scended testes than in scrotal testes (*4, 5*), and two varieties of ovarian tumor, the tubular type of arrhenoblastoma and the dysgerminoma, are often seen in association with the pseudohermaphrodite state (*6*). It has also been reported that the testes in which tumors develop may exhibit aberrant differentiation in the form of tubules lined by immature Sertoli cells (*7*).

A study was undertaken of the nuclear sex of patients in whom testicular tumors had developed. Seventy-five cases were taken from the testicular tumor registry at the Armed Forces Institute of Pathology; the criteria of selection were that normal testicular tissue must be present in the sections and that preoperative radiation therapy must not have been employed. Most of the patients were members of the U.S. Armed Forces and were accepted both at their induction physical examination and by their fellows as males; only two showed cryptorchidism. All varieties of germinal testicular tumors were represented in the group; 29 were seminomas, 14 were embryonal carcinomas, 25 were teratocarcinomas, and 7 were of mixed pattern. This distribution of histological types corresponds to that of the much larger series of Dixon and Moore (*4*).

Sections were stained by hematoxylin and eosin and by the Feulgen technique. In each instance Leydig cells, Sertoli, cells, and the cells of the supporting connective tissue were examined. In all cases the nuclear sex was diagnosed as male. In the 25 teratomas, sexing of the tumor was carried out, and 7 contained female elements. These findings indicate that, in the genesis of testicular tumors, little part is played by gross error of sexual differentiation, and that the "crossed sex" teratomas cannot be explained by the thesis that "female" tumors arise in "female" patients.

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17 July 1958

Effects of Magnesium and Tetraethylammonium Chloride on the Hypothermic Heart

Abstract. Ventricular fibrillation was induced by the injection of magnesium chloride in isolated canine hearts as well as in intact animals. Ventricular magnesium tolerance was greatly reduced during hypothermia. Defibrillation was achieved by intracoronary injection of tetraethylammonium chloride and electrical shock, even at temperatures as low as 21°C, where it could not be achieved by other means.

Great advances in cardiac surgery have been achieved by the use of induced hypothermia. However, there remains the hazard of irreversible ventricular fibrillation at low temperatures.

In a series of experiments (*1*) on myocardial excitability in this laboratory, where both a nonfailing isolated canine heart preparation and intact animals were used (*2*), both at normothermic and hypothermic levels, it was found that magnesium chloride (but not sodium or potassium chloride) in amounts of 1 to 2 milliequivalents injected rapidly into the coronary system invariably produced ventricular fibrillation. The fibrillation threshold to magnesium was greatly reduced during hypothermia.

In a recent publication by Stovner (*3*) it was shown that a block at the neuromuscular junction produced by an excess of magnesium chloride was released by tetraethylammonium chloride and that the magnesium-induced block was temperature-dependent. This led us to examine the effects of tetraethylammonium chloride on normothermic and hypothermic hearts, with special reference to its effect on ventricular fibrillation. In 22 experiments involving 20 dogs, which included isolated heart experiments as well as single, intact animal experiments, it was found that tetraethylammonium chloride invariably allowed electrical defibrillation at temperatures as low as 21°C, and that defibrillation was achieved with great ease, whereas, without the use of tetraethylammonium chloride, defibrillation could not be achieved. Furthermore, the minimum amount of magnesium required to induce fibrillation was more than doubled after the use of tetraethylammonium chloride under these conditions.

The tetraethylammonium chloride dosages introduced into the coronary system were from 1 to 2 mg/kg of body weight. This dose is small enough to avoid those side effects, such as hypotension and gross electrocardiographic changes, which have been associated with the clinical parenteral dosage of 10 mg/kg of body weight. Other cardiovascular effects of tetraethylammonium chloride observed included decrease of coronary venous magnesium content and increase of coronary blood flow, as well as a strong positive inotropic action; the last observation confirms previous work by Acheson and Moe (*4*).

