produce any toxic signs or electrocardiographic changes. Transient and minor electrocardiographic changes were observed with doses of 2.5 mg (100 mg/kg). Doses above 5 mg (200 mg/kg) were lethal. Striking electrocardiographic abnormalities followed by cessation of respiratory and cardiac activity occurred with 4 to 20 mg (160 to 800 mg/kg) in most animals (Table I). Respirations usually stopped within 4 to 6.5 minutes, and cardiac action usually ceased approximately 18 minutes after intraperitoneal injection with higher doses. Artificial respiration was not effective when respirations had ceased.

The most striking electrocardiographic findings following the intraperitoneal administration of stilbamidine were progressive and varying degrees of sino-auricular, auriculo-ventricular, and intraventricular block, occurring in that order. During the development of sino-auricular block, the cardiac rates slowed from the usual control rate of 600 per minute to as low as 10 per minute (Fig. 1).

Varying degrees of auriculo-ventricular block from 10 to 1 to complete auriculo-ventricular dissociation were noted (Fig. 2). After respirations had ceased and the cardiac rate had slowed materially, intraventricular and possibly bundle-branch block occurred. There was no discordant relationship noted between any of the 3 electrocardiographic leads following lethal doses of stilbamidine. The electrocardiographic changes preceded respiratory cessation by 2 to more than 30 minutes. Anoxia following the respiratory cessation may contribute to the late electrocardiographic changes.

Conclusions. 1. Stilbamidine administered intraperitoneally to mice in doses of 4 to 20 mg (160 to 800 mg/kg) caused cessation of respirations in 4 to 6.5 minutes, accompanied by progressive and varying degrees of sino-auricular, auriculo-ventricular and intraventricular block eventuating in death. No significant ST-T changes occurred.

2. The constancy and reproducibility of the electrocardiogram in the normal mouse indicates that the effect of drugs upon the electrocardiogram may profitably be studied in this animal.

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Relationships of Availability of Oxygen to Physical Fitness in Patients with Cardio-respiratory Diseases.* (17631)

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The concept of physical fitness in either normal subjects or patients with various cardio-respiratory diseases refers to the integrated capacity of the heart, lungs, blood and regulatory mechanisms to meet exertional demands. Fitness is measured by the least variable characteristics of the cardio-respiratory responses to exercise(1). The latter is standardized by walking on a motor-driven treadmill at a fixed velocity; hence the rate of energy expenditure is proportional to the body weight(2). Although this work load is only moderate for normal subjects, it may be

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2. Bruce, R. A., Lovejoy, F. W., Jr., Pearson, R., Yu, P. N. G., Brothers, G. B., and Velasquez, T., *J. Clin. Invest.*, 1949, v28, 1423.

exhaustive for patients with functional impairment due to disease. The physical fitness index equals:

$$\frac{\text{average respiratory efficiency during exercise} \times \text{duration of exercise}^{\ddagger} \times 100}{\text{total heart beats for first 3 minutes of recovery (3)}}$$

Normal values range between 12 and 26, with a mean value of 19 in subjects walking for 10 minutes at 2.60 m.p.h. Consecutive chest lead electrocardiograms show abnormalities of the ST-T waves, corrected QT intervals, and QT/TQ ratios only in patients with disease(4).

Various resting measurements of cardio-respiratory function, such as estimations of the lung volumes, cardiac output, etc. contribute towards the understanding of the pathological physiology in patients with disease. The aim of this report is to compare and assess the relative value of several of these laboratory methods to the performance of activity, as measured by the physical fitness index. For these purposes, an heterogeneous group of patients has been assembled. They varied in age between 7 and 70 years, and in disability from virtually none to total.

Methods. Twenty-nine patients on whom multiple laboratory measurements have been made, and 3 who were studied again under clinically different circumstances resulting from therapy were included in this study. The chief clinical categories of disease represented were: congenital cardiovascular disease 12, acquired heart disease 7, chronic pulmonary disease 9, and miscellaneous diseases affecting cardio-respiratory function (mediastinal tumor, constrictive pericarditis) 4. Resting measurements were made of respiratory gas exchange, blood gas composition, lung volumes (by helium dilution technique(5)), and cardiac output by the direct Fick principle. Treadmill exercise tolerance was evaluated at (level) walking rates of 2.6 m.p.h., and at 1.73 m.p.h. for those patients who were unable to walk at the former pace§. Statistical correlations were made by the product-moment method(6), and scatter graphs of significant relationships are included. The effective alveolar ventilation has been derived from the ratio of

$$\frac{\text{Insp. } O_2\% - \text{Exp. } O_2\%}{\text{Insp. } O_2\% - \text{Ideal Alv. } O_2\%}$$

times the observed minute ventilation volume. The effective alveolar perfusion has been derived from the cardiac output and the difference between the pulmonary venous and the mixed venous oxygen content, assuming at least 95% saturation of the former blood value. The "ideal" alveolar pO_2 has been derived from the arterial pCO_2 and expired air R.Q.(7).

