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PROGNOSIS IN MYOCARDIAL INFARCTION — THE BENEFITS OF EXERCISE AS SEEN IN NON-RANDOMISED TRIALS

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ABSTRACT

Previous uncontrolled studies suggest that exercise rehabilitation reduces recurrence rates in post-myocardial infarction patients. Six hundred and ten consecutive post-coronary patients referred to an exercise rehabilitation programme have been followed for an average of 36.5 months (1-8 years). Total deaths amounted to 36 (1.89% p.a.) of which 23 were cardiac deaths, with an annual death rate averaging only 0.85% after the first year of conditioning had been completed. There were also a total of 21 non-fatal recurrences of infarction. Comparison has been made with 700 patients enrolled in the Health Insurance Plan of New York. On the basis of smoothed probabilities for the risk factors reported in the New York series, we should have seen 89 deaths ($P < 0.001$). Correcting for differences between the two groups (age and number of diabetics) gives a predicted mortality for the Toronto series of 63.5 deaths (3.42% p.a.). This discrepancy in favour of the exercised group is significant in terms of an infinitely large control population ($P < 0.001$) and also sample sizes of 610 exercised and 700 control patients ($0.01 > P > 0.001$). Unfortunately, formally to prove such a 45% reduction in mortality by way of a randomised control trial would be extremely costly, possibly prohibitively so.

Key words: Ischaemic Heart Disease, Coronary Disease, Cardiac Rehabilitation, Cardiac Exercise.

INTRODUCTION

Recent trials to determine whether added physical activity influences a patient's prognosis following myocardial infarction have allocated subjects randomly to "exercise" and "control" or "light activity" groups (Table I). In some instances, the final results have yet to be reported, but nevertheless the initial impression formed from such investigations has been that any effect of exercise is quite small, and with the size of the samples studied (300-750 subjects) is unlikely to attain the level of statistical significance postulated for a "positive" result ($P < 0.05$ in most trials).

A large scale randomised experiment is theoretically the best method of resolving whether exercise benefits the "post-coronary" patient. However, despite the apparent superiority of the randomised trial, there is a real danger that a false negative conclusion may be drawn. High drop-out rates are an inevitable source of error, specifically insofar as data from the drop-outs are aver-

aged with values for programme adherents. Interpretation of data may be complicated by an averaging of early mortality (where exercise would be unlikely to have exerted an effect) and late mortality (where an effect may have occurred). Problems may also arise from failure to maintain consistent exercise and control regimens between co-operating centres. Because of the large numbers of patients and staff involved, there may be difficulty in assuring compliance in the exercise group, or preventing contamination of the control group by participation in unauthorised "keep fit" programmes. Finally, it is necessary to accept constraints of sample size, thus causing a large beta error, i.e. a 10% or even 20% statistical chance of missing a positive effect of exercise. For all of these reasons, the data of Table I cannot be accepted as "proving" that exercise has no effect upon prognosis.

A much simpler alternative approach has been to compare the experience of a given "exercise" group with

a more arbitrary "control" series, e.g. exercise "drop-outs", or patients treated conservatively at another centre (Table II). This type of comparison suggests that both recurrence and mortality rates are substantially lower in the exercised than in the control subjects. However, most authors adopting this tactic have made no allowance for factors of sample selection, particularly possible differences in the clinical severity of the disease process between the exercised and the supposed "control" series.

The present report explores reasons for the apparent discrepancy between the findings of random and non-random trials, using as a primary data base information on 610 post-coronary patients who attended the Toronto Rehabilitation Centre Exercise Programme for 1 to 8 years (an average of 3 years) over the period 1968-76. The programme is unusual with respect to the intensity of the prescribed exercise, the compliance rate, and our success in obtaining 100% follow-up information, with details of recurrent fatal and non-fatal reinfarctions as well as deaths from other causes. Furthermore, a detailed assessment of risk factors (Weinblatt et al, 1968; Weinblatt et al, 1973) has allowed us to assess the possible contribution of patient selection to the observed favourable prognosis of our exercised group.

PATIENT SERIES AND METHODS

Subjects. The patients were a consecutive series of 610 men attending the Toronto Rehabilitation Centre for intensive, exercise-based rehabilitation. In each subject, the diagnosis of a myocardial infarction had been verified by the presence of at least two of the following criteria:

1. A classical history of chest pain lasting for 30 minutes or more.
2. A transient but clinically significant rise in either serum glutamic oxalacetic-acid transaminase (SGOT) or creatine phosphokinase (CPK).
3. Serial electrocardiographic changes showing pathological Q-waves and/or S-T segment elevation with T-wave changes indicative of a transmural or subendocardial infarction.

