BIOLOGY AND PHARMACOLOGY OF THE LITHIUM ION

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I. INTRODUCTION

During the last hundred years the treatment of various diseases with lithium salts has now and then been advocated. Most of these applications are now considered useless or contra-indicated, but through Cade's discovery of a beneficial effect of lithium salts on certain psychotic states (34), attention has once more become focused on the biological effects of the lithium ion. No comprehensive treatment of the pharmacology of lithium has appeared since Good's paper in 1903 (97), and accordingly a survey of the literature may be warranted.

Only a limited amount of experimental work has been done with lithium as its main subject, and it should be borne in mind that, in a majority of the papers summarized in this review, lithium was only included in the experiments as one of a series of monovalent cations. Consequently, the stray observations on lithium have rarely been followed by a systematic study of the metabolism and effects of this particular ion.

A review of the lithium literature must be a collection of data from a wide field of biological systems. They are arranged here, somewhat arbitrarily, according to the complexity of the system or organism. In the last chapter a few general trends are outlined and discussed.

II. PHYSICAL AND CHEMICAL PROPERTIES

Lithium was discovered in 1818 by Arfwedson (3) in Berzelius' laboratory. It was isolated from the mineral petalite, and its name is derived from the Greek word for stone.

Lithium is the lightest metal known. It has the atomic number 3, the atomic weight 6.940, and its specific gravity is 0.534. There are two stable isotopes, Li^6 and Li^7, and three radioactive ones, Li^5, Li^8, and Li^9, with short half lives (10^{-21} sec, 0.83 sec, and 0.17 sec, respectively). The pure metal never occurs in nature, and in the following the designation "lithium" always refers to lithium ions or lithium salts.

Lithium belongs to the alkali metal group, which also includes sodium, potassium, rubidium, and cesium. The radii of the hydrated ions of these metals decrease with increasing atomic number, Li^+ having the largest and Cs^+ the smallest radius. The order is reversed when one considers the ionic radii in crystals. The smaller size and larger ionizing potential of lithium tends to ally it somewhat with the elements of group II of the periodic system, particularly magnesium. This resemblance is illustrated by the low solubility of its fluoride, carbonate, and phosphate, and the tendency of the chloride to form hydrates (179). Lithium chloride is the most soluble of the alkali chlorides and is strongly hygroscopic. In the quantitative analysis of the alkalies, lithium chloride may be separated from the other alkali metal chlorides by extraction with amyl alcohol (96) or other organic solvents (282). Lithium colors the flame red, and the emission spectrum is dominated by a strong and narrow line at 670.7 mμ; this line is used in the flame photometric determination of lithium, which is now the method of analysis commonly employed.

III. OCCURRENCE IN NATURE

In spite of the usually very low concentrations of lithium in natural materials, it has from an early date been possible to establish its presence with reasonable certainty by means of qualitative spectrography.

Lithium is found in small amounts in several minerals, particularly silicates, and in low concentration in sea water. The water from many mineral wells also contains lithium, and it was earlier believed that the reputed effect of these waters on rheumatoid diseases was related to the—alleged—curative effect of lithium on gout. The lithium content of the mineral waters is usually about 1 mequiv./l or less (318, 329).

It has been possible to detect traces of lithium in numerous lower and higher plants (11, 13, 16, 17, 98, 152, 155, 285 (review), 325), in plankton, molluscs and annelids (82), in milk from several animals (159, 338), in guinea-pig hair and nails (152), in pig teeth and bone (59), in blood and muscles from various animals (12, 41, 56, 57, 98, 105), in horse hemoglobin crystals (58), and in human urine (128, 155, 286, 296), blood (15, 155, 159), bile (128), and lymph (128). Lithium has also been found in minute amounts in numerous human organs, including muscle, liver, spleen, kidney, brain, lung, intestinal wall, skin, teeth, and bone (59, 67, 82, 128, 155, 159, 296). On the other hand, Alexander and associates (2) were unable to find any lithium in human bone.

