DUNDEE)

PROTOCOL

Fit, healthy University students were selected for the study. Informed consent was obtained from each volunteer. Subjects were not on any other medication at the time of the test.

Each subject took on one occasion a dose of ICI 63,197 of between 0.25 and 8 mg., when the following parameters were measured:-

- a) Blood level of ICI 63,197 at 1, 2, 3, 4, 5, 6, and 8 hours after the dose.
- b) Pulse rate and blood pressure at -10 minutes, 0 and 1, 2, 3, 4, 5, 6, and 8 hours and 3 days after the dose.
- c) Plasma L.H., P.B.I. and cortisol at -10 minutes and 1 hour after a dose.
- d) A blood sample was taken at -10 minutes and 4 hours and 3 days after the dose for Hb, WBC, diff. ESR, alkaline phosphatase, bilirubin, SGOT, 5 NT, urea, sodium, potassium chloride, albumin and globulin.
- e) A urine sample was tested at -10 minutes and 4 hours after the dose for protein (albustix) and sugar (clinitix).
- f) Two 24 hour urine collections, one immediately before and one immediately after dosing.

A note was made of any adverse effects encountered.

RESULTS

Details of subjects studied

No.	Initials	Age (yrs)	Sex	Weight (kg)	Dose ICI 63,197 (mg)
1	ML	23	F	50.5	0.25
2	IL	22	M	77.5	0.5
3	HMcD	21	M	65.5	1
4	PL	22	M	74.0	1
5	MM	20	F	56.5	2
6	IMcL	24	F	56.0	2
7	N	22	F	55.0	2
8	PR	21	M	79.0	3
9	C	23	M	72.0	3
10	APC	21	M	82.5	4
11	CB	23	M	80.0	4
12	CC	21	M	80.0	8

Blood levels of ICI 63,197

These are shown below (µg/ml.):-

No.	Dose of ICI 63,197 (mg)	Time (hrs.)							
		1	2	3	4	5	6	7	8
1	0.25	0.016	0.006	0.004	0.005				ND
2	0.5	0.008	0.017	0.005	0.005				ND
3	1.0	0.005	0.019	0.004	0.006		0.005		0.004
4	1.0	0.017	0.016	0.009	0.006		0.008		
5	2.0	0.018	0.034	0.024	0.018		0.007		
6	2.0	0.034	0.065	0.044	0.039		0.015		0.006
7	2.0	0.062	0.068		0.056	0.044	0.037	0.031	0.025
8	3.0	0.044	0.031			0.006		0	0
9	3.0	0.050	0.056		0.044	0.031		0.018	0.025
10	4.0	0.081	0.041	0.034	0.060		0.01		0.014
11	4.0	0.045	0.056	0.044	0.033		0.016		0.009
12	8.0	0.047	0.085	0.068	0.041		0.029		0.042

ND = not detected, i.e. < 0.004 µg/ml.

The half life varies from 1½ - 3½ hours in this series.

Effect on pulse rate and blood pressurePulse rate (beats/min.)

No.	Dose (mg.)	Time (hrs.)								
		-10 mins	0	1	2	3	4	6	8	3 days
1	0.25	95	80	80	80	80	80	80	80	80
2	0.5	90	90	88	68	80	80	80	80	80
3	1.0	75	75	90	72	80	80	80	80	72
4	1.0	92	84	80	80	84	80	80	80	80
5	2.0	90	96	98	96	96	96	94	96	90
6	2.0	92	84	82	76	80	80	82	80	80
7	2.0	90	88	84	88	84	80	80	88	84
8	3.0	88	72	56	56	-	64	72	72	72
9	3.0	80	76	68	68	-	84	76	80	72
10	4.0	76	78	76	78	78	78	60	60	66
11	4.0	88	84	74	66	68	66	66	60	66
12	8.0	72	86	66	68	66	68	60	64	66

Blood pressure (mmHg.)

No.	Dose (mg.)	Time (hrs.)								
		-10 mins.	0	1	2	3	4	6	8	3 days
1	0.25	$\frac{120}{70}$	$\frac{120}{70}$	$\frac{110}{70}$	$\frac{110}{60}$	$\frac{100}{60}$	$\frac{100}{60}$	$\frac{110}{60}$	$\frac{110}{60}$	$\frac{100}{60}$
2	0.5	$\frac{130}{70}$	$\frac{130}{70}$	$\frac{130}{70}$	$\frac{110}{70}$	$\frac{110}{60}$	$\frac{110}{60}$	$\frac{100}{60}$	$\frac{90}{60}$	$\frac{110}{70}$
3	1.0	$\frac{110}{70}$	$\frac{110}{70}$	$\frac{110}{70}$	$\frac{100}{70}$	$\frac{100}{60}$	$\frac{100}{60}$	$\frac{100}{60}$	$\frac{100}{60}$	$\frac{110}{75}$
4	1.0	$\frac{110}{70}$	-	$\frac{120}{70}$	$\frac{100}{70}$	$\frac{100}{60}$	$\frac{110}{60}$	$\frac{110}{60}$	$\frac{120}{70}$	$\frac{110}{60}$
5	2.0	$\frac{110}{70}$	$\frac{100}{60}$	$\frac{100}{60}$	$\frac{110}{60}$	$\frac{90}{60}$	$\frac{100}{60}$	$\frac{100}{60}$	$\frac{100}{60}$	$\frac{110}{70}$
6	2.0	$\frac{110}{60}$	-	$\frac{110}{60}$	$\frac{110}{60}$	$\frac{100}{60}$	$\frac{110}{60}$	$\frac{110}{70}$	$\frac{110}{70}$	$\frac{110}{65}$
7	2.0	$\frac{140}{80}$	$\frac{130}{75}$	$\frac{105}{75}$	$\frac{110}{80}$	$\frac{110}{70}$	$\frac{120}{80}$	$\frac{120}{80}$	$\frac{120}{80}$	$\frac{140}{80}$
8	3.0	$\frac{100}{70}$	$\frac{120}{70}$	$\frac{105}{70}$	$\frac{100}{70}$	$\frac{100}{70}$	$\frac{105}{70}$	$\frac{115}{75}$	$\frac{100}{60}$	$\frac{110}{70}$
9	3.0	$\frac{140}{80}$	$\frac{120}{70}$	$\frac{100}{70}$	$\frac{110}{80}$	$\frac{115}{80}$	$\frac{110}{70}$	$\frac{120}{70}$	$\frac{130}{80}$	$\frac{140}{80}$
10	4.0	$\frac{110}{60}$	$\frac{100}{60}$	$\frac{100}{60}$	$\frac{90}{60}$	$\frac{80}{50}$	$\frac{100}{60}$	$\frac{100}{80}$	$\frac{100}{60}$	$\frac{110}{60}$
11	4.0	$\frac{140}{70}$	-	$\frac{110}{70}$	$\frac{110}{70}$	$\frac{100}{50}$	$\frac{115}{80}$	$\frac{170}{70}$	$\frac{120}{70}$	$\frac{130}{70}$
12	8.0	$\frac{150}{60}$	$\frac{150}{60}$	$\frac{100}{60}$	$\frac{120}{80}$	$\frac{120}{80}$	$\frac{120}{80}$	$\frac{120}{80}$	$\frac{130}{80}$	$\frac{150}{80}$

