PAPERS AND ORIGINALS

Specificity of Exercise in Exercise-induced Asthma

K. D. FITCH, A. R. MORTON

British Medical Journal, 1971, 4, 577-581

Summary

Ventilatory function after three types of exercise—running, cycling, and swimming—was studied in 10 control subjects and 40 asthmatic patients. All performed eight minutes of submaximal aerobic exercise during each of the programmes, which were conducted in a randomly selected order. Biotelemetric monitoring of heart rates was used to equate the intensity of the exertion undertaken during the three systems of exercise. No control subject showed any significant variation in ventilatory capacity after exercise, and the responses after the three forms of exercise did not differ.

In asthmatics exercise-induced asthma was observed after 72.5% of running tests, 65% of cycling tests, and 35% of swimming tests. In addition, those patients who developed exercise-induced asthma after swimming were noted to have significantly smaller falls in FEV₁ levels than were recorded after running and cycling. These results were statistically significant ($P < 0.01$).

The unexplained aetiology of increased airways resistance after exercise in asthmatics is discussed. This study indicates that swimming should be recommended in preference to running or cycling as an exercise programme for adults and children with asthma.

Introduction

Published studies on exercise-induced asthma have utilized a variety of types of exercise provocation. These have included ascending and descending stairs (McNeil *et al.*, 1966), running along hospital corridors (Jones and Jones, 1966), treadmill walking at a constant speed and incline (Sly, 1970), and cycling on a bicycle ergometer (Poppius *et al.*, 1970) and on a cyclo-ergometer (Pierson *et al.*, 1969). Only one study (Fisher *et al.*, 1970) has compared different methods of exercise, and the effect of swimming on asthma has not been described.

Human Physical Performance Laboratory, Department of Physical Education, University of Western Australia, Western Australia, 6009

K. D. FITCH, M.B.B.S., M.R.A.C.G.P., Medical Consultant
A. R. MORTON, D.P.E., M.Sc., Ed.D., Senior Lecturer

This is surprising, since swimming has been a favoured exercise prescription of numerous doctors over many years for their patients with asthma, and it is worthy of note that two recent Australian Olympic swimming gold medalists have been asthmatics (A. B. Corrigan, personal communication, 1970).

It therefore seemed important to investigate the response of quantitatively comparable different exercises in a group of adults and children with asthma.

This study compared the effect of three different forms of controlled exercise, at a steady state of aerobic work, on the ventilatory function of subjects suffering from asthma. The exercises were in the form of running on a motor-driven treadmill, riding on a bicycle ergometer, and swimming.

Procedures

A fortuitous sample (Kish, 1965) of 40 subjects (24 male and 16 female) was drawn from hospital outpatient clinics and private practices in Perth, Western Australia. The asthmatic subjects included were aged 10 to 51 years, able to swim, and classified as having asthma by the definition of the American Thoracic Society (1962). A control group of 10 subjects (five males and five females) who had no history of asthma or wheezing was also studied. Their ages ranged from 11 to 39 years.

METHODS OF COLLECTING DATA

Three different types of exercise were utilized in an attempt to determine the exercise specificity in exercise-induced asthma. The order of these three exercise programmes for each subject was randomized to control for any possible conditioning or residual effects and they were administered so that no two programmes were conducted at less than three-day intervals.

Before testing, each subject answered a questionnaire which included information concerning family and personal history, particularly of wheeze, exercise history, and past and current medication.

To determine the influence of exercise on airways obstruction the forced expiratory volume in the first second (FEV₁) and the forced vital capacity (FVC) were recorded on a dry spirometer (Vitalograph). These recordings were made as follows:

(a) two pre-exercise values (six minutes and one minute before exercise), and (b) five post-exercise values (immediately, and

5, 10, 20, and 40 minutes after cessation of exercise). The percentage forced expiratory flow

$$(\text{FEV}_T\% = \frac{\text{FEV}_1}{\text{FVC}} \times 100)$$

was also computed from each recording. All values were corrected to body temperature, pressure, and saturation (B.T.P.S.).

