TABLE II.—*Characteristics of the Population in Which the Patients With Mitral-valve Diseases Were Found (Registrar-General's Figures in Parentheses)*

Age in Years	Ratio Males/ Females All Patients	Percentage of all Patients in Each Age-Group	
		Males	Females
All ages	1.7 (1.1)	66.7 (76.6)	69.5 (84.5)
60+	1.6 (1.0)	28.8 (20.1)	25.7 (13.1)
40-59	1.8 (1.6)	4.5 (3.3)	4.8 (2.4)
20-39	1.6 (1.4)		

12 of the 22 patients. Of these 12, four died of congestive heart failure, two of pulmonary oedema, four after cerebral, aortic, or pulmonary emboli, and two after thrombosis of the pulmonary artery. Of the 10 patients in whom death did not appear to be directly attributable to the cardiac disease, six died shortly after surgical operations, one had a haematemesis from a gastric ulcer, one a myocardial infarct, one Hodgkin's disease, and one a cerebral thrombosis.

Sixteen of these elderly patients were female. Records were not complete in every case, but at least seven of them had borne children, one patient having had five offspring. Of the 15 patients about whom information was available, only two had had symptoms attributable to their mitral disease before the age of 50. Six of these 22 patients were known never to have been oedematous, but only two were in sinus rhythm a few weeks before death.

Discussion

We were surprised to find an incidence of rheumatic mitral-valve disease of 2.2% in patients dying in this hospital at 60 years of age or more. This confirms the impression of other authors that the condition is not so rare in the elderly as has been supposed. The discrepancy between our figures and those of the Registrar-General may be attributed to several factors. A relatively small proportion of old people die in a general hospital for acute cases, which is more likely to admit patients with congestive cardiac failure than with more chronic conditions. This produces an artificial elevation of the incidence of patients dying of mitral-valve disease in hospital. On the other hand, in a quarter of our elderly patients the diagnosis was not made before death; all but one of these patients were admitted to a surgical ward. It seems likely that the proportion of undiagnosed cases of mitral-valve disease is even higher in patients dying at home. Death in the elderly patient with mitral disease is often due to unrelated conditions, and mitral-valve disease would therefore not be the certified cause of death. For these reasons we believe that the incidence of rheumatic disease of the mitral valve in the elderly is much higher than that reported by the Registrar-General.

However, the Registrar-General's figures for the incidence of mitral-valve disease in younger patients are probably substantially correct, since such patients are less likely to die from intercurrent disease or to remain undiagnosed. The higher incidence which we found is probably due to the high proportion of these patients who died in hospital.

Summary

Of 1,000 consecutive necropsies on patients aged 60 years and over who died in the Sheffield Royal Hospital, 2.2% showed evidence of rheumatic disease of the mitral valve. The incidence in patients aged 40 to 59 was 6.4% and in patients aged 20 to 39 it was 12.4%.

The figures were shown to be higher than those of the Registrar-General for 1957. The possible reasons for this discrepancy are discussed.

We thank Dr. J. L. Edwards for allowing us to study his post-mortem reports and for helpful criticism. We also thank the physicians and surgeons of the Sheffield Royal Hospital for allowing us access to the records of their patients.

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IPRONIAZID IN TREATMENT OF ANGINA OF EFFORT

BY

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Iproniazid ("marsilid"), a derivative of isoniazid, was found to benefit patients with angina pectoris by Cesarman (1957), who claimed that complete relief from pain was produced in all of 41 patients studied. Subsequent reports have been conflicting, and the extent and nature of the side-effects have proved formidable. However, the early promise of the drug and the suggestion of a fundamentally different mode of action from the commonly used vasodilators were the reasons for this clinical trial, which was begun soon after the favourable report, and before the extent of the toxicity of the drug had become apparent.

The results are present of a controlled assessment of iproniazid in 51 patients with cardiac pain of effort.

Material and Methods

The methods employed were similar to those described previously (Fife *et al.*, 1957, 1958). Of the 51 patients included, 44 were men and 7 women. Their ages ranged from 37 to 65 years, averaging 54; 36 were in the age-group 45-60.

All patients gave a convincing history of angina of effort. Where dyspepsia was a feature, barium-meal examination (with particular search for hiatus hernia) and cholecystogram were performed. If any doubts on diagnosis remained, the patient was excluded from the trial. Evidence of myocardial infarction within the previous six months, and of anaemia or other debilitating disease, were also grounds for exclusion.

A 12-lead electrocardiogram was done in every case, and, if it was normal, six selected leads were taken after exercise to the point of inducing chest pain or tightness. Forty-one patients had electrocardiographic evidence of myocardial ischaemia while resting, and 10 of these had Q-wave evidence of previous myocardial infarction. Of the 10 patients with a normal electrocardiogram at rest, six had transient ST-T abnormalities after exercise. Particular attention was paid to the four with normal

electrocardiogram even after exercise; all of these had a clear response of their effort pain to glyceryl trinitrate.