Effect on plasma, L.H., protein bound iodine and cortisolL.H. levels (m.IU/ml.)

No.	Dose (mg.)	Sex	Time (mins.)						
			-10	10	15	30	60	120	150
1	0.25	F	9.0				41.0	8.0	
2	0.5	M	11.0				8.1	5.0	
3	1.0	M	8.3				5.2	8.0	
4	1.0	M	13.0					4.7	
7	2.0	F		47.0		20.0	17.0		12.5
8	3.0	M		16.5	10.0	18.0	23.0	11.5	
9	3.0	M		16.0	10.0		33.0		17.5

Protein bound iodineCortisol level

No.	Dose (mg.)	Time (mins.)	
		-10	60
1	0.25	7.4	6.9
2	0.5	5.9	6.0
3	1.0	7.4	7.0
4	1.0	4.9	5.2
5	2.0	9.4	9.3
6	2.0	5.1	5.2
7	2.0	4.2	3.7
8	3.0	4.0	5.0
9	3.0	6.2	5.8
10	4.0	5.4	5.7
11	4.0	5.5	5.4
12	8.0	5.4	5.4

No.	Dose (mg.)	Time (mins.)	
		-10	60
1	0.25	17.1	12.0
2	0.5	23.8	10.9
3	1.0	16.0	17.6
4	1.0	20.2	11.2
5	2.0	26.3	29.8
6	2.0	18.9	11.7
7	2.0	22.9	26.9
8	3.0	28.0	22.7
9	3.0	13.4	12.9
10	4.0	23.8	34.3
11	4.0	17.0	17.0
12	8.0	26.8	25.8

Effect on 24 hour cyclic Amp levels ( $\mu$  moles/24 hours)

No.	Dose (mg.)	24 hrs. before dose	24 hrs. after dose
1	0.25	3.71	4.33
2	0.5	2.69	3.95
3	1.0	4.35	4.9
4	1.0	3.13	2.71
5	2.0	2.26	-
6	2.0	2.37	-
7	2.0	3.18	1.68
8	3.0	5.36	3.44
9	3.0	4.96	2.88
10	4.0	3.79	5.25
11	4.0	5.15	1.19
12	8.0	1.4	4.21

Blood tests

Hb, WBC, diff.ESR, alkaline phosphatase, bilirubin, SGOT, 5 NT, urea, sodium, potassium, chloride, albumin and globulin levels at 4 hours and 3 days did not differ significantly from the pre-dose figures.

Urine tests

Neither protein nor sugar were detected in the urine at 4 hours or 3 days.

Possible side effects

These are shown below:-

No.	Dose (mg.)	Possible side effects
1	0.25	Nil.
2	0.5	Mild nausea and light headedness.
3	1.0	Nausea at 1 hour.
4	1.0	Severe dizziness at 15 minutes. Felt as if he had taken "pep pills" from 1 - 4 hours.
5	2.0	Mild nausea.
6	2.0	Nil.
7	2.0	Dizziness and sweating at 30 minutes followed by some nausea.
8	3.0	Dizziness and nausea marked $\frac{1}{2}$ - 2 hours.
9	3.0	At 30 minutes dizzy, pale, sweating. Nausea marked.
10	4.0	Nausea and flushing at 15 minutes. Vomited at 30 minutes. Light headedness for 2 - 3 hours.
11	4.0	Dizziness, flushing of face, sweating from $\frac{1}{2}$ - 2 hours.
12	8.0	At 30 minutes sweaty, flushed and light headed. Vomited at 2 hours.

CONCLUSIONS

No clearly defined results emerged from this study, although certain suggestive ones were seen. The following points may be made:-

- (1) The half life of ICI 63,197 in the human, following a single oral dose is between  $1\frac{1}{2}$  and  $3\frac{1}{2}$  hours.
- (2) No clear effect was seen on pulse rate, although a slight fall was seen in some subjects. Similarly, no clear effect was seen on blood pressure, although in some subjects a fall was seen in the 2 - 4 hour period.



- (3) One female subject (on the lowest dose) showed a surge of L.H. at 1 hour that was back to normal by 2 hours. No effect was seen on P.B.I. No regular effect was seen on cortisol levels although in some subjects there was a fall at 1 hour.
- (4) The 24 hour urinary excretion of cyclic AMP rose in subjects after ICI 63,197, although in others it fell.
- (5) The agent was poorly tolerated at doses above 1 - 2 mg. Nausea, vomiting, dizziness, sweating and flushing were complained of.