In order to standardize the exercise stress each subject on each programme worked submaximally so that a given steady-state heart rate was attained, and then maintained for at least three minutes, with a total exercise time of eight minutes. The steady-state heart rate was between 80 and 85% of the mean maximum heart rate for the subject's age (Astrand and Christensen, 1964). The heart rates used are indicated in Table 1.

TABLE 1—Variation in Steady-state Heart Rate Target with Age

Age	Work Heart Rate
<20 years	160-170 beats/min.
20-25	155-165 "
26-35	150-160 "
36-45	140-150 "
>45	135-145 "

The exercise programmes were as follows:

Running on a Motorized Treadmill.—The treadmill was capable of speeds up to 13 miles (21 km) per hour and gradients up to 30%. Each subject began at a walking pace of 3½ miles (5.6 km) per hour at zero per cent grade and continued at this loading for one minute. This provided a warm-up and familiarization with the treadmill. The speed and inclination of the treadmill were then adjusted at a rate dependent on the fitness level and the age of the individual so that the required heart rate was attained and then maintained until the termination of the test.

Cycling on a Bicycle Ergometer.—Each subject worked at 150 kilopond meters of work per minute for the first minute to gain familiarity with the equipment and to gain a warm-up period similar to that used on the treadmill. The initial pedal speed was 50 complete pedal cycles per minute. The work load was adjusted by increasing, firstly, the pedalling speed and, secondly, the resistance offered by the ergometer's braking system. The rate of increase was dependent on the fitness level and the age of the individual, and was adjusted so that the required heart rate was achieved and then sustained until the termination of the test. A pilot study had indicated the need for increasing the pedalling rate in preference to resistance, otherwise local fatigue occurred before the required stress was evident on the cardiorespiratory system.

Swimming.—To allow for the poorer swimmers in the sample and to control air and water temperature, an indoor pool 12.5 metres in length and heated to a water temperature of 24°C was used. Each subject was instructed to "warm-up" by swimming slowly using either the breaststroke or sidestroke for the first minute. The subjects then either continued breaststroking or changed to the Australian crawl and swam as continuously as possible, using a minimum push off at each end of the pool. The subject was constantly advised concerning the need to increase or decrease speed or change to a more restful swimming stroke so that the required heart rate was attained and then maintained.

During all exercise programmes the subject was connected to a biotelemetry transmitter by two waterproof electrodes placed on the anterior chest wall in the manner prescribed by Blackburn *et al.* (1967). The electrical activity of the heart was then transmitted to a biotelemetry receiver and from this receiver into a heart rate monitor and an electrocardiograph. The latter was used primarily to ensure the accuracy of the heart rate monitor. The telemetry transmitter was housed in a pouch attached to a 3-in (7.5-cm) wide belt during the cycling and running programmes and in a waterproof plastic container worn on the head during the swimming programme.

Ten millilitres of venous blood was obtained from each subject 30 minutes after cessation of their second exercise programme. The blood was analysed to determine the serum IgE and histaminase levels (to be published). Appropriate bronchodilator agents were available at all exercise sessions.

Results

To allow for variation in age, sex, and physique when comparing the results of each ventilatory function test, all values for all subjects were expressed as a percentage of the pre-exercise score. Therefore, FEV₁, FVC, and FEV_T% refer to the appropriate measure expressed as a percentage of the corresponding pre-exercise value. Table II indicates the post-exercise mean lung volumes expressed as a percentage of the pre-exercise value.