The patients were referred for exercise by their personal physicians; recruitment was approximately one of every ten male patients with a non-fatal infarction in the Toronto catchment area, with a predominance of white-collar workers. Cases with "by-pass" operations were excluded from our sample,* but the group was otherwise unselected. Individuals were admitted to the programme not sooner than two months after myocardial

*Two of our 80 by-pass patients died; to avoid all possibility that data had been favourably biased by exclusion of the by-pass group, these two individuals were included in our sample of 610 patients.

infarction (average 8.2 ± 11.7 months,) and they were followed for an average of 36.5 ± 6.5 months (1 to 8 years). During this period they participated in an intensive exercise programme.

Exercise Rehabilitation Programme. The programme consists of a supervised exercise regimen based on walking, walking/jogging, and jogging, the goal being to jog 3 miles in 30 minutes or 36 minutes depending upon age, 5 times weekly. The patient attends the Centre once a week and trains four times a week on his own. Initial and continuing levels of exertion (expressed in the form of a "prescription" specifying distance, pace, and frequency) are prescribed individually from the results of a three-stage sub-maximal exercise test performed on a cycle ergometer. Details of this test are given elsewhere (Kavanagh and Shephard, 1973). After an initial series of lectures in which the patient is introduced to the rudiments of his disease and the principles of cardiovascular training, on-going instruction is given in such basics as pulse-taking and symptom-interpretation, the "jogging" technique, and precautions regarding outdoor exercise in climatic extremes. An exercise training diary is completed on a weekly basis and information is gained from this regarding the patient's subjective and objective responses to effort. Telemetry during actual exercise is carried out whenever indicated, as is a repeat exercise stress test. Otherwise the patient is retested every six months. Weekly attendance is for a period of up to two years, depending on progress. Thereafter the patient attends on an eight-weekly basis, and is exercise-tested annually.

The physical characteristics of the 610 patients under study at the time of entry to the Programme are summarised in Table III.

Controls. The prime source of control statistics is published information for 745 male patients enrolled in the Health Insurance Plan of New York. This group had survived an average of six months following a first myocardial infarction or diagnosis of angina without infarction (Weinblatt et al, 1973). It was selected as a control in preference to the larger Coronary Drug Trial (Stamler et al, 1975) partly because of some socio-economic similarities with the Toronto sample, and partly because the post-infarction prognosis for the New York population was clearly related to the presence of commonly accepted primary risk factors, existing either singly or in various combinations.

Characteristics of Test and Control Samples

General Measures of Clinical Condition. Sixty-eight of our 610 patients had been subjected to coronary arteriography. The findings indicated 53% had three-vessel disease (Table IV), a figure comparable with other angiographic studies (Blümchen et al, 1973). Thus, in this part of our sample there was no evidence we were dealing

with patients having minor coronary vascular disease. The proportion of the total sample receiving angiography (11.1%) was relatively low; however, this reflects the conservatism of the referring physicians rather than a low incidence of severe disease.

On admission, 209 (34.3%) had a history of angina, for which nitroglycerin tablets, or an equivalent coronary vasodilator, was required for symptomatic relief, and when first tested, 192 of our patients (31.4%) developed angina during the progressive exercise test. At the final examination, this proportion had diminished to 96 cases (15.7%). In the New York sample, a history of angina was reported by 13.6% of the patients seen one month after infarction (Weinblatt et al, 1973), and by 11.8% of those surviving for a further 4½ years.* It thus seems fair to conclude that the extent of vascular occlusion was at least as great in the Toronto sample as in the N.Y.H.I.P. group.

Other significant clinical findings in the Toronto sample were an enlarged heart (25 cases, 4.1% of sample), a ventricular aneurysm, symptomless and demonstrated by ventriculography (14 cases, 2.3% of sample), and exercise-induced premature ventricular systoles (unifocal, 51 cases, 8.4%; multifocal 28 cases, 4.7%). The period of hospitalisation (3.4 ± 2.1 weeks) was somewhat longer than the current average (Fernow et al, 1978) but was fairly typical of medical practice at the time of entry to the study.