EFFECT OF ICI 63,197 UPON THE ENDOCRINE SYSTEM IN NORMAL SUBJECTS  
(DR. D. DAVIES, MANCHESTER)

PROTOCOL

Fit, healthy University students who are on no drugs (including the contraceptive "pill") were chosen for this study. They gave informed consent to participation.

Subjects were studied in the fasting state.. Blood samples were taken immediately before and at  $\frac{1}{2}$ , 1,  $1\frac{1}{2}$ , 2, 3, 4, 5, and 6 hours after a single oral dose of 2 mg. ICI 63,197. Blood samples were assayed for:-

- a) Growth hormone
- b) Insulin
- c) Cortisol
- d) Thyroxine iodine
- e) Glucose
- f) L.H. and F.S.H.
- g) Blood level of ICI 63,197 (at 0, 1 and 2 hours)

A note was made of any adverse reactions complained of. A cup of coffee was taken by the volunteers between  $\frac{1}{2}$  and 1 hours, a light meal between  $1\frac{1}{2}$  and 2 hours and a cup of tea between 4 and 5 hours.

RESULTSDetails of subjects studied

No.	Initials	Age (yrs)	Sex	Menstrual cycle	Day of cycle
1	PWC	19	M		
2	ID	23	M		
3	JC	21	F	6/28-35	9
4	AD	18	M		
5	JA	21	F	1/28	7
6	AS	21	F	5/28-30	21
7	PC-Y	21	M		
8	MPY	21	M		

Blood levels of ICI 63,197 ( $\mu\text{g/ml}$ )

No.	Time (hrs.)					
	$\frac{1}{2}$	1	1 $\frac{1}{2}$	2	4	5
1	ND	ND	ND			
2	ND	ND	ND		ND	ND
3	0.04	0.07		0.05	0.03	
4	0.03	0.03		ND	0.05	
5	0.03	0.03		0.025	0.035	
6	ND	0.02		0.03	ND	
7	ND	0.02		0.03	0.03	
8	0.02	0.03		0.02	ND	

ND = not detected, i.e.  $0.004 \mu\text{g/ml}$ .

Effect on Human Growth hormone

No.	Time (hrs.)								
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	5	6
1	33	27	6.9	3.6					
2	1.4	3.6	15	16.5	2.1	1.5			
3	5.7	7.6	5.1	2.6	2.0	1.5	6.4	2.7	1.7
4	1.3	3.7	2.9	1.8	1.3	1.6	1.6	2.4	1.4
5	3.9	2.0	1.6	1.3	1.4	1.3	1.8	1.7	2.0
6	8.8	7.8	2.5	1.5	1.3	1.1	1.3	1.5	1.1
7	2.7	9.4	6.0	10.5	3.7	2.0	2.7	6.0	2.2
8	1.6	2.6	6.0	4.0	1.7	1.4	1.4	1.4	1.3

Effect on Insulin levels

No.	Time (hrs.)								
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	5	6
1	13	13	18	13					
2	10	7	10	10	7	40			
3	60	30	26	74	24	170	25	42	20
4	18	30	19	14	26	50	36	39	32
5	16	17	21	20	75	75	48	70	42
6	22	22	23	18	115	88	52	58	58
7	36	24	21	30	37	38	27	20	24
8	17	18	18	24	18	64	43	24	31

Effect on cortisol level

No.	Time (hrs.)								
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	5	6
1	18.5	15	12						
2	11.5	32.5	26.5		12.5				
3	15.5	14	11		9.5				
4	16.5	12	15		13.5				
5	13.5	13.5	21		15.5		7.0		
6	16.5	13.5	11.5		12.0		16.0		
7	18.0	12.5	24.0		24.0		18.5		
8	16	13.5	12.0		18.0		12.0		

Effect on Thyroxine iodine levels

No.	Time (hrs.)								
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	5	6
1	4.3		3.8						
2	4.5		4.6		4.5				
3									
4									
5	3.7		4.0		3.9		3.9		
6	3.6		3.6		3.4		3.3		
7	4.5		5.5		5.0		5.2		
8	5.1		5.5		5.4		5.6		

Effect on blood glucose

No.	Time (hrs.)								
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	5	6
1	60	70	60	75					
2	70	60	55	55	60	65			
3	60	65	70	75	50	95	60	70	70
4	65	60	70	60	70	85	75	75	70
5	70	65	65	70	85	75	80	85	80
6	80	60	60	55	85	85	80	70	55
7	70	70	55	60	80	80	65	60	75
8	70	60	55	65	65	60	65	65	90

Effect on L.H. (milli.I.U./ml.)

No.	Time (hrs.)								
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	5	6
1	6	5	5	5					
2	3	6	4	3	5				
3	5	5	5	5	6	5	6	4	
4	7	6	7	7	7		7	9	7
5	3	5	5	4	6	6	5	9	6
6	2	2	1	5	3	2	3	2	7
7	ND	1	5	4	3	2	2	1	2
8	1	1	1	3	3	1	1	6	2

ND = not detected i.e. less than 1 m. I.U./ml.

Effect on F.S.H. (milli.I.U./ml.).

No.	Time (hrs.)								
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	5	6
1	1	1	1	ND					
2	ND	ND	ND	ND	ND			ND	
3	6	5	6	5	5	5	5	5	
4	1	1	1	1	ND		ND	ND	ND
5	4	4	3	2	3	3	2	3	3
6	5	7	5	7	7	6	5	5	5
7	4	4	7	4	5	4	4	4	5
8	6	4	6	6	6	0	6	5	8

ND = not detected i.e. less than 1 m.I.U./ml.