TABLE II—Mean Dynamic Lung Volumes after Exercise and Stated as a Percentage of the Pre-exercise Value

Exercise	Measurement	Post-Exercise				
		Immediate-ly After	5 min	10 min	20 min	40 min
Asthmatics						
Swimming	FEV ₁	106.18	80.60	82.12	86.02	92.28
	FVC	93.52	84.35	84.52	88.45	93.02
	FEV _T %	110.20	92.30	94.08	93.95	96.28
Cycling	FEV ₁	107.15	71.90	70.75	79.75	90.80
	FVC	99.28	77.82	77.95	86.10	94.85
	FEV _T %	105.05	89.92	88.35	89.65	92.40
Running	FEV ₁	98.38	68.78	66.92	74.35	87.70
	FVC	94.50	77.72	77.92	82.82	92.75
	FEV _T %	101.85	86.50	83.70	86.28	91.52
Normal Subjects						
Swimming	FEV ₁	100.00	98.50	100.10	101.40	101.40
	FVC	96.40	98.50	99.00	99.60	100.10
	FEV _T %	102.00	98.60	99.30	99.90	99.80
Cycling	FEV ₁	101.20	96.30	98.40	97.80	96.00
	FVC	100.50	100.10	101.60	101.00	99.98
	FEV _T %	99.30	94.70	95.80	95.50	94.90
Running	FEV ₁	100.90	97.90	98.10	98.60	97.00
	FVC	98.70	97.70	99.10	98.30	98.20
	FEV _T %	100.60	98.50	97.40	99.00	96.50

Means and variances for each of the three lung function tests (FEV₁, FVC, and FEV_T%) were computed. The significance of the differences between means were tested over different exercises and different time periods by a three-way analysis of variance with a treatment by treatment by subjects design (Lindquist, 1953). When significant main effects were obtained, the simple main effects were tested by the Scheffe method for post hoc comparisons. The above procedures were applied to the data obtained from both the asthmatic and the non-asthmatic subjects.

FEV₁ CHANGES

The mean FEV₁ changes after three different types of exercise are shown in Table II and graphically presented in Fig. 1. In the controls none of the mean FEV₁ differences between exercises, at any time period, was significant.

Table III indicates that there was a significant difference in the fall in the FEV₁ in asthmatic subjects after different types of exercise. Scheffe post hoc comparison results showed that there was a significantly greater reduction in FEV₁ at the 0.01 level after both cycling and running than after swim-

TABLE III—Analysis of Variance Summary Table for FEV₁ Scores of Asthmatic Subjects

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F Ratio
A (exercise)	8,711.56	2	4,355.78	8.05*
B (time)	105,312.62	5	21,062.52	94.82*
C (subjects)	36,283.50	39	930.35	
AB	4,322.56	10	432.26	4.13*
AC	42,199.94	78	541.02	
BC	43,314.56	195	222.13	
ABC	40,857.25	390	104.76	
Total	261,001.75	719		

* Significant at 0.01 level.

FIG. 1—Changes in mean FEV₁ after different types of exercise.

ming. This result was obtained 5, 10, and 20 minutes after the cessation of exercise, while no significant differences were found immediately after or 40 minutes after cessation of exercise. At no time period was there a significant difference between the mean FEV₁ for cycling and the mean FEV₁ for running.

Scheffe post hoc comparisons across the time factor for each exercise were computed following a significant F ratio (Table III). These indicated that the pre-exercise mean FEV₁ was significantly different from the post-exercise mean FEV₁ obtained 5, 10, and 20 minutes after completion of the exercise programme. The mean FEV₁ differences obtained immediately after and 40 minutes after the cessation of exercise were not significantly different from the pre-exercise mean FEV₁.

The data from both the asthmatic and the control groups indicated that in most cases a drop in FEV₁ was not apparent immediately after the exercise. In the asthmatic group the immediate post-exercise FEV₁ was equal to or greater than the pre-exercise value in 65%, 60%, and 50% of the subjects after swimming, cycling, and running respectively. In the non-asthmatic group the immediate post-exercise FEV₁ was equal to or greater than the pre-exercise value in 80% of the subjects following each of the exercises.

The subjects were also classified into various categories of reduced ventilatory function after each type of exercise. A χ^2 test was then applied to determine whether the distribution of the subjects into these various categories differed significantly after different types of exercise. The obtained frequencies, the expected frequencies (shown in parentheses), and the χ^2 value are given in Table IV. This obtained χ^2 was significant at the 0.01 level.