Major prognostic variables are compared in Table V. Quantitative data for the serum cholesterol were available in 73% of the Toronto series, and exceeded 270 mg/100 ml, (7 mmol/l) in 45 (10.1%) of the 446 cases. The average reading for this abnormal group was 314 ± 42 mg/100 ml (8.1 mmol/l) and in a further 11 (6.7%) of the remaining 164 patients the cholesterol was merely recorded as "elevated". A high serum cholesterol was plainly more frequent in the New York series. This discrepancy might reflect not only a greater average severity of the disease process in the New York population, but also the development of interest in dietary modification from the 1960's to the present day.

All of our blood pressure readings were taken by sphygmomanometer cuff in the sitting position, diastolic values indicating the disappearance of the Korotkoff sounds. The average resting values on entry to our post-coronary rehabilitation programme (highest of left and right arm readings) were 128.6/87.7 mmHg, 17.1/11.7 kPa. This may be compared with the figures of 146/92 mmHg, 19.5/12.3 kPa cited for those em-

ployees of the Hawthorne works (Paul et al, 1963) who developed a myocardial infarction between the ages of 40 and 55 years. The proportion of hypertensives ($> 150/100$ mmHg, 10.0/6.7 kPa) was 23.1% in Toronto, again somewhat lower than in the New York series (33.4% $> 165/90$ mmHg). However, our use of *post-infarction* values could explain at least a part of this discrepancy. Those of our patients with a high pressure showed a further small but statistically significant reduction of the systolic reading over the course of training (6.7 ± 19.1 mmHg, 0.89 ± 2.55 kPa)

Persistent electrocardiographic abnormalities were more frequent in the Toronto sample than in the New York patients on entry to the study. Resting tracings were abnormal in 97.2% of our subjects. When exercising at a heart rate corresponding to 75% of aerobic power, 145 of the group (23.8%) showed a horizontal or downward-sloping S-T segmental depression ≥ 0.2 mV; 79 cases (13.0%) also showed 3 or more premature ventricular beats in 10 seconds (51 unifocal, 28 multifocal), and in 10 cases (1.6%) there was an upward-sloping junctional depression ≥ 0.4 mV; nevertheless the *average* S-T segmental depression at 75% of aerobic power (-0.10 ± 0.13 mV) was relatively slight for the Toronto group.

Compliance

The Toronto group was unusual with respect to both the intensity of the training undertaken and the degree of compliance with the required regimen. Twenty-two of the group progressed to the point of running in marathon events (Kavanagh et al, 1974; Kavanagh et al, 1977), one covering the 42.1 km in as little as 190 minutes. Four hundred and twenty-eight of the patients (70.2%) continued to attend the Centre regularly, and many of the remaining patients persisted with exercise; 505/610, 82.8%, engaged in at least 3 sessions of training per week throughout the study period, and even at the end of our investigation only a very small number of patients (27/610, 2.8%) were taking no training at all. The principle activities were of the endurance type – walking, jogging, and sometimes cycling. These were supplemented, in order of frequency, by golf, swimming, tennis, squash, curling, bowling, skating, cross-country and down-hill skiing, and ice-hockey. Occasional patients also participated in dancing, calisthenics, horse-riding, sailing, and canoeing.

Deaths

A total of 35 patients died over the average follow-up of three years. Twenty-three were plainly a fatal consequence of the ischaemic heart disease (19 recurrences, one complicated by viral myocarditis, and 4 "electrical" deaths). One patient died during coronary angiography, and his death might thus be regarded as attributable at least in part to ischaemic heart disease. In the remaining 11 cases death was due to other causes (4 cerebro-

*The prognosis was similar for those having angina without prior myocardial infarction (275 cases, 4.5 year mortality, 17.5%) and for those with myocardial infarction (470 cases, 4.5 year mortality, 17.5%).

vascular accidents — 1 haemorrhage and 3 incidents of thrombosis; 3 neoplasms — brain, liver, and lung; 1 case of renal failure; 2 vehicular accidents — one in which the patient was a passenger, and the other who died of residual head injuries four days later and was found at post-mortem not to have had a fresh infarction; 1 surgical death during an emergency cholecystectomy).