Qualitative and semiquantitative spectrographic analyses indicate the presence of traces only of lithium in animal organs. It is therefore astonishing that Lundegårdh and Bergstrand (208), by flame photometric analyses of human livers, usually found lithium concentrations around 0.2–0.6 mequiv. lithium per kg wet weight. Quantitative analyses by others have shown a much lower content of lithium in animal organs. Bertrand (12), using a combined chemical and spectrographic method, determined the lithium content of tissues from a large series of animals. He found in invertebrates an average lithium concentration of 0.07 mequiv./kg dry weight (range 0.01–0.83) and in vertebrates (no determinations

on human tissues) an average of 0.017 mequiv. lithium per kg dry weight (range 0.003–0.11). By a later modification of the method (18), he determined the lithium content of blood from the horse and man (14, 15) and found the concentration to be of the order of 0.003–0.009 mequiv./l of blood. The lithium concentration was somewhat higher in horse blood than in human blood; the concentrations in serum and in erythrocytes were about equal. Keilholz (155) analyzed several human organs, including the liver; his results showed a lithium content of about 0.01–0.03 mequiv./kg wet weight with only slight variation from organ to organ.

It is not known whether the traces of lithium naturally present in the organism play any physiological role.

IV. MORPHOGENETIC EFFECTS

Herbst's discovery in 1893 (127) that exposure of developing sea urchin eggs to lithium salts resulted in uniform exogastrulation, paved the way for a large amount of work on the effect of lithium ions on determination and differentiation in animal embryos. The literature on this subject is very extensive, and a review is outside the scope of this paper. Needham (240) and Lehmann (180) have treated the findings in a more general context, and only some of the main observations with a few references will be presented here.

Morphogenetic effects of lithium ions have been observed in representatives of almost the entire animal kingdom, ranging from protozoa to birds. Similar effects have apparently not been seen in mammals, but the lack of data obviously may be due to the technical difficulties involved in such experiments. Bass and associates (8) found that various agents, including lithium chloride, reduced the percentage of deliveries when administered to pregnant mice, but no evidence of a direct embryotoxic effect was obtained.

Lithium treatment has been shown to influence the morphology of ciliates (79), sponges (29), and planarians (30, 276). Sea urchin embryos, besides being the first studied, are also the best studied organisms as regards the influence of lithium ions and a variety of other agents. Among the many contributors to the field (108, 139, 180, 240) the Swedish school (Hörstadius, Runnström, Lindahl, Gustafson, and others) might be singled out for its emphasis on the connection between morphology and metabolism. When applied to the sea urchin embryo at an early stage of development, lithium ions exert a "vegetalizing" effect, *i.e.*, the entoderm is developed at the expense of the ectoderm. The vegetalizing effect of lithium ions is intensified by agents such as cyanide and carbon monoxide, while "animalizing" (ectodermizing) agents such as pyocyanin, thiocyanate ions, iodide ions, and lack of sulphate ions may reverse the vegetalizing action of lithium. An excess of potassium ions also antagonizes the effect of lithium. According to Runnström's "double gradient" hypothesis (279–281), determination of the sea urchin embryo is controlled by the interaction between two antagonistic morphogenetic gradients, which extend along the egg axis and show maximum intensities at the vegetal and animal poles, respectively. The action of these principles may be influenced by a variety of chemical agents, including

lithium ions. It has been suggested (7, 112) that the lithium-sensitive processes regulate mitochondrial development.

Other animal embryos susceptible to the action of lithium ions are those of the annelid worm, Nereis (126), the squid, Loligo (259), and the snail, Limnaea. In the last organism, which has been extensively studied by Raven and collaborators (62, 114, 264), lithium treatment not only leads to exogastrulae and head malformations, but also stimulates the amoeboid movements of the egg. In Limnaea, calcium ions antagonize lithium (62), whereas potassium ions are without such an effect (74). Lithium effects have also been observed in tunicates (46, 77, 242, 262), cyclostomes (263), and teleosts (307, 308).

Amphibian embryos have been studied in great detail (6, 180, 240, 252). In these, lithium acts primarily on the presumptive notochord, which under its action is converted wholly into somite material. An interference by lithium with the normal function of the precordal plate may result in cyclopia (development of one-eyed monsters), a phenomenon which has also been observed in cyclostomes and molluscs. In extreme cases the hypomorphosis extends to all three germ layers, which may remain in a completely undifferentiated state. In these organisms, as in the sea urchin embryos, the action of lithium ions is not unique; other compounds show similar, although less pronounced, effects, and an antagonistic action of various agents is also observed.

Finally, Naz and Rulon (239) found that lithium treatment of hens' eggs gave embryos with partial inhibitions of one or many regions or structures.