Results. Table I presents the statistical relationships between the physical fitness index of exercise tolerance and various respiratory measurements in 29 patients with disease. Figure 1 shows that the physical fitness score tends to vary inversely with the observed mid-capacity pO_2-mixed arterial gradient and directly with the mean capillary pO_2 of the tissues of the body‖. Despite large co-

‡ To the limits of tolerance, or an arbitrary maximum of 10 minutes.

§ More satisfactory correlations would be demonstrated if all the patients were able to walk at the rate of 2.60 m.p.h., even for a short period of time. Patients with *intermediate* functional capacity may be able to endure exercise for 10 minutes at 1.73 m.p.h., but not able to continue for as long as that at 2.60 m.p.h. The lower fitness score, due to the shortened time, would be significantly different from that obtained for the slower rate. Since 9 of the 12 patients included here did walk 10 minutes at 1.73 m.p.h., some of them might fall within the above category. Unfortunately comparative studies on these particular patients were not made.

‖ The mid-capacity pO_2 is the terminal pO_2 of expired air (at the mid-capacity level of pulmonary capacity. It differs from the Haldane-Priestley alveolar pO_2 in that the reserve volume

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TABLE I.
Relationships of Physical Fitness Index of Exercise Tolerance and Various Resting Physiological Factors in Cardio-Respiratory Diseases.

Factor		Mean ± S.D.	Range	Coefficient of variation, %	Coefficient of correlation*
Observed Mid-capacity pO_2-mixed arterial pO_2 gradient	mm of Hg	43.7 ± 21.1	9-98	48.2	—.634 ± .10
MC pO_2-"Ideal" alveolar pO_2	"	21.3 ± 8.1	2-35	38.0	—.417 ± .14
"Ideal" alveolar pO_2-m. art. pO_2	"	26.8 ± 20.6	(—11)-57	76.9	—.421 ± .14
Inspired pO_2-"Ideal" alveolar pO_2	"	50.5 ± 8.5	33-67	16.8	—.109 ± .11
Mixed Arterial pO_2	"	71.8 ± 17.1	37-102	23.8	+.641 ± .10
Mean Capillary pO_2	"	46.5 ± 9.6	26-61	20.6	+.675 ± .09
Mixed Venous pO_2	"	34.6 ± 6.6	18-49	19.1	+.542 ± .12
A — V pO_2 difference	"	37.0 ± 15.3	9-83	41.4	+.540 ± .13
A — V O_2 content diff.	ml/l	50.2 ± 18.0	14-94	35.8	—.013 ± .18
% Mid-capacity Vol.		50.3 ± 13.5	32-83	26.8	—.262 ± .17
% Residual Air Vol.		35.9 ± 10.4	20-71	29.0	+.101 ± .18
% Effective Alveolar Ventilation		47.8 ± 12.2	30-89	25.5	+.325 ± .15
% Effective Alveolar Perfusion		81.5 ± 14.4	49-97	17.7	+.353 ± .15
Cardiac Index	l/M²/min.	3.29 ± 1.09	1.5-6.4	33.1	+.086 ± .17
Oxygen Index		4.03 ± 2.1	1.5-9.8	52.1	+.087 ± .17

* Standard Error of Coefficient of Correlation equals $\frac{1 - r^2}{\sqrt{N - 1}}$

efficients of variation in the several measurements obtained from this heterogeneous group of patients, moderately significant correlations were obtained for each of these relationships. Less significant, or even doubtful correlations, were obtained for the relations of fitness for exercise to the subdivisions of the observed oxygen gradient. For example the "ideal" alveolar pO_2-mixed arterial pO_2 gradient showed a poor correlation ($r = -0.421 \pm .143$). Somewhat more significant correlations were obtained between the fitness score of exercise tolerance and various pO_2 values, especially the arterial blood, but also mixed venous blood, and even the arterio-venous pO_2 difference in mm of mercury. In contrast to the last finding, there was no relationship between fitness and the arterio-venous oxygen difference expressed as contents in volumes percent.

Although the percentage residual air volume, or functional residual air volume (mid-capacity volume), effective alveolar ventilation, effective alveolar perfusion, cardiac index (cardiac output per square meter of body surface area), or oxygen index of supply to demand (arterial oxygen content divided by A – V oxygen difference(9)), commonly deviate from the normal values in patients with cardio-respiratory diseases, none of these *resting* measurements correlated significantly with exercise tolerance¶ (Table I).