In the 23 clear-cut cases of a fatal recurrence of cardiac disease, the average period of exercise had been 19.6 ± 17.8 months, the second episode occurring 28.9 ± 25.5 months after the primary infarction. Fatal recurrences were as follows:

Year	Non-fatal Recurrences	All Recurrences (fatal & non-fatal)
One (N = 610)	1.15%	3.11%
Two (N = 503)	1.19%	2.58%
Three (N = 335)	0.90%	1.19%
Four (N = 209)	0.48%	0.96%
Five (N = 124)	2.42%	3.23%
Six-eight (N = 41)	0.00%	0.81%

There seem two clusters of events. Early deaths may reflect the continuing influence of the primary infarction upon cardiac rhythm and myocardial infarction, while the later group of deaths are more certainly due to progression of the disease, this effect being concentrated amongst those who for various reasons dropped out of the programme. Certainly, 8 of the 23 patients who sustained a fatal recurrence had been attending the exercise class for six months or less, and one man had participated in only one rehabilitation session. Ten were exercising regularly up to the time of their fatal recurrence; 2 were exercising sporadically; 11 had ceased to participate in the programme entirely. In only 4 of the 11 non-exercisers was there a medical reason for non-

participation (alcoholism and anginal symptoms, organic psychosis, and 2 with orthopaedic problems). Eight of the 23 were sudden deaths, 7 of which were unassociated with physical exertion. One died while he was exercising away from the Centre; on the day in question this patient was apparently recovering from a bout of influenza, and despite warnings to the contrary he had been following a heavy work schedule and exceeding his exercise prescription.

The majority of the 23 showed several features associated with a poor prognosis. Two were patients who had undergone by-pass surgery, and in whom subsequent angiography had shown that the graft had blocked prior to referral to the exercise programme. Three had an enlarged heart, and in 2 ventricular aneurysms had been demonstrated. Four patients had suffered from severe anginal symptoms for a considerable period prior to their primary infarction; 12 developed this symptom at their initial exercise test and in 9 the angina was refractory to treatment and was still induced by minimal effort prior to the fatal recurrence. The exercise electrocardiogram showed horizontal or downward-sloping S-T segmental depression ≥ 0.2 mV in 10 cases and T-wave inversion after exercise in 6 cases; 5 cases showed premature ventricular systoles at rest, and in 2 individuals multifocal extrasystoles persisted during exercise. Five of the patients were hypertensive, and 3 had a serum cholesterol ≥ 270 mg/100 ml (≥ 7 mmol/l).

Non-fatal Recurrence of Infarction

A further 21 cases developed a non-fatal recurrence of the infarction over the 36.5 month period of observation. In general, the clinical characteristics of this group were similar to those of patients who sustained a fatal recurrence. The average time from infarction to non-fatal recurrence was 27.6 ± 20.3 months (22.8 ± 17.6 months after joining the programme). The annual rates for non-fatal and all recurrences were as follows:

TABLE I

The apparent benefit of additional physical activity following myocardial infarction (randomised trials).
Values shown per 100 person years.

Follow-up period	Exercise Group		Control Group		Author
	Recurrences* %/year	Deaths %/year	Recurrences %/year	Deaths %/year	
Average about 1½ yr.	4.4	0.8	3.1†	0.9†	Rechnitzer et al preliminary data (1975)
1.3 yr.	6.9	2.9	13.0	8.6	Sanne et al (1972)
4 yr.	8.5	4.5	10.0	5.5	Wilhelmsen et al (1975)**
	No data yet available				Naughton (1977)

* Also includes fatal recurrences.

** This is a second report on the study of Sanne et al (1972); partly because of poor compliance with prescribed exercise, the benefit of exercise was no longer statistically significant.

† Control group also engaged in programme of light physical activity; subjects were also selected on the basis of age and absence of various complications.

TABLE II

**The apparent benefit of additional physical activity following myocardial infarction (non-randomised trials).
Values shown per 100 person years.**

Follow-up period (yr)	Exercise Group		Control Group		Nature of Control Group	Author
	Recurrence† %	Death %	Recurrence %	Death %		
1	9.4	3.1	25.0	10.9	Patients not willing to exercise	Brunner (1968)
2	2.5	—	7.0	5.6	Patients not willing to exercise & drop-outs	Heller (1968, 1972)
5* (0.5-5.0)	1.12*	0.3*	5.6*	0.4*		
2.7	—	2.0	—	4.5-6.0	Reports in the literature	Hellerstein (1968)
5* (0.3-5.0)	1.0*	0.8*	7.3*	2.4*	Exercise group in London, Ontario; controls in Toronto	Rechnitzer et al (1971)
7* (2.1)	1.5*	1.1*	5.0*	1.9*		
2.1	4.9	3.6	12.3	6.9	Controls who for various reasons did not join project in London, Ontario	Rechnitzer et al (1972)
5	—	0.7*	—	2.4*	Physically inactive post-infarction patients	Gottheiner (1968)
Up to 4	10.3	3.1	—	11.2	Concurrent community experience	Bruce (1974)

† Also includes fatal recurrences.