The morphologic work on lithium has been accompanied by studies of its metabolic effects, and various authors have sought clues to the morphogenetic effects of lithium in its influence on protoplasmic structure or its effects on oxygen uptake, carbohydrate metabolism, rate of protein synthesis, or combinations of these. A competition between lithium and potassium or calcium has also been considered. Some of the experimental data bearing on these questions are summarized below, but for a more complete survey of the discussion the reader is referred to the reviews cited.

Although several important observations have been made recently, a complete explanation of the phenomena is not yet possible. There is still truth in Needham's statement (240, p. 495) that "the nature of the action of Li^+ . . . remains highly obscure".

V. METABOLIC EFFECTS IN TISSUE PREPARATIONS AND IN LOWER ORGANISMS

Physical state of protoplasm and protoplasmic extracts. Runnström observed in 1928 (277) that lithium treatment of fertilized sea urchin eggs caused "coarsening" and other changes in the structure of the cytoplasm. Similar changes have been observed repeatedly since then, but it is not known whether they are of primary importance in the determination of the embryo. Electron microscope studies and measurements of viscosity and flow birefringence in protoplasmic extracts have revealed an antagonism between the effects of lithium ions (about 0.25 M) and other vegetalizing agents, on the one hand, and animalizing substances with thiocyanate as a typical representative, on the other. This phenom-

enon has been observed in extracts from amphibian and sea urchin embryos and in solutions of myosin, euglobulin b, Szent-Györgyi's structure protein I, nucleohistone, and hyaluronic acid (49, 73, 260, 261, 265, 266). Most of these systems are characterized by a content of large molecules of a fibrous nature or with a tendency to be converted into a fibrous state. The details of the lithium action are unknown, but the antagonism observed between lithium and potassium or calcium with regard to both morphogenesis and certain metabolic processes has led to the suggestion that the lithium ions may displace the potassium or calcium ions from active centers on the molecules.

That inorganic ions, including Li^+, may influence the physical state of colloidal solutions, has been known for a long time. In numerous papers (reviews by Gellhorn (90) and Höber (137)), it has been attempted to correlate these effects with a wide variety of biological functions, including the movement of spermatozoa and cilia, muscle contraction, and muscle and nerve excitability, and Höber, in particular, has stressed the parallelism between the biological "activity" of the inorganic ions and their place in the so-called lyotropic or Hofmeister series. Some of the observations made by this school are reported later in connection with work on spermatozoa, cilia, muscles, etc.; but it must be kept in mind that much of this older work does not lend itself readily to an interpretation that is in accord with modern theories concerning the biological role and function of the inorganic ions. In a praiseworthy attempt to restrict the number of variables, the early investigators often exposed their preparations to solutions of a single salt and neglected important factors such as the presence of "balanced" salt solutions and proper substrates and control of the pH.

The concept of a "lyotropic" series of biological activity of inorganic ions attracted much interest for several decades. But work during the last ten years or so with radioactive isotopes has indicated that in the living organism there is often a qualitative, rather than a quantitative, difference between the biological activity of even closely related ions, *e.g.*, between Na^+ and K^+. The place occupied by Li^+ is discussed later.

Isolated enzymes. While the specific relation between a number of multivalent cations and the activity of certain enzymes has been known for a long time, it has until recently been the general belief that alkali metal ions, due to their weak tendency to form complexes with proteins, were involved only by their contribution to the ionic strength of the medium and were without a more specific influence on enzymes. During recent years, however, several instances have been observed of an obligatory requirement of an enzyme for one of the monovalent cations. It has been found that a number of enzymes are activated by potassium ions, and some of the studies have also been concerned with the effect of lithium ions.

Muscle pyruvic phosphoferase, which catalyzes the reaction: phospho(enol) pyruvate + adenosine diphosphate $\rightleftarrows$ pyruvate + adenosine triphosphate, was shown by Lardy and associates (27, 28, 175) to require, in addition to magnesium ions, the presence of potassium or ammonium ions for maximum activity. These studies were later extended by Kachmar and Boyer (153), who showed that K^+,

NH_4^+, or Rb^+ were indispensable for the enzyme activity. Na^+ was found to possess a real but weak activating capacity, while Li^+ gave little or no activation. Both these ions counteracted K^+, and the inhibition varied linearly with the concentrations of Na^+ and Li^+, the latter ion being the strongest inhibitor. The nature of this inhibition was not subjected to a more detailed study, but an obvious explanation seems to be that the two ions with little or no activating capacity displace the strongly activating potassium ions from the enzyme molecule.