Our results seem to suggest an important role for magnesium in the mechanism of ventricular fibrillation during hypothermia. Its effects might be exerted through a slowing of conduction or by interference with the effect of transmitter substances at the membrane level. Its fibrillatory action is apparently directly antagonized by tetraethylammonium chloride. In addition, tetraethylammonium chloride increases myocardial contractility, probably by increasing coronary flow as well as by acting directly on the muscle.

In four human beings undergoing cardiac surgery for correction of congenital or acquired heart defects under artificial hypothermia, electrical defibrillation of the ventricles has been achieved only after introduction of 1 to 2 mg of tetraethylammonium chloride per kilogram of body weight, by coronary perfusion (*5*).

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5. The surgery was performed on these patients under the direction of Dr. John B. Grow, chief of surgery, and Dr. George Wittenstein, senior resident surgeon, National Jewish Hospital.

7 July 1958

Ion-Exchange Equilibria on Single Beads

Abstract. Equilibria on single ion-exchange resin beads show that large differences may exist between beads from the same batch. They may be so large that a significant contribution to deviations from ideality can be due to this heterogeneity effect. Correlation between swelling and equilibrium properties shows that bead-to-bead variations are due to differences in cross-linking.

Ion-exchange equilibria on single beads can be studied by radioactive tracer methods (*1*). Below are given some results for the $Ag^+ - H^+$ system on Dowex 50 X-4 resin. The beads were taken from the 20–50 mesh sieve fraction. The tracer was Ag^{110}, obtained by neutron bombardment of silver foil in

the Brookhaven reactor. The temperature was 23° ± 2°C, and the ionic strength was 0.1*M*.

Besides determination of the equilibrium quotient κ for the reaction

$$Ag^+ + H^+R^- \rightleftarrows Ag^+R^- + H^+ \qquad (1)$$

measurements were made of the volumes of the beads by means of a microscope with a calibrated ocular micrometer.

Figure 1 shows the "equivalental" volumes and equilibrium quotients for three different beads plotted against the mole fraction of silver in the resin. Although the data for a given bead may show a spread as large as 20 percent, the variation from bead to bead is much larger —in fact almost 170 percent in "equivalental" volume and 260 percent in equilibrium quotient. There is also a correlation between the swelling and the equilibrium quotient: the larger the "equivalental" volume, the smaller the equilibrium quotient. This is what is to be expected if the degree of cross-linking is different for different beads, and it is very likely that, to a first approximation, bead-to-bead variations are due to differences in cross-linking.

Thirty-six different beads were studied. Values for the experimentally determined equilibrium quotient centered around 2.5 and 4.7, with a spread from 1.8 to 6.5. This large spread may be an extreme case; however, it should be emphasized that resins may contain beads with widely different cross-linkings. This is not unexpected in view of the variations in swelling properties noted by several workers in the field (*2*).

This heterogeneity effect may be of little practical importance. It is important, however, for an understanding of the ion-exchange process, that it may sometimes be so large that it contributes significantly to deviations from ideal behavior. When different models such as ion-pair formation, specific and nonspecific interactions, and so on, are discussed, the heterogeneity effect must be eliminated. For basic research with ion exchangers it would thus be very helpful if very homogeneous resins could be made available in the future (*3*).

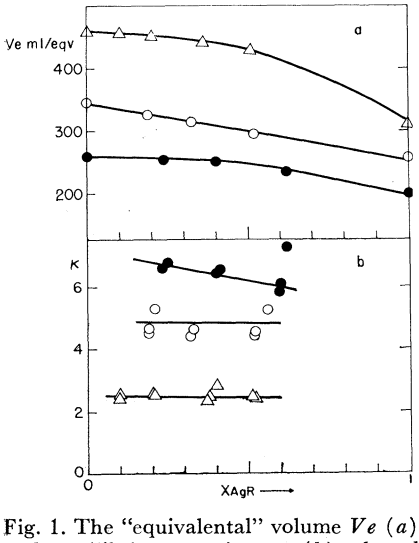

Fig. 1. The "equivalental" volume *Ve* (*a*) and equilibrium quotient κ (*b*) plotted against the mole fraction of silver in resin, X_{AgR}, for three different beads of a batch from a DVB 4 resin. Open circles, bead 1; solid circles, bead 2; triangles, bead 3.