Possible side effects

These are shown below:-

No.	Possible side effects
1	Nausea and flushing 10 mins. after tablet. Gone by $1\frac{1}{2}$ hours but fainted at 2 hours.
2	Flushing and slight nausea noted at 10 minutes.
3	Flushing and slight nausea noted at $1\frac{1}{2}$ - $3\frac{1}{2}$ hours.
4	Nausea present $\frac{1}{2}$ - 3 hours.
5	Nausea 30 minutes. Vomited at 45 minutes.
6	Marked nausea 1 - $1\frac{1}{2}$ hours.
7	Flushed, sweating and restless at 1 hour. Nausea throughout.
8	Sweating at 1 hour.

**CONCLUSIONS**

- (1) ICI 63,197 did not have any significant effect upon any parameters measured, in the setting of the study.
- (2) Every subject experienced some type of adverse reaction, especially nausea and flushing.



EFFECT OF ICI 63,197 UPON ORAL & INTRAVENOUS GLUCOSE TOLERANCE TESTSDR. D. DAVIES, MANCHESTER.PROTOCOL

Two fit, healthy young volunteers were chosen. They gave informed consent to taking part in the study. They underwent a glucose tolerance test (GTT) on 4 occasions each. Twice the GTT was an oral one, once with a placebo tablet and once with a single dose of 2 mg. ICI 63,197, and on the other two occasions the GTT was an intravenous one, again both with placebo and 2 mg. ICI 63,197. Tests were carried out at 7 day intervals.

Blood samples were taken 60 mins., 30 mins. and immediately before the glucose load was given and for the intravenous test 2, 5, 10, 20, 30, 40 and 60 minutes after, and for the oral test 30, 60, 90, 120 and 150 minutes after.

Blood samples were assayed for:-

- (a) Glucose
- (b) Insulin
- (c) Free fatty acid levels.

Possible side effects were noted.

RESULTS

Two male subjects were studied.

Oral GTTEffect of Glucose levels

No.	Regime	Time (mins.)							
		-60	-30	0	30	60	90	120	150
1	Placebo	80	75	70	100	130	80	45	45
1	Active	75	80	65	110	95	75	70	75
2	Placebo	35	35	65	100	70	60	40	45
2	Active	60	55	55	65	85	70	60	60

Effect on Insulin levels

No.	Regime	Time (mins.)							
		-60	-30	0	30	60	90	120	150
1	Placebo	16	16	13	76	125	35	18	14
1	Active	14	18	16	56	44	16	14	16
2	Placebo	18.5	15.5	14	84	92	54	52	18
2	Active	12	12	14.5	12	47	52	32	22.5

Effect on FFA levels (mEq/l)

No.	Regime	Time (mins.)							
		-60	-30	0	30	60	90	120	150
1	Placebo	2.24	2.24	2.12	2.67	1.00	1.05	1.24	1.90
1	Active	1.17	1.03	1.08	1.01	0.61	1.08	2.34	2.09
2	Placebo	0.80	0.69	0.93	1.42	0.74	0.77	0.83	1.09
2	Active	1.14	1.59	1.64	2.27	3.18	0.89	0.73	0.93

Intravenous GTTEffect on Glucose levels

No.	Regime	Time (mins.)									
		-60	-30	0	2	5	10	20	30	40	60
1	Placebo	55	55	65	165	165	155	140	110	95	70
1	Active	75	75	70	215	175	170	145	115	100	75
2	Placebo	65	60	60	130	140	145	120	90	75	60
2	Active	65	70	70	315	250	230	200	175	155	115

Effect on Insulin levels

No.	Regime	Time (mins.)									
		-60	-30	0	2	5	10	20	30	40	60
1	Placebo	19	18	20	53	45	40	34	34.5	34.5	27
1	Active	17	20	17	52	62	56	62	52	52	25.5
2	Placebo	13	9.4	9.4	31	70	44	33	33	31	20
2	Active	7.8	9.4	9.4	7.8	9.4	14	33	41	51	44

Effect on FFA levels (mEq/l)

No.	Regime	Time (mins.)									
		-60	-30	0	2	5	10	20	30	40	60
1	Placebo	0.99	1.28	1.39	1.31	1.28	1.31	0.83	0.54	0.51	0.48
1	Active	1.84	1.82	1.82	2.0	1.86	1.91	1.68	1.05	1.09	0.9
2	Placebo	0.81	0.88	0.93	1.41	1.29	1.31	1.29	1.52	1.14	1.29
2	Active	1.55	1.20	1.22	1.73	1.83	1.97	2.25	1.69	1.50	0.78

**Possible side effects**

No side effects were seen.

**CONCLUSIONS**

Although only 2 subjects were used, ICI 63,197 seemed to suppress the insulin rise following the glucose load in both subjects in the oral test.

EFFECT OF ICI 63,197 IN HISTAMINE INDUCED BRONCHOSPASM IN ASTHMATIC PATIENTS  
(DR. J.W. KERR, GLASGOW)

PROTOCOL

Allergic asthmatic patients with reversible airways obstruction were chosen for the study. Pregnant women and patients under 18 or over 45 years were excluded.

Patients were studied on the occasions when they took either ICI 63,197 2 mg. orally, or an identical placebo tablet, in a double blind randomised fashion. 2 hours later, bronchospasm was induced with an intravenous injection of histamine, and the forced expiratory volume in seconds ( $FEV_1$ ) and the vital capacity were measured before and at 5, 10, 15, 20 and 25 minutes thereafter.

A note of possible side effects were made.