* All figures are biased downwards, since the *average* participation of subjects (cited in parenthesis) was less than the stated follow-up period.

TABLE III

Initial physical characteristics of subjects participating in present study. (Mean $\pm$ S.D.)

TABLE IV

		Initial value		Summary of findings in 68 of 610 Toronto patients who received angiography.	
Age (yr)	=	48.1 $\pm$ 7.3		1 vessel disease	8 cases
Height (cm)	=	173.3 $\pm$ 7.1		2 vessel disease	24 cases
Weight (kg)	=	76.0 $\pm$ 9.2		3 vessel disease or equivalent	36 cases
Excess weight (kg) ^a	=	7.8 $\pm$ 7.3		Left ventricular abnormality	33 cases
Skinfold thickness (mm) ^b	=	15.8 $\pm$ 5.0			
Resting blood pressure (mmHg)	=	(Syst.)	(Diast.)		
	=	133 $\pm$ 17/85 $\pm$ 9			
	(kPa)	=	17.7 $\pm$ 2.3/11.3 $\pm$ 1.2		
Maximum oxygen intake (ml/kg·min)	=	24.9 $\pm$ 7.1			
(mmol/kg·min)	=	1.11 $\pm$ 0.32			

^aExcess relative to "ideal" weight proposed by Society of Actuaries (1959); Shephard, 1974).

^bAverage of triceps, subscapular and suprailiac folds.

TABLE V

A comparison of major risk factors between the Toronto and New York samples (percent of sample).

Risk Factors	Toronto ^c		New York
	Sole Factor	All Cases	All Cases
Serum cholesterol > 270 mg/100 ml	0.0	7.4	23.9
Persistent electrocardiographic abnormalities ^a	70.0	97.2	62.1
Hypertension > 150/100 mmHg (20.0/13.3 kPa ^b)	0.8	23.1	33.4
Elevated serum cholesterol + ECG abnormality	4.9	7.4	16.2
ECG abnormality + hypertension	19.8	22.3	22.8
Elevated serum cholesterol + hypertension	0	2.5	8.9
Elevated serum cholesterol + hypertension + ECG abnormality	2.5	—	?
None of the above risk factors	2.0	—	?

^aPersistent abnormalities in the resting electrocardiogram indicative of myocardial infarction.

^bThe criterion of hypertension adopted in the New York study was a pressure > 160/95 mmHg (21.3/12.6 kPa).

^cThe comparison is a conservative one, since the table has excluded from the high risk category 11 patients reported as having a "high" cholesterol and 7 patients noted only as "hypertensive".

TABLE VI

An estimate of anticipated deaths for the Toronto population, based on the experience of the New York group and adjusted for a 36.5 month interval of observation.

Risk Factor			Number of cases	Probability of death in 36.5 months	Total anticipated deaths
Cholesterol* > 270 mg/100 ml	Hypertension* > 150/100 mmHg	Persistent ECG abnormality			
Yes	Yes	Yes	15	16.72	2.51
Yes	Yes	No	0	7.11	0
Yes	No	Yes	30	7.14	2.14
Yes	No	No	0	2.88	0
No	Yes	Yes	121	26.53	32.10
No	Yes	No	5	11.91	0.60
No	No	Yes	427	11.96	51.07
No	No	No	12	4.95	0.59
			Grand Total		89.01
					= 4.80% per annum

*In order to make our assessment a conservative statement of risk, we have excluded from the high risk category 11 patients reported as having a "high" cholesterol and 7 patients noted only as "hypertensive".

At the time of finalisation of this report, all patients had been followed for one further year. During this additional time, there were 4 fatal recurrences, 4 non-fatal recurrences, and 3 unrelated deaths (cancer of the lung, cancer of the liver, and haematemesis from a gastric ulcer). The low long-term recurrence rate is thus being sustained.