Definite benefit from glyceryl trinitrate was claimed by 43 of the 51 patients; three were doubtful, and five had no benefit. The latter appeared to be using the drug in the correct manner, and their tablets were supplied from fresh stock.

No patient with a diastolic pressure above 120 mm. Hg was included. In 25 patients the diastolic pressure at the time of selection was over 95 mm. Hg, and in 26 it was less than that figure.

The severity of the angina was classified in arbitrary fashion as mild, moderate, or severe, according to the frequency of the attacks and the ease with which they were induced. Only two patients had frequent angina at rest.

The trial was conducted on a "double-blind" basis, using control tablets identical in appearance with iproniazid. The dosage was 50 mg. thrice daily after meals, and drug and placebo were each given for a three-weeks period in varying sequence. The first week was discounted, and the symptoms during the last two weeks were recorded as "much improved," "some improvement," or "unchanged or worse." Approximately half of the patients received the control tablet first. Most of the patients had previously participated in assessments of other drugs for angina.

Each patient was asked to complete a daily report card recording frequency of attacks of pain, side-effects of the tablets, etc.; and the number of pain-free days in each two-weeks recording period was noted.

Results

The results are shown in Tables I and II. Iproniazid appeared to benefit 31 patients, and the placebo 24 patients, a difference which is not statistically significant. When the patients were asked to compare the two tablets, 14 thought that iproniazid was better and 12 preferred the placebo; 12 thought that both were equally helpful, and 13 that both were useless. Again,

TABLE I.—Clinical Response to Iproniazid and Placebo

	No. of Patients			
	Severity of Angina			Total
	Severe	Moderate	Mild	
Iproniazid helpful, placebo not	7 (3)	6 (2)	1	14 (5)
*Placebo helpful, iproniazid not	2	3	2	7
Both equally helpful	4	3	5	12
helpful, iproniazid better	0	0	0	0
*Both helpful, placebo better	0	5 (5)	0	5 (5)
Neither helpful	3	9	1	13
Total	16 (3)	26 (7)	9	51 (10)

Figures in parentheses are those described as "considerably improved." They are included in figures outside the parentheses.

* For statistical purposes these groups were combined ("placebo better") to give four groups; and mild and moderate cases were combined.

TABLE II.—Relation Between Clinician's Assessment and Number of Pain-free Days While on Iproniazid and Placebo

	Benefit from Iproniazid			Benefit from Placebo		
	Considerable	Some	Nil	Considerable	Some	Nil
No. of patients	5	26	20	5	19	27
Total pain-free days	54	167	41	68	156	27
Average (pain-free days per patient)	10.8	6.4	2.1	13.6	8.2	1.0

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this distribution of numbers is within that which might occur if both tablets were equally inert.

Towers and Wood (1958) found that the greatest benefit occurred in the severe cases, and Table I suggests that the present series might support this view. However, when the severe cases were compared with the remainder by statistical calculation it emerged that the apparent superiority of the drug over the placebo in the severe cases was just under the 5% level of statistical significance. The possibility is not excluded, however, that a larger series might have shown a significant benefit of the drug in severe cases.

Table II, which shows information about pain-free days derived from the patients' report cards, does not suggest any significant difference between iproniazid and the placebo in this respect.

Side-effects from the therapy were similar to those reported by previous workers, and were much commoner from iproniazid than from the placebo. Thirty-six patients attributed symptoms to iproniazid and seven to the placebo. The commonest of symptoms from iproniazid were dizziness, tiredness, weakness, and palpitation; but numbness of limbs, difficulty in micturition, impotence, constipation, dyspepsia, and other symptoms were also complained of occasionally. There was no correlation between improvement in the angina and the presence or absence of side-effects. Jaundice was not encountered.

Discussion

Despite an extensive search over the years for a long-acting vasodilator capable of suppressing wholly or partly the pain of angina pectoris, none has been found to stand the test of time and remain by common agreement a remedy of proved efficacy. The report by Cesarman (1957) that iproniazid was effective in relieving anginal pain was thus especially interesting, as it appeared to act by some means other than coronary vasodilatation. The early favourable reports by Cesarman (1957) and Cossio (1957, 1958) were confirmed by Towers and Wood (1958), who, however, dispensed with a control series.

It had early been recognized that side-effects from iproniazid were common, but a serious toxic action on the liver in certain patients was reported (*New Engl. J. Med.*, 1958) and this has limited any potential clinical usefulness it might possess.

Further controlled trials of the drug in angina pectoris have failed to confirm its value, and Dewar *et al.* (1959) and Snow and Anderson (1959) found it no better than dummy tablets in their patients. Our own results are in line with this experience. When our 51 patients were considered as one group, iproniazid was no more effective than the placebo in relieving cardiac pain of effort.