RESULTS

Details of patients studied

No.	Initials	Age (yrs)	Sex	Diagnosis
1	AS	60	M	"pollen asthma"
2	DI	22	M	hay fever and asthma
3	ED	22	F	asthma
4	IN	41	M	asthma

Effect on FEV<sub>1</sub> (litres)

No.	Time after i/v histamine (mins.)											
	Placebo						ICI 63,197					
	0	5	10	15	20	25	0	5	10	15	20	25
1	1.90	1.70	1.70	1.75	1.80	1.90	2.0	1.80	1.70	1.80	2.00	2.00
2	4.15	4.45	4.20	4.00	4.65	4.70	4.50	4.50	4.50	4.30	4.40	4.40
3	0.65	0.70	0.65	0.65	0.65	0.65	0.75	0.55	0.50	0.50	0.50	0.65
4	1.80	1.45	1.30	1.30	1.90	1.90	1.65	0.8	0.75	0.8	0.8	0.8

Effect on vital capacity (litres)

No.	Time after i/v histamine (mins.)											
	Placebo						ICI 63,197					
	0	5	10	15	20	25	0	5	10	15	20	25
1	3.70	3.50	3.55	3.70	3.80	3.80	3.60	3.50	3.50	3.50	3.60	3.60
2	5.60	5.40	5.15	5.20	5.65	5.60	5.50	5.30	5.30	5.30	5.35	5.40
3	1.50	1.45	1.50	1.50	1.50	1.50	1.50	1.30	1.16	1.15	1.15	1.25
4	3.40	3.05	2.75	2.60	2.60	2.60	2.10	1.90	1.90	2.05	2.05	2.10

Possible side effects

Two patients complained of nausea following ingestion of ICI 63,197 and one was sick. No side effects were noted during the placebo periods.

CONCLUSIONS

No evidence was obtained from these 4 patients to show that ICI 63,197 gave any protection from the falls in FEV<sub>1</sub> and VC induced by intravenous histamine.

EFFECT OF ICI 63,197 WITH AND WITHOUT SALBUTAMOL UPON FORCED EXPIRATORY  
VOLUME IN ASTHMATICS. (DR. K.N.V. PALMER, ABERDEEN).

PROTOCOL

Asthmatic patients between the ages of 18 and 45, who had reversible airways obstruction, were included in the study. Pregnant women were excluded. The aim of the study was to look for possible potentiation of the effect of salbutamol upon bronchospasm induced by an aerosol of histamine.

Patients were seen on 4 occasions, when one of the following were given:-

- a) 2 mg. salbutamol
- b) 2 mg. ICI 63,197
- c) 2 mg. salbutamol + 2 mg. ICI 63,197
- d) placebo.

Drugs were given in a double blind manner in random sequence. Two hours after taking the tablet a dose of histamine by aerosol was given. This dose had been previously determined as one that would produce a measurable broncho-spasm.

Before and at 1, 5, 15 and 30 minutes after the histamine the forced expiratory volume in 1 second ( $FEV_1$ ), pulse rate and blood pressure were measured.

RESULTS

Only 2 patients were included in the study as in the second severe side effects occurred.

Details of the patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)
1	RR	32	M	71
2	DW	34	M	70

Effect upon FEV<sub>1</sub> (litres)Patient No. 1

Regime	Histamine challenge (time in mins.)				
	0	1	5	15	30
placebo	2.75	1.7	1.75	2.4	2.65
ICI 63,197	2.95	3.25	3.75	3.70	3.90
salbutamol	2.8	4.0	4.05	4.05	4.10
combination	2.55	2.10	2.10	2.65	2.95

Patient No. 2

Regime	Histamine challenge (time in mins.)				
	0	1	5	15	30
placebo	2.45	1.25	1.25	1.30	1.32
ICI 63,197	3.15	2.2	2.25	2.72	3.0

Effect on pulse rate (beats/min.)Patient No. 1

Regime	Histamine challenge (time in mins.)				
	0	1	5	15	30
placebo	88	80	76	72	70
ICI 63,197	64	60	60	66	64
salbutamol	68	72	72	72	72
combination	76	56	58	60	60

Patient No. 2

Regime	Histamine challenge (time in mins.)				
	0	1	5	15	30
placebo	76	93	88	80	72
ICI 63,197	64	76	84	80	76



Effect on blood pressurePatient No. 1

Regime	Histamine challenge (time in mins.)				
	0	1	5	15	30
placebo	115/80	115/80	110/75	105/65	110/65
ICI 63,197	110/55	110/60	110/60	110/60	110/60
salbutamol	110/55	110/60	110/60	110/60	110/60
combination	120/70	120/70	120/70	120/75	120/80

Patient No. 2

Regime	Histamine challenge (time in mins.)				
	0	1	5	15	30
placebo	110/75	125/75	110/70	105/65	100/65
ICI 63,197	110/70	120/80	120/80	110/75	110/70

Possible side effects

Patient No. 1 had no side effects during the study. Patient No. 2 took ICI 63,197 at the first sitting. 20 minutes after ingestion the patient complained of severe nausea, followed by copious vomiting. The patient was markedly agitated and restless and became pale, cold and clammy. These features slowly wore off over the next 2 hours. Because of these symptoms this patient was not given ICI 63,197 on a second occasion and the triallist was unwilling to expose further patients.

CONCLUSIONS

In both patients there was some evidence that the effect of histamine upon  $FEV_1$  was reduced by ICI 63,197. In the one patient taking salbutamol there was clear protection against histamine bronchospasm but when combined with

ICI 63,197 this effect of salbutamol disappeared. The data is insufficient to draw any conclusions.

Severe nausea and vomiting occurred in one patient.

EFFECT OF ICI 63,197 ON THE EFFECTS OF INHALED ISOPRENALINE (DR.H.BEUMER, UTRECHT)PROTOCOL

Patients with mild/moderate emphysema who were known to respond to inhaled isoprenaline by bronchodilatation were chosen for the study. They were tested on two occasions, upon which they took either a single dose of ICI 63,197 or an identical placebo in random order, double blind. Measurements were done on each occasion as follows:-

Time (mins.)

0	ICI 63,197 or placebo tablet given.
60	Pulse rate, nitrogen washout and functional reserve capacity measured.
90	Pulse rate, nitrogen washout and functional reserve capacity measured.
120	As at 90 mins.

RESULTS

12 patients were studied.