The largest discrepancies between the number of frequencies occurred in the "less than 15% drop" category and in the "greater than 45% drop" category. In both categories the result favoured swimming over cycling or running as an exercise, as swimming produced more subjects with a small reduction

in ventilatory function and fewer subjects with a large reduction in ventilatory function. The distribution of the asthmatic subjects by their ventilatory function response to different exercise is presented graphically in Fig. 2.

No control subject had a drop of more than 15% in FEV₁ after any of the exercise programmes.

FIG. 2—Number of asthmatic subjects showing reduced ventilatory function after different types of exercise (n=40).

FVC CHANGES

The analysis of variance for the FVC scores showed that there was no significant difference in the reduction in FVC in asthmatic subjects after different types of exercise at any of the time periods. The F ratio for the time factor, however, was significant beyond the 0.01 level, and therefore Scheffe post hoc comparisons were computed across the time factor for each exercise. These results showed a significant drop in FVC after each exercise. The maximum drop occurred five minutes after the cessation of exercise and was followed by a gradual return towards the pre-exercise values. There was no significant difference in FVC across either exercise or time for the control subjects.

In the asthmatic group the immediate post-exercise FVC was equal to or greater than the pre-exercise value in only 12.5%, 27.5%, and 17.5% of the subjects after swimming, cycling, and running, respectively. In the control group the immediate post-exercise FVC was equal to or greater than the pre-exercise value in 40%, 70%, and 60% of the subjects after swimming, cycling, and running respectively.

FEV_T%

The asthmatic subjects showed a significant difference in FEV_T% with different exercises immediately and 10 and 20 minutes after cessation of the exercise. Immediately after all exercise there was an increase in mean FEV_T% followed by a drop. The reduction in FEV_T% reached its maximum five minutes after swimming and then started to return towards the pre-exercise value, while after cycling and running the maximum drop occurred 10 minutes after cessation of the exercise.

Analysis of variance for the control subjects indicated that there was no significant difference in FEV_T% between exercises but that all exercises produced significant differences over time. With the application of the Scheffe test, however, the only difference which was significant was between the pre-exercise value and the value obtained five minutes after the cessation of the cycling exercise.

As with the FEV₁ results, the data from both the asthmatics and non-asthmatics showed that in most cases a drop in FEV_T% was not apparent immediately after exercise. In the asthmatic group the immediate post-exercise FEV_T%

TABLE IV—Differences between Distributions of the Percentage Drop in FEV₁ after Different Types of Exercise in 40 Asthmatics

Percentage Drop in FEV ₁	Swimming Frequencies*	Cycling Frequencies*	Running Frequencies*	Total
<15 ..	17 (8)	3 (8)	4 (8)	24
15-24 ..	9 (9)	11 (9)	7 (9)	27
25-34 ..	3 (7)	10 (7)	8 (7)	21
35-44 ..	5 (6.67)	5 (6.67)	10 (6.67)	20
45-54 ..	6 (6.67)	7 (6.67)	7 (6.67)	20
>54 ..	0 (2.67)	4 (2.67)	4 (2.67)	8
Total ..	40	40	40	120

Obtained $\chi^2=26.444$, significant at 0.01 level, D.F. = (6-1) (3-1) = 10.

* Expected frequencies are shown in parentheses

was equal to or greater than the pre-exercise value in 80%, 72.5%, and 67.5% of the subjects after swimming, cycling, and running respectively. In the non-asthmatic group the immediate post-exercise FEV_T% was equal to or greater than the pre-exercise value in 90%, 70%, and 70% of the subjects after swimming, cycling, and running respectively.

All subjects, control and asthmatic, completed each exercise test at the first attempt. The restriction of exertion to age-adjusted submaximal levels controlled by biotelemetric monitoring was considered the principal reason, though the excellent motivation displayed by all test subjects was a significant factor. None developed clinical bronchoconstriction or wheeze during the performance of any exercise, a fact that was confirmed by spirometric estimation immediately the test was completed. In 60 (50%) of the 120 tests performed on asthmatics the initial post-exercise FEV₁ reading was the highest recorded for that subject on the day of that particular test item.