Cohn and Monod (43) purified the enzyme β-galactosidase (lactase) from *Escherichia coli*; this enzyme catalyzes the hydrolysis of lactose and also of the "unnatural" substrate *o*-nitrophenyl-β-D-galactopyranoside. The authors studied the effect of a series of monovalent cations and were able to differentiate between their "affinity" (inverse of the apparent dissociation constant ion-enzyme complex) and their "activance" (activity of the enzyme when saturated by the ion). With lactose as substrate the "affinity" of the ions decreased as follows: Na > K > Cs > Li > Rb > NH_4, while the "activance" showed the series: K > Rb > NH_4 > Cs > Na > Li. Therefore, the affinity and the activating capacity of the ions vary independently. The presence of lithium was actually found to result in slight inhibition, and it could be shown that this inhibition was not due to a denaturation of the enzyme. The authors suggest that the monovalent cations may all have a certain activating capacity; the low enzyme activity observed in the absence of added cations might be due to a low activance of the hydrogen ions present, and the slight lithium inhibition, as compared with the control experiments, might be explained by a still lower activance of this ion.

Happold and Struyvenberg (117) found that, in the presence of pyridoxal phosphate, a dialyzed preparation of tryptophanase from acetone-dried *E. coli* could be re-activated by the addition of ammonium, potassium, or rubidium ions. Sodium and lithium (and magnesium) ions appeared to inhibit the non-activated enzyme slightly; the effect of these ions on the K^+-activated enzyme was not studied.

Yeast aldehyde dehydrogenase, which catalyzes the reaction. acetaldehyde + pyridine nucleotide + $H_2O \rightleftarrows$ acetic acid + reduced pyridine nucleotide, was studied by Black (22). Without additions the enzyme activity was low, but it could be stimulated by potassium, rubidium and, to some extent, ammonium ions. Sodium, cesium, and lithium ions showed little or no activating capacity, and these enzymes inhibited the K^+-activated enzyme, with lithium as the most powerful inhibitor. Apparently the inhibition was not due to a simple competition with K^+, since the optimum activating concentration of this ion was not significantly increased when Li^+ was added.

Stadtman (302) investigated a phosphotransacetylase isolated from *Clostridium kluyveri* (reaction: acetyl phosphate + coenzyme A $\rightleftarrows$ acetylcoenzyme A + inorganic phosphate). This enzyme shows an obligatory requirement for potassium or ammonium salts. Sodium and lithium chloride were not able to activate the enzyme, but inhibited completely the slight activity observed in the absence of added potassium or ammonium. The K^+ or NH_4^+-activated enzyme was also inhibited by these ions, and Na^+ was the strongest inhibitor.

Von Korff (327) found very similar properties for the acetate-activating enzyme isolated from pig or rabbit heart. This enzyme catalyzes the reaction: acetate + adenosine triphosphate + coenzyme A ⇄ acetylcoenzyme A + inorganic pyrophosphate + adenosine monophosphate. It could be shown that the activity of the enzyme was stimulated by potassium, ammonium, and rubidium ions when the acetylcoenzyme A formed in the reaction was trapped either as acethydroxamic acid or as citrate; in the latter case an obligatory requirement for stimulatory ion could be demonstrated. The K^+-activated enzyme was strongly and about equally inhibited by sodium and lithium ions.

Foulks and associates (81) tested the effect of lithium on carbonic anhydrase prepared from human erythrocytes and found no inhibition with lithium concentrations as high as 0.2 M. Mathews and associates (216) found that the hyaluronidase inhibitor of human serum (which is not an enzyme) is strongly activated by magnesium and cobalt ions, while beryllium and lithium ions activate to a small extent.

It may be a coincidence, but it nevertheless seems noteworthy that several of the enzymes mentioned here catalyze processes in which a transfer of an energy-rich bond takes place. Furthermore, one is tempted to assume that the similar—but quantitatively not identical—effects of sodium and lithium ions in these reactions may have some bearing on the transport of lithium in tissues and on the effects of lithium in nerve and muscle preparations.

Homogenates, breis, and tissue slices. Lindahl (190) and Lindahl and Öhman (196) investigated the influence of lithium ions on the methylene blue reduction time in a brei of cytolyzed sea urchin eggs; with a proper choice of substrate, cofactors, *etc.*, Li^+ had an inhibitory action, although not a very strong one. From this observation the authors conclude that lithium interferes with carbohydrate metabolism in these organisms. An inhibitory action of lithium on dehydrogenase activity was also observed by Lallier (169, 170, 171) in a homogenate of *Rana fusca* embryos.