Effect on pulse rate

\* = time after isoprenaline inhalation

No.	Placebo			ICI 63,197		
	Control	30 mins.*	60 mins.*	Control	30 mins.*	60 mins.*
1	80	84	84	72	70	72
2	76	84	80	80	84	84
3	84	80	76	84	88	80
4	60	52	60	68	64	60
5	72	72	68	80	72	80
6	68	64	72	86	60	68
7	92	92	88	100	88	80
8	80	84	80	96	96	96
9	84	76	76	84	84	84
10	80	72	76	80	72	72
11	96	100	88	96	88	88
12	120	120	120	124	124	118

Effect on Nitrogen washout

\* = time after isoprenaline inhalation

No.	Placebo			ICI 63,197		
	Control	30 mins.*	60 mins.*	Control	30 mins.*	60 mins.*
1	64.0	64.0	64.0	64.0	64.0	64.0
2	64.0	64.0	64.0	63.9	64.0	64.0
3	64.0	64.0	63.9	64.0	64.0	64.0
4	48.2	47.4	55.1	54.0	64.0	55.2
5	64.0	64.0	64.0	64.0	64.0	64.0
6	64.0	57.6	55.9	64.0	58.9	55.4
7	27.5	26.7	25.7	28.0	29.3	25.3
8	64.0	64.0	64.0	64.0	64.0	64.0
9	64.0	64.0	64.0	64.0	63.9	64.0
10	64.0	64.0	64.0	64.0	64.0	64.0
11	64.0	64.0	64.0	64.0	64.0	64.0
12	64.0	64.0	64.0	64.0	64.0	64.0

Effect on functional reserve capacity

No.	Placebo			ICI 63,197		
	Control	30 mins.	60 mins.	Control	30 mins.	60 mins.
1	6.57	6.61	6.60	5.77	6.22	5.95
2	4.57	5.34	5.30	5.05	4.83	4.27
3	5.22	5.09	5.51	5.78	5.04	5.56
4	4.36	4.40	4.54	5.12	5.27	4.65
5	6.55	6.24	6.60	6.39	6.16	6.20
6	4.70	4.26	4.41	4.82	4.17	4.20
7	2.60	2.48	2.57	2.38	3.30	2.72
8	6.69	5.69	6.43	6.30	6.25	6.48
9	4.99	4.58	4.62	5.17	5.09	5.13
10	5.24	4.57	4.97	4.93	4.66	4.97
11	6.69	6.88	6.81	6.65	6.84	6.71
12	4.16	4.43	4.43	4.19	4.25	4.39

CONCLUSIONS

No effect of ICI 63,197 was demonstrated over and above placebo upon pulse rate, functional reserve capacity and nitrogen washout after the inhalation of isoprenaline. However, it must be noted that no effect of isoprenaline per se was detected. This is probably due to the fact that the first measurement at 30 minutes after inhalation was too late.

EFFECT OF ICI 63,197 IN ENDOGENOUS DEPRESSION (DR. D. ECCLESTON, EDINBURGH)

PROTOCOL

Patients with classical endogenous depression who were not on any other medication were chosen for the study. Patients under the age of 18 or over 60 were excluded. Patients were given 2 mg. ICI 63,197 TDS for 21 days and were to leave the trial at that time if no beneficial effect had been seen.

Depression was rated (Hargreaves scale) daily, as were possible side effects.

RESULTS

4 patients completed 21 days treatment each. The trial was then abandoned, due to side effects and a worsening of depression in all 4 patients, apparently due to ICI 63,197.

Detailed results are not available, but the trialist reported the following:-

- (1) All 4 patients became markedly worse over the 21 days of treatment. This worsening was considered more than would be expected from the natural history of their respective illnesses. They were all given ECT on stopping ICI 63,197.
- (2) In one patient the effect of ECT was considered to be greater than expected from the patient's clinical state.
- (3) All 4 patients complained of nausea in the first 3 - 5 days of the trial, although this wore off with no intervention.

- (4) One patient developed a tendency to bruise with a positive Hess's test. The agent was withdrawn whereupon the capillary fragility disappeared over the next 3 - 4 days.

ICI 63,197 IN SCHIZOPHRENIA (DR. R.V. MAGNUS, BIRMINGHAM)

PROTOCOL

Chronic inpatient schizophrenics were chosen for the study upon the basis that they had sufficient symptomatology to show a significant change. Patients under 18 or over 50 years of age were excluded, as were pregnant women and people with physical illness.

Patients were given 1 placebo tablet TDS for 6 days, followed by 1 mg. ICI 63,197 (1 x 1 mg. tablet) TDS for 7 days, followed by 2 mg. ICI 63,197 (1 x 2 mg. tablet) TDS for 7 days if the agent was tolerated. All tablets were identical.

On entry to the trial, the following were recorded:-

- (a) age, sex, weight
- (b) diagnosis
- (c) rating of schizophrenia
- (d) blood sample for Hb, WBC, diff. ESR, urea, bilirubin, alkaline phosphatase and SGOT.

On days 6, 13 and 20, the following were recorded:-

- (a) rating of schizophrenia
- (b) clinical assessment
- (c) possible side effects
- (d) pulse rate and blood pressure
- (e) blood sample for the tests mentioned above.



RESULTSDetails of patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)	Diagnosis
1	CJT	19	M	140	Schizo-affective disorder
2	MW	19	M	156	High grade sub-normal with chronic schizophrenia
3	FM	49	M	112	Chronic paranoid schizophrenia
4	WJ	54	M	150	Chronic schizophrenia
5	WH	52	M	-	Paranoid schizophrenia
6	SP	28	F	112	Chronic hebephrenic schizophrenia

Effect on clinical state

No patient showed any significant change in their schizophrenic state.