It was noteworthy that both the observed mid-capacity pO_2 to mixed arterial pO_2 gradient, and the mean tissue capillary pO_2,

is not forcibly expired, and it represents the terminal mixture of air from both functioning and non-functioning alveoli (alveoli ventilated but not adequately perfused). The mixed arterial pO_2 is that obtained from systemic arterial blood. It is the mixture of pulmonary venous blood and variable amounts of venous admixture of unoxygenated blood (including alveoli perfused but not adequately ventilated). The mean capillary pO_2 is derived from Barcroft's formula(8), and equals the mixed venous $pO_2 + \frac{\text{A — V } pO_2 \text{ difference}}{3}$. The mixed venous pO_2 has been estimated from the observed oxygen saturation and carbon dioxide content values of the blood from the right heart, and the oxygen dissociation curve for blood.

8. Barcroft, J., *Factors in the Architecture of Physiological Function*, Macmillan Co., Cambridge, England, 1934, 219.

9. Little, J. M., *Am. J. Med.*, 1949, v7, 207.

¶ This need not, of course, apply to *homogeneous* groups of patients, such as predominantly emphysema, or congestive heart failure.

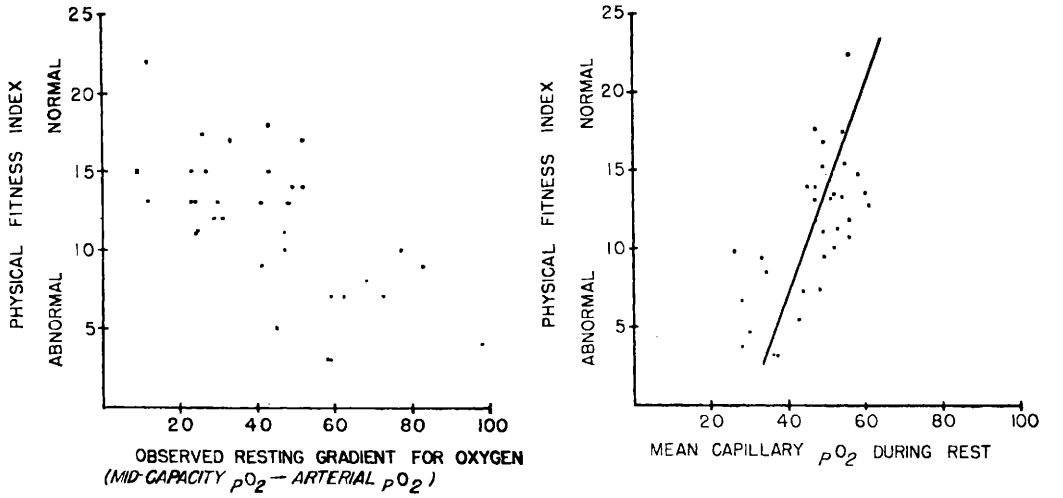

FIG. 1.

Relationship of physical fitness indices of patients with various cardio-respiratory diseases to the observed mid-capacity pO_2 to mixed arterial pO_2 resting gradient, and the calculated mean tissue capillary pO_2 during rest.