Studies concerning the effect of lithium on tissue slices have given varying results. Kisch (161) found that 0.2 M solutions of a series of alkali metal chlorides inhibited the oxygen uptake of all tissues investigated (brain not included in the experiments), and lithium chloride did not differ in any respect from the other salts. Mudge (238) investigated oxygen uptake and potassium accumulation in rat kidney cortex slices which, after leaching for some hours at room temperature in isotonic sodium chloride, were incubated aerobically in Warburg vessels at 25°C in media of varying composition. When lithium was substituted for sodium in the leaching solution or in the incubation medium, there was a marked inhibition of the potassium uptake into the slices, associated with a 30–40% inhibition of respiration. Taggart and associates (311) observed that *p*-aminohippurate accumulation in rabbit kidney cortex slices was inhibited by the addition of lithium chloride or by substitution of Li^+ for either Na^+ or K^+ in the incubation medium.

The respiration of brain slices was markedly stimulated by the addition to the medium of solid KCl, RbCl, or CsCl to a final concentration of 0.1 M (63).

The stimulation could only be seen when a little Na^+ was also present in the medium, and the phenomenon was specific for brain as opposed to other tissues. Addition of NaCl or LiCl was without any effect on the respiration. In these experiments the media were made hypertonic by the salt addition, and this may possibly explain the somewhat different findings by others. Canzanelli and associates (35), who also worked with brain slices, substituted K^+ for Na^+ in the medium but with maintenance of the isotonicity. In their experiments the oxygen uptake was stimulated by potassium ions, but only up to a potassium concentration of 0.04 M; further addition of K^+ resulted in a depression. When the same procedure was followed for Li^+, the respiration was also first stimulated and later depressed, the optimum lithium concentration being about 0.1 M.

Utter (324), in experiments with brain homogenates, found that sodium ions inhibited anaerobic glycolysis at low concentrations, while potassium and lithium ions did so only at rather high concentrations. Lasnitzki (177) investigated the effect of lithium and potassium on glycolysis in slices of tumor tissue; K^+ had a stimulatory effect, while Li^+ was inert.

In connection with work on the motility of human spermatozoa (see later) MacLeod and associates (210) studied the effect of lithium on the metabolism of rat testicular tissue. Aliquots of about 150 mg testicular tissue were incubated in media containing varying concentrations of lithium chloride in Ringer-glucose. Lithium concentrations which markedly influence human spermatozoa had no detectable effect on respiration and anaerobic glycolysis of the testicular tissue, but a definite stimulation of aerobic glycolytic activity was shown by concentrations as low as 0.01 M, and when the concentration of lithium chloride was increased to 1.00 M, aerobic glycolysis was about three times the control value. On the hypertonic side the lithium ion began to inhibit oxygen consumption, and at high concentrations of lithium respiration was considerably depressed.

Finally, it has been observed that the fatty acid metabolism of liver and kidney slices is dependent on the ionic composition of the medium (91, 92), and the effects of lithium were also investigated. The original papers should be consulted for a detailed account of the rather complex findings.

Isolated frog skin. Under suitable conditions a difference in electrical potential may be recorded across an isolated surviving frog skin, the outside of the skin being negative in relation to the inside. This property of the skin is dependent on an active metabolism; if the skin is poisoned or if its oxygen supply is cut off, the potential difference falls to zero.

It was discovered at an early date that the maintenance of the electrical potential was also influenced by the ionic composition of the fluids bathing the skin. A considerable amount of work has been concerned with the effects of different ions in varying concentrations on the electrical properties of the skin, and it has been established through the work of Ussing and others (182, 198, 321–323) that the maintenance of the electrical potential is due to an active transport of sodium ions from the outside of the skin to the inside.

As early as 1904 Galeotti (84) observed that Li^+ was the only ion, besides Na^+, that, when present in the bathing solution, enabled the isolated skin to maintain

an appreciable potential (50–100 mV), while the substitution of other cations for Na^+ caused a fall of the potential. The reason for the latter observation is, according to recent investigations, that these ions cannot be transported actively by the skin. Later studies (121, 122, 235–237, 312, 313, 316) confirmed the similarity of the effects of lithium and sodium ions on the isolated skin. An interesting difference between the two ions could, however, be demonstrated when the skin potential was recorded continuously or at short time intervals after the addition of the test solution to the anatomical outside of the skin. If the outside solution was lithium chloride, the potential showed rhythmical oscillations, which were described as "quasi-periodic" by the early investigators (312, 313), and it was reported that the application of various narcotic drugs to the skin abolished the oscillations without causing a significant decrease of the potential.

