with the physical fitness index of exercise performance. The vital capacity has been expressed in these terms in order to correct for variations in individuals due to age, sex, and height. This relationship to the ability to perform moderate exercise of level walking is not a perfect one, however. Some patients with either acquired or congenital heart disease may have appreciable venous admixture via abnormal channels, or perfusion of inadequately ventilated alveoli, which permits incomplete saturation of the arterial blood with oxygen. Thus these individuals may have diminished exercise tolerance from hypoxemia independent of significant changes in vital capacity. Furthermore, the vital capacity volume may be a poor index of exercise performance in some emphysematous patients who exhibit a nearly normal vital capacity volume, but are unable to expel the air at a normal velocity because of diminished pulmonary elasticity. In such individuals the maximum breathing capacity is reduced and affords a more reliable appraisal of ventilatory performance. In this heterogeneous group of randomly selected patients, it should be noted that the breathing requirement showed a correlation with the fitness index which the mean exercise ventilation volume failed to exhibit.

Although in a previous study the physical fitness index was found to be proportional to the physically dissolved oxygen in the blood(1), we have not been able to demonstrate a direct relationship between the vital capacity and the arterial pO_2. Nevertheless, the simplified measure of working capacity used herein may reveal relationships to some of the physiological factors, which in an integrated fashion, determine the overall capacity for exertion. The interrelations of such factors, however, do not always follow because of the multiplicity of pathological processes which are responsible for functional impairment.

Summary. Simultaneous analyses of various ventilatory measurements in 44 randomly selected patients with cardio-respiratory diseases have been assembled. A significant relationship was found between the physical fitness index and the percentage ratio of the observed to predicted vital capacity. The limitations of this relationship, as well as other relationships of physical fitness score to various ventilatory measurements, are discussed.

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Cardiovascular Changes Induced by Rapid Expansion of the Extracellular Fluid. (17921)

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It has been shown(1) that marked alterations in glomerular filtration rate and renal blood flow follow the expansion of extracellular fluid which occurs when large volumes of a modified Locke's solution are infused intravenously in dogs. In order to assess the role of general cardiovascular changes in this response we have examined vascular pressures and volume during and after such infusions.

Methods. Two series of observations were made on each of 4 trained, unanesthetized female dogs weighing 12 to 15 kg. In 5 experiments 1100 cc, and in 3 experiments 1600 cc, of a modified Locke's solution* were

1. Wesson, L. G., Anslow, W. P., Jr., Raisz, L. G., Bolomey, A. A., and Ladd, M., *Am. J. Physiol.*, in press.

* The solution contains 153 mEq/l of sodium, 134 mEq/l of chloride, 27 mEq/l of bicarbonate, 4 mEq/l of potassium, 4 mEq/l of calcium, and 100 mg/100 cc of glucose.

infused at rates varying between 140 and 220 cc/min. Femoral arterial pressure was measured by a mercury manometer. Venous pressure was measured by the method of Birch and Sodeman(2) with a plastic catheter of small diameter inserted in the jugular vein except in one experiment where the saphenous route was employed. The catheter was of such a length that the tip lay in the great veins or right auricle. The reference point for venous pressure was taken as a point mid-way between the sternal angle and the surface of the back between the spines of the scapula. Plasma protein concentration was determined by the copper sulfate specific gravity method(3).

Results. Venous pressure rose from control values of 3.5 to 8.0 cm of water to peak values of 13 to 38 cm, 3.5 to 8 minutes after the infusion was begun and always before it had been completed. When 1600 cc were given the peak value was higher than when 1100 cc were infused.† Regardless of the height attained, venous pressure decreased rapidly after the peak and attained stable values within 13 to 25 minutes after completing the infusion. In 6 experiments the pressure decreased to or below the control level. In 2 experiments pressure stabilized at values 4.5 and 5 cm above control values, the absolute levels remaining below 8 cm of water.

Mean arterial pressure increased from control values of 90 to 120 mm of mercury to 115 to 155 mm, the average increase being 30 mm. The pressure decreased from this peak to within 10 mm above or below the control within 30 minutes in all but 2 experiments. In one of these the pressure showed a progressive increase from 85 to 130 mm in 2 hours. In the second the pressure remained elevated at a level intermediate between the peak and the control values.

The plasma protein concentration reached its minimal value of 46 to 61% of the control immediately after completing the infusion (no values were recorded during the infusion). This circumstance corresponds to an expansion of plasma volume by 64 to 117%. The hematocrit at this time had decreased to 51 to 73% of the control value. The disproportion between the changes in protein concentration and hematocrit reflects the fact that isotonic electrolyte solutions increase the plasma volume without changing red cell volume. After 70 minutes the plasma protein concentration had returned to 82 to 87% of the control (corresponding to plasma volume expansion of 15 to 20%), and hematocrit to 90 to 107% of the control. No changes were observed in the next 50 minutes, after which time observations were discontinued.