As with the fatal recurrences, the annual rates for all recurrent events tended to decrease as the programme continued. The 36.5 month review showed that 3 of those with a non-fatal recurrence had been exercising for less than 6 months. Only 5 were exercising regularly at the time of recurrence, 4 were participating in a spasmodic fashion, and 12 were not exercising at all. In only 3 cases were there medical reasons for non-participation (exertional angina), and our data do not support the view of a general association between severe disease and exercise non-compliance. There was one enlarged heart, but there were no aneurysms in the group with non-fatal recurrence. Five had a lengthy history of angina prior to the primary infarction; 7 showed angina during the initial exercise test at the rehabilitation centre, and in 3 this symptom was still present during the final exercise test prior to recurrence. The exercise electrocardiograms showed S-T segmental depression ≥ 0.2 mV in 8 cases, and 4 cases also showed T-wave changes. The resting record showed premature ventricular beats in 11 cases, and in 2 patients (1 unifocal, 1 multifocal) the abnormality became more marked (3+ extrasystoles in 10 sec) with exercise. Five of the group were hypertensive, and 3 had a serum cholesterol ≥ 270 mg/100 ml (≥ 7 mmol/l).

Comparison Between Exercise and Control Groups

The published analysis of the New York data (Weinblatt et al, 1968; Weinblatt et al, 1973) presents smoothed cumulative probabilities of death for the period 0.5-3.0 years after infarction in relation to 3 prognostic factors (persistent abnormalities of the resting electrocardiogram, hypertension, and elevation of serum cholesterol). In order to compare statistics with our average period of observation (36.5 months), all probabilities of death have been multiplied by a ratio of 36.5/30; this seems permissible, since the overall mortality rate in the New York study was very similar for 30 months (4.01% per annum) and for 54 months (3.88% per annum). The association between the several variables and the likelihood of death is shown in Table VI, along with the expected number of fatalities. If our sample had behaved in the same manner as the New York population, there would have been 89 deaths, for an annual mortality of 4.80%. In fact there were only 35 deaths; the difference from the New York group is highly significant ($\chi^2 = 28.4$, $P < 0.001$). It must also be stressed that only 23 (or 24 if one includes the death associated with coronary arteriography) of the Toronto deaths occurring in the 36.5 month review could be attributed to a

recurrence of the myocardial infarction (66-68% of deaths) compared with 81% in the N.Y.H.I.P. series. Furthermore, after the first year of exercise, our group sustained no more than 11 fatal infarctions in 1,294 patient years (a cardiac fatality rate of only 0.85% per annum).

DISCUSSION

The present results show that the post-coronary patients who exercised vigorously at the Toronto Rehabilitation Centre had a much lower mortality than patients enrolled in the Health Insurance Plan of New York. The overall mortality was only 39% of the anticipated figure, and the advantage was even greater after the first year of exercise. In non-exercised patients, the annual mortality rate is relatively constant from 6 months to 5 years post-infarction, and it is thus striking that the prognosis of our group should change coincident with the development of conditioning; in other words, the benefit of exercise is seen not only relative to an external control, but within the sample itself. The death rate does not show any advantage over the Southern-Ontario "controls" currently engaged in light activity, but the total recurrence rate for years 2-8 is again far superior to that for two random controlled experiments (Table I). However, before attributing the advantage of the Toronto Rehabilitation Centre group to exercise, several alternative hypotheses must be weighed.

Limitations of the Data. Information was necessarily collected as patients were referred to the Rehabilitation Centre and the data is thus less than perfect from an epidemiological point of view (Seigel and Loncin, 1968). While the duration of observation averaged three years, some patients were followed for little more than a year, and others for as long as eight years. Further, while the average date of entry was some eight months after infarction, some patients were recruited as soon as two or three months after their heart attack, and in others the interval was as long as a year. Mortality is greatest during the first six months after infarction; thus, the segment of our sample who entered the rehabilitation programme less than six months after the acute episode would have tended to increase rather than to decrease the mortality rate for the Toronto series.

Improvement in Treatment. Both the acute and long-term treatment of myocardial infarction is continually evolving. For example, over the period under review some 10% of the Toronto sample received propranolol, particularly in the first two years after their attack. It is thus arguable that a part of the advantage over the New York group could reflect either more frequent diagnosis of infarction or advances in treatment since 1961-1965 (the period of the N.Y.H.I.P. study). The first possibility can be dismissed, since there has been a small decline in the incidence of myocardial infarction since the early 1960s. Some 10% of our sample

were receiving β -blocking drugs, but almost none were taking anticoagulants. In any event, recent statistics (Fox and Skinner, 1966; Stamler et al, 1975; H.I.P.N.Y., 1975; Kentala and Sarma, 1976) suggest that following myocardial infarction the improvements in prognosis due to the use of β -blocking drugs, anticoagulants, modifications of diet, and other modern forms of therapy are at best marginal; annual mortality rates of 4%-6% are still the normal expectation.