Towers and Wood (1958) were particularly impressed by the value of iproniazid in severe and intractable angina, and Snow and Anderson (1959) felt unable to deny that benefit might occur from the drug in certain severe cases. In the present trial, comparison of the severe cases with the remainder in their response suggested a possible benefit of the drug in the severe cases. Indeed, such was our impression during the course of the trial. This apparently better action in the severe cases did not reach the 5% level of statistical significance.

however, but the series was too small to allow of its dismissal. Iproniazid may have a value in severe angina.

The use of a drug with a very high incidence of side-effects tends to destroy the double-blind design of the therapeutic trial, as the clinicians can hardly fail to recognize which is the active drug. In such circumstances conclusions must be particularly cautious, and cannot claim the total lack of possible bias as fully double-blind trials.

With this in mind we would limit our conclusions to stating that we have been unable to confirm any striking value of iproniazid in angina pectoris; that, except in severe cases, it was of no greater efficacy than the placebo; and that even in the severer cases any possible benefit was at best marginal, numbers of such cases being too small, however, to be statistically conclusive.

Side-effects were frequent and troublesome, and were mainly similar to those experienced by others. Toxic jaundice was not encountered.

Summary

A controlled clinical trial of iproniazid in 51 patients with angina of effort is reported.

With the possible exception of its use in severe cases, it was of no greater efficacy than the placebo.

Even in severe cases proof of its value was not conclusive.

Toxic effects were frequent and may sometimes be serious.

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Changing social attitudes towards mental health, the development of an awareness of the benefits that accrue from early treatment, and a growing public confidence in the service which is available are factors probably contributing to the increase in voluntary "boarders" entering mental hospitals in New Zealand. These comments are made in the annual report on mental health statistics which has just been released. The rate of voluntary boarders entering hospital has risen from 13.4 per 100,000 of population in 1938 to 46.7 in 1958—an increase of almost 300%. In the same period the increase in the admission rate for patients was 19.8%. A total of 3,741 people were admitted to mental hospitals in New Zealand in 1958. Of the persons "discharged out-right" from mental hospitals in 1958, 19.8% were in mental hospitals for less than one month, 49.9% were in hospital one month and under three months, and 20.3% were in between three months and six months.

ANTIBIOTIC SENSITIVITY TESTS

THE SPECIAL REQUIREMENTS IN OPHTHALMOLOGY

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Little is known of the concentrations that are reached in the conjunctival sac from the application of drops and ointments, but it is established that the intraocular levels reached with penicillin, streptomycin, polymyxin, and neomycin after subconjunctival injection are considerably in excess of the blood levels reached from systemic administration. The usual sensitivity tests, being based on the blood concentrations reached by the different antibiotics on systemic administration, do not give full information for guidance in local treatment, for an organism may be insensitive to a relatively low concentration of an antibiotic and yet respond to a higher concentration. That this is the case with some organisms commonly met with in ocular infection is shown by the findings recorded in the accompanying Table.

It will be seen that in a series of 24 penicillin-resistant strains of *Staphylococcus aureus* found insensitive to disks containing 10 units of penicillin, no fewer than 14 were sensitive to tablets containing 50 units of penicillin, while 22 of the 24 responded to 250 units. (Increasing the concentration does not, of course, affect all organisms. Thus in 69 strains of different Gram-negative bacilli insensitive to 10 units of penicillin, only 4 (all *E. coli*) were found to be sensitive to tablets containing 50 units, and only one more organism, *Proteus vulgaris*, showed sensitivity to 250 units.) Similarly, of 23 strains of pneumococcus, an organism known for its resistance to neomycin, only 3 responded to the standard test of 30 µg. of neomycin, but the incidence of positive responses rose to 17 with 150 µg.; while all the 23 responded to 750 µg. Chloramphenicol,

Sensitivity of Some Micro-organisms in Relation to Different Concentrations of Some Antibiotics

	<i>Staph. aureus</i> (Penicillin- resistant)	Pneumo- coccus	<i>Ps. pyocyanea</i>		<i>Pr. vulgaris</i> and Allied Organisms		<i>E. coli</i>
			(a)*	(b)*	(a)*	(b)*	
	No. of strains used						
	24	23	17	8	21	13	10
	No. sensitive						
Antibiotic							
Penicillin :							
10 units ..	0	23	0		0		0
50 " ..	14		0		0		4
250 " ..	22		0		1		4
Neomycin :							
30 µg. ..		3	17	8	21	13	10
150 " ..		17					
750 " ..		23					
Chloramphenicol:							
30 µg. ..		23	15		13	1	8
150 " ..						7	
500 " ..			17		18		10
750 " ..						9	
Polymyxin:							
10 µg. ..				0			
50 " ..				6			
100 " ..				8			

* (a)(b) Two different experiments with a different range of antibiotics.