Their rating scores are shown below:-

No.	Day 0	Day 6 <sup>1</sup>	Day 13 <sup>2</sup>	Day 20 <sup>3</sup>
1	15	13	12	12
2	13	13	13	10
3	9	9	9	12
4	16	17	11	11
5	14	14	14	12
6	21	21	20	25

1 = end of 6 day placebo period

2 = end of 7 days at 1 mg. ICI 63,197 TDS

3 = end of 7 days at 2 mg. ICI 63,197 TDS

Possible side effects

These are shown below:-

No.	Possible side effects
1	Nil
2	Slight nausea at 2 mg. TDS
3	Marked nausea at 2 mg. TDS
4	Nil
5	Nil
6	Nil

Effect on pulse and B.P.

These are shown below:-

Pulse (beats/min.)

No.	Day 0	Day 6	Day 13	Day 20
1	80	72	80	72
2	80	72	72	72
3	80	80	72	80
4	80	72	72	72
5	72	72	80	80
6	80	-	100	100

B.P. (mmHg)

No.	Day 0	Day 6	Day 13	Day 20
1	120/70	120/70	130/70	140/75
2	130/75	120/70	120/70	130/80
3	130/90	120/70	120/70	130/70
4	130/80	120/70	130/70	130/80
5	135/70	120/70	140/80	130/70
6	130/70	-	130/70	130/80

Effect on blood tests

No significant effect was seen upon Hb, WBC, diff. ESR, urea, bilirubin, alkaline phosphatase or SGOT.

CONCLUSIONS

- (1) ICI 63,197 had no effect upon the schizophrenic state.
- (2) ICI 63,197 had no significant effect upon pulse rate, blood pressure on the blood tests used.
- (3) 2 out of 6 patients complained of nausea at 2 mg. ICI 63,197 TDS.

ICI 63,197 IN ANXIETY STATES (DR. R.V. MAGNUS, BIRMINGHAM)

PROTOCOL

Inpatients with established anxiety states were selected for the study. Those under 18 or over 50 years of age were excluded, as were pregnant women and people with overt physical illness.

Patients were given 1 placebo tablet TDS for 5 days, followed by 1 mg, ICI 63,197 (1 x 1 mg. tablet) TDS for 7 days, followed by 2 mg. ICI 63,197 (1 x 2 mg. tablet) TDS for 7 days, if the patient could tolerate it. All tablets were identical.

On entry to the trial the following were recorded:-

- (1) age, sex, weight
- (2) diagnosis
- (3) severity of anxiety
- (4) anxiety rating using the Taylor Manifest Anxiety Scale
- (5) blood sample for Hb, WBC, diff.ESR, urea, bilirubin, alkaline phosphatase and SGOT.

At the 5<sup>th</sup>, 12<sup>th</sup> and 19<sup>th</sup> days the following were recorded:-

- (1) Taylor Manifest Anxiety score
- (2) clinical assessment
- (3) pulse rate and blood pressure
- (4) possible side effects
- (5) blood sample for tests above

RESULTSDetails of patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)	Diagnosis	Rating of anxiety
1	VM	18	M	154	Anxiety state	Severe
2	AC	32	F	112	Anxiety state	Moderate
3	MN	24	F	116	Anxiety state	Moderate
4	RT	44	F	120	Anxiety state with obsession	Severe
5	KH	22	M	130	Anxiety state	Moderate

Effect on anxiety

Clinically, patients No. 1 and 5 became somewhat worse on ICI 63,197, patients No. 2 and 3 showed no change while patient No. 4 showed an improvement. The Taylor scores are shown below:-

No.	Day 0	Day 5 <sup>1</sup>	Day 12 <sup>2</sup>	Day 19 <sup>3</sup>
1	31	31	39	39
2	15	22	23	23
3	29	29	29	25
4	36	35	29	16
5	27	22	36	25

1 = end of placebo period

2 = end of 1 mg. TDS for 7 days

3 = end of 2 mg. TDS for 7 days

Possible side effects

These are shown below:-

No.	Possible side effect
1	Vomited x 1 on 2 mg. TDS. Then settled.
2	Nil
3	Nil
4	Nausea on 2 mg. TDS. Maxolon 10 mg. TDS given with good effect
5	Nausea on 2 mg. TDS. Maxolon 10 mg. TDS given with good effect

Effect on pulse and blood pressure

Pulse rate and B.P. throughout the study are shown below:-

Pulse rate (beats/min.)

No.	Day 0	Day 5	Day 12	Day 19
1	80	80	88	80
2	100	80	80	80
3	80	80	72	72
4	88	-	80	72
5	88	72	88	80

B.P. (mmHg)

No.	Day 0	Day 5	Day 12	Day 19
1	140/80	130/70	130/70	130/70
2	130/70	130/70	130/70	130/70
3	120/70	120/70	110/70	110/70
4	140/70	130/70	130/70	120/70
5	130/80	120/70	130/70	130/70

**Blood tests**

No significant changes were seen in the values of Hb, WBC, diff. ESR, bilirubin, alkaline phosphatase, urea, and SGOT during this study.

**CONCLUSIONS**

- (1) ICI 63,197 did not significantly affect anxiety
- (2) ICI 63,197 did not significantly affect pulse rate, blood pressure or the blood tests used.
- (3) ICI 63,197 produced nausea or vomiting in 3 out of 5 patients, all at 2 mg. TDS.

ICI 63,197 IN HYPERTENSION (DR. F.J. ZACHARIAS, FEBINGTON)PROTOCOL

Patients with a sustained diastolic hypertension in the range 100 - 115 mmHg were chosen for the study. They were to be on no other drugs. Patients under 18 or over 60 years of age, and pregnant women were excluded.

Patients took ICI 63,197 2 mg. QDS for 4 weeks in the first instance, and this could be continued as clinically indicated.

On entry to the trial, the following were recorded:-

- (a) age, sex, weight
- (b) diagnosis
- (c) blood pressure (standing and lying)
- (d) blood sample for Hb, WBC, diff.ESR, bilirubin, alkaline phosphatase SGOT and urea.