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3. A detailed report on this work is in preparation. The research described in this study was performed under the auspices of the U.S. Atomic Energy Commission and was presented at the meeting of the American Chemical Society held in San Francisco in April 1958. I am grateful to Dr. William Rubinson for help with the English text and to Dr. W. C. Bauman and Dr. R. E. Anderson of the Dow Chemical Company for the resin used in the study. Through the courtesy of the Dow Chemical Company a special batch of DVB 4, as homogeneous as possible, is being synthesized, and it will be interesting to see how homogeneous a resin batch can be.

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23 June 1958

Activation Energy of Ventricular Contraction in Anionically Modified Solutions

Abstract. The activation energy of ventricular contraction and relaxation in chloride and nitrate-Ringer's solution was studied on the driven rat ventricle strip by measurement of the specific contraction and relaxation velocities over a 17°C range of temperature. Nitrate ion produced a small but significant reduction in the activation energy of contraction.

Previous communications from this laboratory (*1*, *2*) have shown that nitrate and thiocyanate ions potentiate the hypodynamic ventricle's response to glucose and *k*-strophanthoside by augmenting the velocity of the effect as well as by increasing the magnitude of the final tension attained. According to previous interpretations, the increase in twitch-tension observed in amphibian skeletal muscles surviving in the presence of "abnormal" anions results from the influence of these anions in prolonging the duration of the active state. On the basis of work appearing from his laboratory it was proposed by Sandow (*3*) that the site of action of these anions was the excitable membrane rather than the contractile elements. Hill and Macpherson (*4*) concurred in this explanation but suggested as one of the alternatives the possibility that NO_3^-, Br^-, and I^- might act on the muscle by reducing the activation energy of the contractile process. As far as we were aware this proposition had not been directly tested, and it was the object of the investigation described in this report (*5*) to evaluate this idea with respect to the contractile velocity of the isolated rat's ventricle.

In the succeeding portions of this report the influence of anions on the activation energies of contraction and relaxation is described. These energies were tested by studying the velocities of contraction and relaxation as a function of temperature. The use of shortening velocity as the mechanical counterpart of the rate of liberation of chemical energy can be justified formally by two successful models of muscular contraction: Hill's (*6*) and Polissar's (*7*). In Hill's equation for muscular shortening

$$v(P + a) = b(P_o - P) \qquad (1)$$

the constant *b*, having the dimensions of velocity (muscle-length × sec^{-1}) increases rapidly with temperature, the Q_{10} being about 2.05 for frog muscle in the range between 0° and 10°C (*6*). The value of *a* (g wt/cm^2 of muscle cross-section) car, according to Hill, be derived from force-velocity as well as from heat-length data. The velocity of contraction in Polissar's (*7*) kinetic model is the mechanical counterpart of the net reaction rate of $L \rightarrow S$ in which *L* and *S* are the long and the short configurations of the contractile elements, respectively. Similarly, the speed of relaxation is an expression of the kinetics of conversion of $S \rightarrow L$. The two reactions are assumed to proceed by different metabolic paths, the initial stages of each process being sufficiently characterized by first-order kinetics.

Strips from the right ventricles of young adult Slonaker-Wistar rats, unselected as to sex, were prepared as described in earlier publications (*8*, *9*). They were mounted on immersible electrodes and maintained in muscle baths having a capacity of 220 ml. The media used were the "chloride" and the "nitrate" reference solutions, the composition of which has been described (*2*); in the presence of 100 percent O_2 as the gas phase, the *p*H of the solutions was 8.3.

The ventricle strips were stimulated at 85 shocks per minute from a constant-current square wave generator (*10*), the contractions being transduced by a mechanoelectrical myograph consisting of a Statham No. 315 G7A (0.15 to 500 ± 0.15 oz) strain gauge. The passive legs of the bridge and the batteries providing the source of the d-c potential were contained in a Statham type CB7 control box which was connected to the gauge