These observations have recently been confirmed and extended by Teorell (316) with modern techniques. He placed the frog skin as a diaphragm in a special chamber, the construction of which permitted an automatic and continuous recording of the electrical potential and the impedance across the skin; 18 c/s A.C. was used for the resistance measurements. When the outside of the skin was exposed to solutions containing 0.020–0.300 M lithium chloride, rhythmical variations of the potential as well as of the electrical conductance could be seen. Usually the rhythm had the character of a slightly damped sinusoidal oscillation lasting for hours; the amplitude of the potential waves was of the order of 5–10 mV, and the conductance variations amounted to $\pm 10\%$. The oscillation frequency was regular and ranged between 0.1 and 1 period per minute. No oscillations were observed when the outside solution was sodium chloride.

In his discussion Teorell advanced the hypothesis that lithium ions may be subject to an active transport like sodium ions, but no direct evidence on this point was at hand. He further suggested that the rhythmical variations of the electrical characteristics induced by lithium ions might be due to a competition between Na^+ and Li^+ for a common transport system.

The direct evidence asked for by Teorell is provided in Zerahn's recent publication on active transport of lithium in the isolated frog skin (340). It had previously been demonstrated (323) that the total current which can be drawn from a short-circuited frog skin comes from active transport of sodium ions; the net sodium flux through the skin, determined with isotopic tracers, is exactly equal to the short-circuit current, and other ions, *e.g.*, K^+ and Cl^-, contribute insignificantly, or not at all, to the current. Zerahn now observed, however, that when part of the sodium in the outside solution was replaced by lithium, the net sodium flux was in all cases lower than the total short-circuit current. The part of the current not accounted for by the sodium transport comprised about the same fraction of the total current as Li^+ did of $Na^+ + Li^+$ in the outside solution. The active nature of the lithium transport was established in other experiments in which it was demonstrated that lithium ions could be transported by the skin against both an electrical and a chemical gradient.

During the transport some lithium was accumulated in the skin, mainly in the epithelial layer (341), and it is noteworthy that the "lithium current"

equalled the sum of the lithium entering the skin and the lithium transported all the way to the inside solution.

Zerahn's experiments show conclusively that lithium ions are transported actively through the frog skin. In the short-circuited skin Na^+ and Li^+ appear to be transported in proportion to their molar concentrations in the outside solution, but preliminary experiments (341) indicate that in a skin which retains its potential, the lithium transport is considerably less efficient than the sodium transport. Lithium appears furthermore to inhibit the active transport of both ions when present in concentrations above a certain level. Accordingly, the lithium ion is only to a certain extent treated by the frog skin as a sodium "isotope".

The gills of goldfish show an active uptake of sodium ions. This uptake was, in experiments reported by Sexton and Meyer (295), not influenced by addition to the sodium bath of potassium and cesium, whereas addition of lithium caused a significant depression of the sodium uptake. Fish in a solution containing lithium but no sodium showed an uptake of lithium. These data indicate that in gills, as in frog skin, lithium may be transported by the mechanism normally responsible for sodium transport.

Lithium ions may also influence the bioelectrical potentials in other tissues, *e.g.*, the gastric wall (227, 228), fish eggs (310), and plants (50, 248), but the parameters of these systems are not sufficiently well known to permit an evaluation of the lithium effect.

Nerve and muscle preparations. According to present-day theories, the bioelectrical phenomena of excitable tissues are closely associated with ionic movements across the cell membrane. Numerous reviews are available of the important experimental and theoretical advances in this field during the last decade (71, 106, 133, 203, 204), and only a very brief survey of the main hypotheses can be given here as a background for the presentation of the—rather few and scattered—data on the effect of lithium on these tissues.

The resting membrane potential of nerves and muscles (outside positive) is related to the asymmetrical distribution of ions between the interior of the cell and the surrounding medium, but the mechanisms involved are not clearly understood. It has been thought that the resting potential might be determined, at least partly, by a Donnan equilibrium in which K^+ and Cl^- played the dominant roles as freely diffusible ions. This assumption was based on experiments in which the external potassium concentration was increased to three times the normal value or more, and under these conditions the above hypothesis appears to hold true. Recent experiments with intra-axonal microinjection of various ions (107) seem, however, to indicate that under ordinary conditions the resting potential is dependent, not on ratios of any one ion species, but on the activity of the metabolically driven "sodium pump", *i.e.*, the active extrusion of sodium ions against the chemical and electrical gradients.