Sample Attrition. A progressive attrition of the sample has been a serious criticism of randomised trials of exercise in "post-coronary" patients. It is arguable that those defecting from the "exercise" group may have had a poor prognosis, while those of the "control" group contaminated by an increased interest in physical training may have had an above average prognosis. In the present study, there was a remarkably good and sustained compliance with the required regimen. Further, since all 610 patients were included in the data analysis, any effect due to "drop-outs" acted against rather than for the hypothesis of benefit from exercise. *In particular, 23 of the 27 individuals with zero exercise compliance later sustained a fatal or non-fatal recurrence of their infarction.*

Adjustment for Prognostic Variables. A final explanation of the difference between the two populations might be that "risk-factors" were much more prevalent in the N.Y.H.I.P. data. In socio-economic terms there were similarities between the two groups, but also some differences, including a high proportion of Jews (50%) and a substantial proportion of blue-collar workers (~ 50%) in the U.S. sample. In Toronto, the majority of patients were white collar employees. There have been suggestions that blue-collar workers have a poorer prognosis, probably related to their smoking habits. However, as noted below, smoking behaviour does not seem to account for the favourable experience of the Toronto sample. Adjustment for differences in other risk factors must take account of (i) the availability of data, and (ii) the possibility that exercise itself modifies the importance of either the risk factor itself, or the risk-taking behaviour of the patient. Our data suggest that after infarction the prognosis of exercising individuals is influenced a little by age or hypertension, and that an elevated cholesterol reading does no more than double the risk of a recurrence (Kavanagh et al, 1979). Nevertheless, as an estimate of the maximum possible effect of risk differences we have applied the N.Y.H.I.P. risk ratios to our comparison. Although our patients were given periodic advice regarding other forms of risk-reduction behaviour, the group showed remarkably little change in cigarette consumption, body weight or blood pressure. The risk data used is thus that obtained on admission to the exercise programme.

1. **Serum Cholesterol.** The absolute accuracy of our

serum cholesterol readings can be accepted with some confidence, since the laboratories concerned underwent regular standardisation as a condition of their participation in an international trial of dietary lipids. While the proportion of abnormally high readings was lower in Toronto than in the New York series, this probably reflects the recent practice of dietary modification more than a difference in the average severity of disease or an inter-laboratory difference in the analytical procedure. In any event, allowance has been made for the influence of this variable in comparing our data with the N.Y.H.I.P. data.

2. **Hypertension.** There were differences in the criterion of hypertension between the Toronto and the New York series. In the N.Y.H.I.P. data the requirement was a pressure higher than 165 systolic or 90 diastolic mm Hg in 3 readings (2 taken by paramedical staff, and 1 by a physician). Our measurements were obtained post-infarction, our subjects were thoroughly habituated, and we chose a higher diastolic criterion. It is thus probable that we included fewer marginal cases than the N.Y.H.I.P. study. Again, any discrepancy in this respect would have tended to reduce the predicted death rate for our sample.

3. **Electrocardiogram.** Resting electrocardiographic abnormalities were fewer in the New York series than in Toronto (62.1% versus 97.2%). It could be argued that we reported more minor abnormalities than the New York group. However, in our judgment, the discrepancy is a real expression of differences in clinical state. Firstly, the New York population included patients with angina but no overt episode of infarction. Omitting such cases, the proportion of the New York series with resting ECG changes immediately rises from 62.1% to 77.6%. Secondly, our study excluded by design patients that did not show either resting ECG changes or substantial enzyme changes; this would necessarily have boosted the proportion of abnormal resting ECGs in our series. Lastly, we were careful not to report minor changes as an abnormal ECG (see methods). No adjustment has thus been made to our data for differences in the reporting of ECG abnormalities.

4. **Age.** Weinblatt et al. (1968, 1973) found that age had a substantial influence on annual mortality rate during the period 6 to 30 months post-infarction. For those aged less than 45 years, the mortality was 2.1% per year, for those aged 45-54 it was 4.0% per year, and for those aged 55-64 it was 5.4% per year. The actual data for our exercise programme suggest a less severe age gradient, deaths for the whole study totalling 4.2% of those under 55 years, and 5.1% of those older than 55 years at entry. However, making the liberal assumption that the age effect was as large as in the N.Y.H.I.P. study, and adjusting for the relative age distribution of the two populations, the expected number of fatalities

in Toronto would drop to 72.1% of the previously cited estimated figure, that is, 64.2 deaths, or a mortality rate of 3.46% per year.