At weekly intervals through the trial the following were recorded:-

- (a) blood pressure
- (b) body weight
- (c) possible side effects
- (d) the blood tests mentioned above.

RESULTSDetails of patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)	Diagnosis
1	CCS	45	M	85.0	Hypertension
2	RJT	-	M	67.7	Essential hypertension with asthma
3	SN	64	M	77.3	Essential hypertension



Effect on blood pressure

The standing B.P.s (mmHg) during treatment with ICI 63,197 are shown below. There was no significant difference between standing and lying B.P.

No.	Week of treatment												
	0	1	2	3	4	5	6	7	8	9	10	11	12
1	$\frac{180}{110}$	$\frac{150}{100}$	$\frac{145}{95}$	$\frac{165}{100}$	$\frac{145}{100}$	$\frac{150}{95}$							
2	$\frac{210}{115}$	$\frac{180}{110}$	$\frac{175}{110}$	$\frac{195}{115}$	$\frac{180}{115}$	$\frac{180}{120}$	$\frac{165}{105}$	$\frac{220}{115}$					
3	$\frac{125}{115}$	$\frac{180}{115}$	$\frac{180}{105}$	$\frac{165}{110}$	$\frac{170}{110}$	$\frac{175}{110}$	$\frac{165}{105}$	$\frac{150}{105}$	$\frac{170}{110}$	$\frac{165}{105}$	$\frac{170}{110}$	$\frac{175}{110}$	$\frac{180}{115}$

Effect upon body weight

No significant change was seen in body weight during treatment with ICI 63,197.

Possible side effects

These are shown below:-

No.	Possible side effects
1	Nil
2	Severe indigestion, dizziness, flushing. Eventually refused to continue.
3	Nausea, severe heartburn, flushing. Agent finally stopped due to side effects.

Effect on blood tests

No significant change was seen in Hb, WBC, diff. ESR, bilirubin, alkaline phosphatase, SGOT or urea.

CONCLUSIONS

- (1) ICI 63,197 did not significantly affect the B.P. of these hypertensive subjects.
- (2) There was no effect on body weight on the blood tests used.
- (3) 2 of the 3 had severe gastrointestinal side effects with dizziness and flushing.

EFFECT OF ICI 63,197 IN OBESE SUBJECTSDR. D. DAVIES, MANCHESTER.PROTOCOL

Patients in the age range 30 - 55 years with a body weight at least 30% over the ideal for their age, sex, height and build, were selected for the study. The trial was a double blind cross-over study of ICI 63,197 2 mg. TDS against identical placebo tablets given TDS, 6 weeks each. Patients were reviewed at fortnightly intervals when body weight, skin fold thickness, pulse rate and blood pressure were noted. A record of possible side effects was kept. Blood samples were taken at each visit for haemoglobin, white cell count, differential count, ESR, platelet count, bilirubin, alkaline phosphatase, SGOT, SGPT, Albumin, Globulin and urea. Urine was also checked for the possible presence of sugar, protein or blood.

RESULTS

Four patients had entered the study before it was discontinued, due to the appearance of angina pectoris in two patients while on the active preparation.

Details of patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)
1	SMcK	19	M	142.4
2	MT	50	F	166.0
3	AT	38	F	101.8
4	BA	33	F	83.0

Effect on body weight

No.	Baseline	Placebo			Active		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
1	142.4	134.0	134.8	134.2	140.6	138.0	138.0
2	166.0			163.7	161.0	161.0	160.6
3	101.8				103.8	106.2*	
4	83.0				82.0	82.8	83.3*

\* trial stopped due to appearance of angina

Effect on skin fold thickness (cms.)

No.	Baseline	Placebo			Active		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
1	R3.1 L3.3	R2.7 L3.1	R2.7 L3.0		R2.9 L3.1		R2.8 L3.1
2	2.2	2.2		2.0	1.9	2.1	2.1
3	R3.0 L3.1				R3.2 L3.1*		
4	R3.0 L2.8				R3.0 L2.9	R2.7 L2.7	R2.7 L2.7*

\* trial stopped due to appearance of angina  
R = right arm  
L = left arm

Effect on pulse rate (beats/min.)

No.	Baseline	Placebo			Active		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
1	84	72			56	72	60
2	80	88		96	80	72	80
3	80				88	80*	
4	72				64	72	72*

\* trial stopped due to appearance of angina

Effect on blood pressure (mmHg)

No.	Baseline	Placebo			Active		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
1	120/80	115/80	130/70		120/80	130/75	115/80
2	190/100	200/110		120/80	170/100	150/100	190/110
3	145/85				120/80	110/80	
4	110/70				110/70	110/70	120/75

Effect on blood tests

No abnormality was detected in Hb, WBC, diff. ESR, platelets, bilirubin, alkaline phosphatase, SGOT, SGPT, albumin, globulin or urine during the study.

Effect on urine tests

No abnormal urine findings were detected during the study.

Possible side effects

Three patients (Nos. 1, 2 and 4) complained of marked dyspepsia, flatulence and nausea while taking the active agent. In two patients (Nos. 3 and 4) classical angina of effort appeared for the first time ever while on the active regime. For this reason, the trial was abandoned.

Neither patient who took the placebo run had any side effects while on that regime.

CONCLUSIONS

As far as a possible anti-obesity effect is concerned this trial is inadequate to draw any conclusions. No effect was seen on pulse rate or blood pressure and blood and urine tests remained normal. Upper gastrointestinal

side effects were marked with the agent. The appearance of angina pectoris in two patients who had never had this symptom and in whom the cardiovascular system was clinically normal was apparently due to the compound. This view is strengthened by the fact that since withdrawal no more attacks have been recorded even on severe exercise. The mechanism whereby this was produced must be speculative but it could be due to the potentiation of endogenous catecholamines by ICI 63,197 on exercise, or perhaps the mobilisation of free fatty acid which could increase myocardial oxygen requirements.