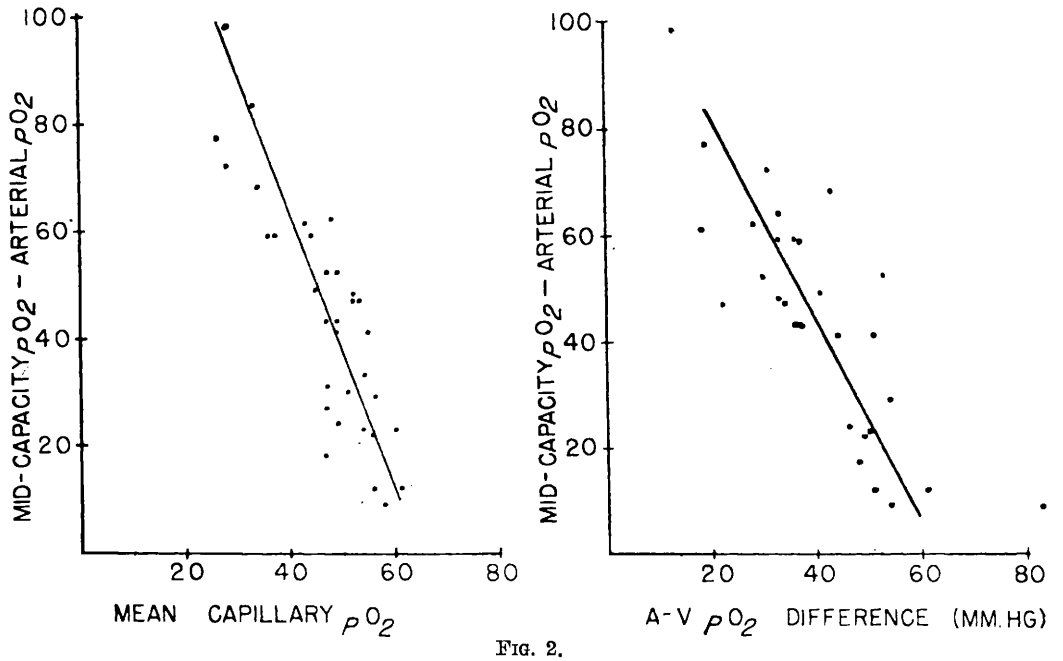

FIG. 2.

Relationship of the observed resting mid-capacity pO_2 to mixed arterial pO_2 gradient (of the same patients) to the calculated mean tissue capillary pO_2, and the arterio-venous pO_2 difference during rest.

which exhibited moderately significant relationships to fitness for exercise, were definitely related to each other (Fig. 2). As the observed oxygen gradient widened, the capillary pO_2 diminished ($r = -0.881 \pm .039$). Furthermore there was a significant relationship between the observed oxygen gradient and the A – V pO_2 difference

($r = -0.801 \pm .067$).

The latter relationship is largely dependent upon the oxygen dissociation curve.

Comments. Assuming that the physical fit-

ness index is generally a satisfactory measure of clinical exercise tolerance, one then has a quantitative measure which may be compared with other laboratory data. Such comparisons have been made on an heterogeneous group of patients in order to test the relationships under unfavorable circumstances. If physiological relationships can be demonstrated, they should be applicable to various types of cardio-respiratory pathology. Three such relationships, of moderate significance, have been demonstrated by these analyses. One is that exercise tolerance varies inversely with the magnitude of the resting observed gradient of the lungs (mid-capacity pO_2 - mixed arterial pO_2). The others are that exercise tolerance varies directly with the estimated mean tissue capillary pO_2 derived from Barcroft's formula and the arterial pO_2. Furthermore, the observed gradient and the mean capillary pO_2 are closely related to each other in an inverse manner. The observed gradient also varies inversely with the A – V pO_2 difference (in relation to the oxygen dissociation curve for blood). Hence exercise tolerance is dependent upon the availability of oxygen to the tissues. Possibly correlations of higher significance would be derived if suitable measurements were made serially during the performance of exercise. Although the recognition of hypoxemia during rest suggests reduced tolerance for exertion, the best measure of this loss of reserve is the determination of exercise tolerance itself, because there is no assurance that the hypoxemia evident at rest will not be increased by exertion. Inasmuch as oxygen is neither absorbed nor distributed unless the heart is circulating the blood, the ultimate limiting factors of exercise tolerance are circulatory in nature. Finally many of the factors which may influence the magnitude of the observed oxygen gradient in patients with cardio-respiratory diseases may fail to exhibit, from resting measurements, adequate predictions of exercise tolerance, or working capacity.

Summary. Significant correlations were obtained in patients with diverse cardio-respiratory diseases, and varying disability, between the oxygen gradient of the lungs, the oxygen tension of the peripheral tissues during rest, and the physical fitness index of exercise tolerance. Working capacity is proportional to the availability of oxygen to the tissues, and the limiting factor is circulatory in nature.

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Aspartic Acid Decarboxylase in Bacteria.* (17632)

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Billen and Lichstein(1) presented evidence for the existence of an aspartic acid decarboxylase in *Rhizobium trifolii*. The present report is an extension of these studies with *Rh. trifolii* and other species of microorganisms.

Methods. The organisms were grown in a medium of the following composition: 1% each of yeast extract and tryptone, 0.6% glucose, 0.5% dipotassium phosphate, and 0.1% *DL*-aspartic acid. Incubation was carried out for 16-18 hours at 30°-37°C depending on the optimum for the organism. Cells were harvested by centrifugation, washed twice with distilled water, and concentration determined in terms of bacterial nitrogen per ml of suspension by measuring turbidity in a Klett-Summerson photoelectric colorimeter and converting into terms of nitrogen content by use of previously standardized graphs. Dried cells were prepared by drying the washed cell suspensions *in vacuo* over Drier-

* Aided in part by RG 1581 of the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

1. Billen, D., and Lichstein, H. C., *J. Bact.*, 1949, v58, 215.