Discussion

CONTROL SUBJECTS

Analysis of data confirmed previously published findings (Jones and Jones, 1966; Kjellman, 1969; Pierson *et al.*, 1969) that normal subjects do not develop post-exercise bronchoconstriction. No control subject recorded any significant increase in airways obstruction (assessed as at least 15% reduction in pre-exercise FEV₁ values) after any test. No differences were observed between the results obtained after the three types of exercise undertaken.

ASTHMATIC SUBJECTS

In 39 of the 40 asthmatics (97.5%) the post-exercise decrease in FEV₁ values was 15% or greater after one or more exercise tests. Poppius *et al.* (1970) defined exercise-induced asthma as a fall of at least 25% of the pre-exercise value. In the present study 34 subjects (85%) developed exercise-induced asthma after at least one of the test procedures. This may be compared with 100% reported by McNeil *et al.* (1966), 90% by Jones *et al.* (1962), 44% by Pierson *et al.* (1969), 42% by Poppius *et al.* (1970), and 25% by Kjellman (1969) and Sly (1970).

The one subject who did not show any significant fall in FEV₁ or FVC on any occasion was a 29-year-old male teacher, a former middle-distance athlete of national standard who continued to compete at athletic meetings.

The typical pattern of response was the reduction of ventilatory indices beginning five minutes after exercise. Maximal falls were recorded 10 minutes after exercise and returned to approximate pre-exercise values at the last reading (Fig. 1). Overt wheeze was very evident in many subjects. No subject, however, required bronchodilator therapy after any test, even though severe reductions were closely observed in some patients—for example, FEV₁ 650 ml and FVC 930 ml in a 33-year-old woman 10 minutes after a cycling test, predicted values being FEV₁ 2.93 l. and FVC 3.41 l.

Statistical analysis of results obtained after the different types of exercise disclosed interesting comparisons. No significant difference was noted in the values measured after treadmill running and cycling on the ergometer. Reductions in FEV₁ values of 15% or greater were recorded after 92.5% of cycling tests compared with 90% after running, the analogous figures for 25% reduction or greater in FEV₁ being 65% cycling and 72.5% running. Previous workers (Jones *et al.*, 1963; Fisher *et al.*, 1970) have observed that less satisfactory results were obtained with the bicycle ergometer. Variable responses to this apparatus may have been the consequence of slow pedal speeds with heavy resistance causing muscle fatigue or of failure to monitor the cardiac rate.

Analysis of the results of spirometry after swimming showed distinct differences from those recorded on the same patients after running and cycling. Not only was the proportion of

patients with 25% or more reduction in FEV₁ significantly less (35%; $P < 0.01$) but less severe airways obstruction was noted in those who did react with bronchoconstriction. Explanation of this lessened effect on bronchial lability after swimming is difficult. Selection of subjects was not made because of superior swimming ability, and in fact only two subjects swam regularly for most of the year. The majority of patients were infrequent swimmers, often, they stated, because of their asthma. The distances achieved in eight minutes (125-400 metres) varied markedly according to their swimming ability, the stroke used, and the age and fitness of the subjects. Conventional crawl stroke with side breathing was performed by only 15% of subjects, breaststroke being preferred by 60%, while the remaining 25% of the swimmers used a variety of styles and strokes.

DRUG THERAPY

On instruction, as many patients as possible omitted their usual drug therapy on each test day. Of the eight patients in whom it was considered inadvisable to cease medication six were taking disodium cromoglycate with or without concomitant bronchodilators and two took only bronchodilator agents. Such medication was kept constant for each of the three exercise tests. All but one of these eight subjects responded with a 25% or greater reduction in FEV₁ on one or more occasions. The exception, a 29-year-old man on combined disodium cromoglycate and bronchodilators, displayed consistent levels of 18-22% reduction in FEV₁ after each procedure. It was considered that most, if not all, patients inhaling disodium cromoglycate on test days could not have participated in the series if this drug had been withheld. All were severe asthmatics and had noted greatly enhanced exercise tolerance since beginning disodium cromoglycate.