5. *Smoking.* In the Toronto sample, 22.2% had never smoked, and 42.0% had stopped smoking at the time of their heart attack; of the remaining 35.8%, 29.0% claimed to have greatly reduced their cigarette consumption. These statistics seem in line with recent North American experience. As noted above, exercise participation had little influence on smoking or other forms of risk-taking behaviour, any changes of life-style being made at the time of the acute clinical episode. Unfortunately, smoking habits are not cited in the N.Y.H.I.P. reports (Weinblatt et al, 1968; Weinblatt et al, 1973); however, in the Coronary Drug Project there were 38.4% continuing smokers. Smoking habits at the time of the first attack have surprisingly little influence on subsequent prognosis (Weinblatt et al, 1968), but mortality in those who continue to smoke is almost twice as great as in those who stop smoking or who never smoked (H.I.P.N.Y., 1975; Kavanagh et al, 1979).

6. *Angina.* Angina had a substantial adverse effect on prognosis, particularly in the first four weeks after the primary myocardial infarction. The percentage of cases with a history of angina was larger in the Toronto than in the New York series (34.3% and 11.8% respectively). On this criterion, the Toronto group would appear to have more severe disease than the New York subjects. However, no specific adjustment of mortality is needed, since in the N.Y.H.I.P. series death rates from 6 months to 4½ years were comparable for myocardial infarction alone and myocardial infarction together with angina.

7. *Diabetes.* Diabetes is well recognised as an adverse factor in prognosis. In the New York series, 11.6% were described as having diabetes. In the Toronto group, 4 patients required regular Insulin injections, and 6 took oral hypoglycaemic agents (total 1.6%). Again, assuming that diabetes acted independently of the age factor, the overall mortality of the Toronto series would need an adjustment of 1.1% relative to the New York group, reducing the anticipated number of deaths to 63.5 or 3.42% per annum.

Overall Assessment of Exercise

After allowance for the proportion of patients with a high serum cholesterol, hypertension, and residual abnormalities of the resting electrocardiogram, the experience of the exercised group is 39% of expectation (35/89). Over 70% of our patients were under the age of 55, as compared to 54% in the N.Y.H.I.P. study. If additional and very liberal allowances are made for this factor as well as for the lower incidence of diabetes, the observed mortality becomes 55% of the predicted figure (35/63.5). Mortality in the N.Y.H.I.P. series is suff-

iciently similar to other North American experience that it might be considered representative of a very large sedentary post-coronary population; on this basis, the difference between the predicted fatalities (63.5 cases) and actual experience would be very significant ($P < 0.001$). If one assumes the 63.5 deaths apply only to a sample of 700 control patients the difference from the exercised population of 610 men still remains quite significant ($\chi^2 = 10.1$, $0.01 > P > 0.001$). Unfortunately, a "controlled" experiment to prove such a 45% reduction in mortality is a formidably expensive undertaking (Rechnitzer et al, 1975). Indeed, in one randomised trial it has already been shown that a reduction in mortality to 66% of the control series for the period 0.6 to 4.0 years is not "statistically significant" (Naughton, 1977).

The present study was not designed to answer the question as to how exercise might exert a beneficial effect. Various possible hypotheses have been tabulated by Fox & Skinner (1966). However, one new feature of our work was the demonstration that the benefit of exercise apparently increases with prolongation of the programme. This is logical, since many patients make only tentative attempts at exercise during their first year of rehabilitation, and their maximum oxygen intake continues to increase for several years. It may be that those attempting to obtain a more conventional statistical proof of the effects of exercise should direct their attention to mortality data for the third through the eighth years of rehabilitation, rather than the first 2-3 years, as in many current studies.

Finally, attention must be directed to other aspects of rehabilitation than mortality alone. Provided it is established that exercise is not having an adverse effect on mortality (and it would seem that the results of this study support that contention) then it may be more important to consider the quality rather than the quantity of life. Depression is a major concern following a myocardial infarction (Kavanagh et al, 1975; 1977), and there can be little question that a patient who has rehabilitated himself to the point where he is fully active, is capable of living a more rounded and happier life than an individual who has imposed upon himself the life of a semi-invalid. On this count alone, further investment in exercise programmes for the post-coronary patient would seem well justified.

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Note — It will be noted that in some of the statistics, standard deviations exceed the mean. This has been queried with the authors, who assure us that their figures are correct.

Ed.

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