During rest the nerve membrane is readily permeable to potassium ions and only sparingly so to sodium ions. The conditions change radically when activity sets in, *i.e.*, when a propagated impulse (recorded electrically as the action po-

tential) is generated. The sodium permeability increases rapidly due to the operation of the so-called "sodium carrier" mechanism, sodium ions enter the nerve, and the active membrane behaves during the rising phase of the action potential roughly as a sodium electrode, resulting in a reversal of the electrical potential. As the peak of the action potential is reached, the sodium permeability decreases, and an increase of the permeability to potassium ions develops; potassium ions leak out along their electrochemical gradient, and the resting potential is restored. The net result of an impulse is the uptake of a small quantity of sodium and the loss of a small quantity of potassium. Later, during periods of rest, the excess sodium ions are pumped out, and the potassium ions re-enter the axon, *status quo* being thus established.

Experiments have shown that the spike height and the rate of rise of the spike vary linearly with the logarithm of the ratio $Na_{outside}$: Na_{inside}, and this relation is valid whether the ratio is changed by an alteration of the sodium concentration in the medium or in the cell interior.

Overton found in 1902 (249) that when frog muscles were placed in a sodium-free medium, *e.g.*, an isotonic sucrose solution, they gradually lost their ability to contract and to conduct impulses, and these properties re-appeared when the muscles were again placed in a sodium chloride solution. This phenomenon was due solely to the sodium ion, since other nonelectrolytes had the same effect as sucrose, and since other soluble and nontoxic sodium salts were as effective in restoring the muscle excitability as was sodium chloride. The sodium concentration in the medium could be lowered to one tenth of the physiological value before muscle excitability was abolished. Li^+ was the only other cation that was able to maintain, or restore, the excitability, and the limiting concentration was of the same order of magnitude. High concentrations of lithium in the medium eventually caused an irreversible inactivation of the muscles; whereas a concentration of 0.035 M or less apparently did not impair the excitability even after long incubation, 0.050 M lithium chloride caused an irreversible loss of excitability in about twenty-four hours, and 0.100 M solutions did so in a few hours. Overton was unable to abolish the excitability of frog nerves by exposing them to sodium-free media, but he considered the presence of a sodium-containing periaxonal lymph space responsible for this.

Subsequent workers in experiments on skeletal muscle (148, 187, 201, 342) and heart muscle (69, 70, 140, 151, 160, 197, 199, 202, 226) also found that lithium may be substituted for sodium in the medium without loss or with only a small loss of excitability, but that prolonged exposure to strong lithium chloride solutions leads to irreversible changes. When any of the other alkali metal ions or ammonium ions are substituted for the sodium ions, excitability decreases rapidly. Stein and associates (303) recorded the resting and action potentials of frog heart muscle with intracellular electrodes. When lithium chloride was added to the Ringer solution a decrease of the action potential amplitude could be observed, while the resting potential was not affected. Partial substitution of lithium for sodium led to a still more pronounced decrease of the spike height. An antagonism between lithium and potassium could not be demonstrated,

since alterations of the electrical characteristics evoked by high or low potassium concentration were not prevented by the addition of lithium chloride (4–150 mequiv./l) to the perfusate.

Experiments with isolated nerves have given almost identical results. Höber (135) observed that frog nerves retained their ability to conduct impulses for a long time in solutions of sodium or lithium salts and for much shorter periods in ammonium or potassium salt solutions. The influence of monovalent cations on the resting potential was studied by Netter (241) and Höber and Strohe (138) in frog nerves and by Wilbrandt (335) in crab nerves; they all found that sodium and lithium ions affected the resting potential insignificantly, whereas potassium, rubidium, cesium, and ammonium ions lowered it to a varying extent. In agreement with this is Hodgkin's (132) observation that the addition of sodium or lithium to the medium surrounding isolated Carcinus axons caused only an insignificant change in the membrane conductance, while a large increase in conductance was observed after the addition of rubidium, potassium, or cesium.