This study supports the conclusion of Poppius *et al.* (1970) that partial protection from exercise-induced asthma is afforded by the inhalation of disodium cromoglycate. It was noted earlier that the immediate post-exercise FEV₁ was the highest recorded in 50% of all tests conducted on asthmatic subjects and followed each of the three specific exercise forms investigated. This response has been observed by others (Jones *et al.*, 1962; McNeil *et al.*, 1966; Poppius *et al.*, 1970). In the present series simultaneous measurements of FVC were not increased and hence the FEV_T was raised. This may represent a bronchodilator effect of catecholamines released during exercise.

BENEFIT OF EXERCISE

In a recent statement the Committee on Children with Handicaps of the American Academy of Pediatrics (1970) recommended that children with asthma should participate in sport and physical education and that every effort should be made to minimize restrictions. Swimming has often been prescribed by doctors for their patients with asthma and many seem to have gained considerable benefit from this exercise though few data are available. This study confirms that swimming provokes less exercise-induced asthma than either running or cycling and is therefore preferable.

Possible factors operating to reduce the incidence and severity of post-swimming bronchoconstriction include the horizontal position of the exercise and the effects of hydrostatic pressure. Airways resistance, however, was not increased until after the completion of the exercise. It has been considered that the efficient control of respiration during swimming is a likely reason, but in the present series only a small proportion of subjects used the classical breathing techniques taught by swimming coaches. Higher levels of lactic acidemia consequent on exercise involving both arms and legs should tend to increase the reduction in ventilatory capacity after swimming if this factor is important (Ward *et al.*, 1969). The smaller post-

exercise rise in body temperature after swimming than after running or cycling may warrant further investigation.

The mechanism of exercise-induced asthma remains obscure. Hypocapnia (Fisher *et al.*, 1970), release of a humoral substance (McNeil *et al.*, 1966), metabolic acidosis providing release of a bronchoconstrictor agent (Seaton *et al.*, 1969), lactic acidemia causing increased ventilation and hypocapnia (Ward *et al.*, 1969), and hyperventilation reflexly causing bronchoconstriction (Crompton, 1968) have been mentioned by recent authors. It has been suggested (Rebuck and Read, 1968) that the condition may not be a single homogenous entity, and the variable protective effect of anticholinergic and bronchodilator agents tends to confirm this theory. Nevertheless, the highly specific nature of the response, its onset and abatement, its acceptance as a provocative test of labile bronchi in latent asthma (Jones, 1966), and the frequency and consistency with which it can be provoked imply that it is the consequence of specific aetiological factors. Certainly we must agree with Rebuck and Read (1969) that continuous measurement of blood gas tensions, blood analysis, and lung volumes during and after exercise is perhaps the most promising method of solving this fascinating problem.

This study was supported by a grant from the Arnold Yeldham and Mary Raine Medical Research Foundation. We are grateful to Mr. B. Elliott and Mr. T. Manford for technical help, to Mr. N. Stocker for Figs. 1 and 2; to Mr. N. Stenhouse, Director of the Raine Medical Statistics Unit, University of Western Australia, for help with statistical analysis; and to Mr. Laurie Potter, who generously donated the use of his health studio with heated indoor pool facilities.

Requests for reprints should be addressed to Physical Education Department, University of Western Australia, Nedlands, Western Australia, 6009.