The heart rate usually increased from control levels of less than 100 to 130-150 beats per minute during the infusion and decreased rapidly thereafter. The animals appeared to tolerate the infusion well. There was no evidence of respiratory or circulatory distress. The changes in urine flow were similar to those described elsewhere(1).

Discussion. Infusion of isotonic solutions in the dog at a rate of 200 cc/min is rapidly accommodated by the circulation. Landis, Brown, Fauteux and Wise(4) inferred that saline could escape from the vascular compartment at rates of 4.5 to 6.0 cc/kg per min., since an infusion at this rate was necessary to maintain a constant elevation of venous pressure. Estimating blood volumes as 8% of body weight in the experiments reported here it can be calculated from changes in the plasma protein concentration that fluid escaped from the vascular compartment at rates

2. Birch, G. E., and Sodeman, W. A., *J. Clin. Invest.*, 1937, v16, 845.

3. Phillips, R. A., Van Slyke, D. D., Hamilton, P. B., Dole, V. P., Emerson, K., Jr., and Archibald, R. M., *J. Biol. Chem.*, 1950, v183, 305.

† The lowest peak occurred in the one experiment where venous pressure was measured from the saphenous vein. This circumstance raises the question as to whether the peak pressures measured from the jugular vein in these experiments represent generalized systemic changes. Since the infusion was given under pressure through the contralateral jugular vein it is possible that local reflections of the infusion pressure at the tip of the catheter from which venous pressure was recorded were responsible for the high peaks obtained via the jugular route.

4. Landis, E. M., Brown, E., Fauteux, M., and Wise, C., *J. Clin. Invest.*, 1946, v25, 237.

as high as 55 cc per minute in a 13 kg dog. This value is comparable to that reported by Landis and his co-workers.

The increases in filtration rate and renal plasma flow which follow such infusions as we have studied do not attain their maximal values until an hour or more after the termination of the infusion(1). Slow infusions do not increase the venous or arterial pressure, and the increments induced by rapid infusions have generally disappeared within 30 minutes after the end of the infusion. We conclude, therefore, that except for the early abrupt increase in filtration rate, which may in part be related to increased arterial pressure and hemodilution, the changes induced in renal function by such infusions are not related to changes in venous or arterial pressure, increased plasma or blood volume or protein dilution.

Summary. The intravenous infusion of 1100 to 1600 cc of a modified Locke's solution at rates of 140 to 220 cc/min. in dogs causes only a transient increase in venous and arterial pressure and pulse rate. These values usually return to control levels within half an hour. Plasma and blood volume as measured by changes in plasma protein concentration and hematocrit are increased markedly at first, but return to within 20% of control values 70 minutes after the infusion.

These systemic changes do not coincide in time with the increase in filtration rate and renal plasma flow induced by such infusions, and it is concluded that the changes in renal function cannot be attributed to them.

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On the Mechanism of Action of Aminopterin.* (17922)

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In studies on the metabolism of folic acid and its derivatives, it was observed that rat liver slices form from pteroylglutamic acid (PGA) a substance or substances utilized for growth by *Leuconostoc citrovorum* 8081(1). The existence of a factor of unknown chemical nature, referred to as citrovorum factor (CF), was first described by Sauberlich and Baumann(2) and its relation to folic acid was indicated by Sauberlich(3). Using the liver slice system, conditions influencing the synthesis of CF were studied(1), and it was found that the presence of certain reducing agents, particularly ascorbic acid, stimulated the formation of CF, both from synthetic PGA and from compounds present in normal rat liver. It was suggested that a reductive step may be involved in the enzymatic synthesis of CF. The 4-amino analogue of PGA, aminopterin, is one of the most potent inhibitors of the functions of PGA. However, in contrast to the reversible antagonism that often exists between metabolites and structural analogues that interfere with their biological action, aminopterin proved to be reversed very inefficiently by PGA. Thus, Franklin, *et al.*(4) reported that even high levels of PGA were unable to counteract the toxic effects in mice caused by feeding aminopterin at a level of 1 mg per kg of diet.

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1. Nichol, C. A., and Welch, A. D., PROC. SOC. EXP. BIOL. AND MED., 1950, v74, 52.

2. Sauberlich, H. E., and Baumann, C. A., *J. Biol. Chem.*, 1948, v176, 165.

3. Sauberlich, H. E., *J. Biol. Chem.*, 1949, v181, 467.

4. Franklin, A. L., Stokstad, E. L. R., and Jukes, T. H., PROC. SOC. EXP. BIOL. AND MED., 1948, v67, 398.