References

- American Academy of Pediatrics (1970). *Pediatrics*, **45**, 150.
 American Thoracic Society (1962). *American Review of Respiratory Diseases*, **85**, 763.
 Astrand, P. O., and Christensen, E. H. (1964). In *Aerobic Work Capacity in Oxygen and the Animal Organism*, ed. F. Dickens, E. Neil, and W. Widdas. New York, Pergamon Press.
 Blackburn, H., *et al.* (1967). In *Physical Activity and the Heart*, ed. M. J. Karvonen, and A. J. Barry. Springfield, Thomas.
 Crompton, G. K. (1968). *Thorax*, **23**, 165.
 Fisher, H. K., Holton, P., Buxton, R. St. J., and Nadel, J. A. (1970). *American Review of Respiratory Diseases*, **101**, 885.
 Jones, R. H. T., and Jones, R. S. (1966). *British Medical Journal*, **2**, 976.
 Jones, R. S. (1966). *British Medical Journal*, **2**, 972.
 Jones, R. S., Buxton, M. H., and Wharton, M. J. (1962). *British Journal of Diseases of the Chest*, **56**, 78.
 Jones, R. S., Wharton, M. J., and Buxton, M. H. (1963). *Archives of Disease in Childhood*, **38**, 539.
 Kish, L. (1965). *Survey Sampling*, p. 19. Chichester, Wiley.
 Kjellman, B. (1969). *Scandinavian Journal of Respiratory Diseases*, **50**, 41.
 Lindquist, E. F. (1953). *Design and Analysis of Experiments in Psychology and Education*, p. 237. Boston, Houghton Mifflin.
 McNeill, R. S., Nairn, J. R., Millar, J. S., and Ingram, C. G. (1966). *Quarterly Journal of Medicine*, **35**, 55.
 Pierson, W. E., Bierman, C. W., and Stamm, S. J. (1969). *Journal of Allergy*, **43**, 136.
 Poppius, H., Muittari, A., Kreis, K.-E., Korhonen, O., and Viljanen, A. (1970). *British Medical Journal*, **4**, 337.
 Rebuck, A. S., and Read, J. (1968). *Lancet*, **2**, 429.
 Seaton, A., Davies, G., Gaziano, D., and Hughes, R. O. (1969). *British Medical Journal*, **3**, 556.
 Sly, R. M. (1970). *Annals of Allergy*, **28**, 1.
 Ward, F. G., Gomes, S., and McNeill, R. S. (1969). *British Medical Journal*, **3**, 176.

Response of HL-A Identical Unrelated Individuals in the Mixed Lymphocyte Culture Test

JILL M. JOHNSTON, HELEN V. BASHIR

British Medical Journal, 1971, **4**, 581-584

Summary

The immunological responsiveness as measured in the mixed lymphocyte culture test has been studied in 13 pairs of HL-A identical unrelated individuals. In all combinations stimulation occurred and it was frequently of a similar magnitude to that observed against non-HL-A identical subjects.

It is postulated that another locus, adjacent to the HL-A locus, is also responsible for the non-stimulation observed between HL-A identical siblings, and that observations made in the related situation should not be transposed to the unrelated situation without some reservation.

Introduction

The pre-eminence of the HL-A system in histocompatibility is now widely accepted and its importance is based on the

results of studies carried out in families. It has been shown that cells from HL-A identical siblings do not react in mixed lymphocyte culture (Amos and Bach, 1968; Bach, 1970) and that renal allografts exchanged between HL-A identical siblings are almost invariably successful (Hors *et al.*, 1970). On the basis of these observations the HL-A system has been adopted as the system on which selection of donors for cadaveric renal transplantation programmes is based. However, very little is known about histoidentity as defined by the HL-A system in the unrelated situation (van Rood and Eijssvoegel, 1970) and this work was undertaken in order to study this aspect, using the mixed lymphocyte culture test to measure true immunological identity between unrelated subjects.

Subjects and Methods

Lymphocytes from normal healthy staff members and from prospective renal allograft recipients were typed for their HL-A antigens by the lymphocyte cytotoxicity test. Computer analyses of the frequencies and associations of the antigens as determined in this laboratory have been carried out (Sharp *et al.*, 1970, 1971). Subjects in whom all four HL-A antigens could be unequivocally identified and whose phenotypes occurred more than once were selected for study in the mixed lymphocyte culture test. The HL-A phenotypes of the 17 subjects in the study are listed in Table I.

Tissue Typing Laboratory, N.S.W. Red Cross Blood Transfusion Service, Sydney, N.S.W. 2000, Australia

JILL M. JOHNSTON, B.Sc., Scientific Officer

HELEN V. BASHIR, D.C.P., M.C.P.A., Medical Officer-in-Charge