Hodgkin and Katz (134) studied the effect of sodium ions on the electrical activity of the giant axons of Loligo. They reported that a single experiment with an artificial sea water containing lithium instead of sodium indicated that the actions of these two ions were almost identical; also, experiments with Carcinus axons showed that propagation occurred satisfactorily in a solution containing lithium instead of sodium. Their experiments were of relatively short duration, and they did not observe any blocking effect of lithium. Huxley and Stämpfli (145) had exactly similar experiences with single, myelinated nerve fibers from the frog; if sodium in the Ringer solution was replaced by lithium, the resting potential as well as the overshoot and the rate of rise of the spike all remained essentially unchanged. These experiments were also of short duration (never more than about thirty minutes); no depolarization or conduction block was observed.

Lorente de Nó (203) and Gallego and Lorente de Nó (85) exposed frog nerves with intact sheaths to mixtures of Ringer solution and 0.11 M solutions of various alkali metal chlorides. Rb^+ and K^+ caused a rapid decrease of the demarcation potential; NH_4^+, Cs^+, and Li^+ had similar effects but with considerably slower time courses. In the case of lithium the observations were as follows: At a concentration of 0.011 M lithium ions did not have any measurable effect on the demarcation potential. When the lithium concentration was raised, an initial phase of increased demarcation potential could be seen, followed by a phase of depolarization. The time of onset and the rate of the depolarization depended on the lithium concentration; the depolarization began earlier and its rate was higher when the concentration was increased. The hyperpolarization was 1–5 mV and lasted for about two to three hours, depending on the lithium concentration in the medium. Measurements were discontinued after the test solution had been in contact with the nerve for 700 minutes, at which time the demarcation potential had decreased about 10–15 mV. Whereas the depolarization caused by potassium and rubidium was fully reversible in 0.11 M sodium chloride even after it had become total, the depolarization evoked by lithium ions began to become irrevers-

ible after 500–600 minutes, at a time when the demarcation potential still had a relatively high value.

These observations were extended by Gallego and Lorente de Nó (86) in experiments on frog nerves that had been deprived of sodium ions by being placed in a 0.11 M solution of diethanoldimethylammonium chloride for several hours. This treatment rendered the nerves inexcitable, and restoration of the excitability was now followed at short time intervals by recording the action potential of the impulses that were able to propagate from the central segment of the nerve (surrounded by Ringer solution) into the peripheral segment (surrounded by test solution). At the same time measurements of changes in membrane potential were made. The experiments showed that lithium ions—in contrast to ammonium ions, which were also studied—were able to replace sodium ions and restore to the nerve the ability to conduct impulses. About 10–15 minutes after the nerves had been exposed to 0.11 M lithium chloride, impulses could be recorded from the peripheral segment, and the amplitude of the action potential increased steadily until a maximum was reached 25–30 minutes later. The maximum spike height reached was about 60 % of the control value (spike height in Ringer solution) in A fibers; in C fibers it was practically equal to the controls. After the maximum was reached, the spike height decreased gradually, and about two hours after the beginning of the experiment almost all fibers had once more become inexcitable. The conduction velocity underwent a similar gradual rise and fall.

The membrane potential changes observed in these experiments were similar to those recorded in the earlier publication (85); but it could be noted that in "sodium-free" nerves the initial phase of hyperpolarization was absent, and the depolarization began earlier and ran a more rapid course than in the nerves not previously deprived of sodium ions. The authors considered the possibility that the inexcitability that was eventually produced by lithium might be caused solely by the depolarization. If this were the case, a hyperpolarization created by an externally applied anodal current should have restored the nerve excitability; but experiments showed that nerve fibers which had become inexcitable by long exposure to lithium ions did not respond to the break of the anodal current. This led to the conclusion that the action of the lithium ions must result in specific changes in the properties of the nerve membrane. Furthermore, it was shown by a study of electrotonic potentials that lithium ions affected the so-called L fraction of the membrane potential differently from sodium ions.

Gallego and Lorente de Nó's observations concerning the demarcation potential were confirmed by Lundberg (207) in experiments with sciatic nerves and spinal roots from the bullfrog and by Ramos and Calva (258), who worked with isolated spinal roots from the cat.

In contrast to Gallego and Lorente de Nó but in accordance with Ramos and Calva, Cerf (37–39) found that in a frog nerve partially depolarized by prolonged exposure to isotonic lithium chloride the ability to conduct impulses and the height of the action potential could be restored to a considerable extent by electrotonic hyperpolarization. If nerves from adrenalectomized frogs were

studied, the depolarization caused by lithium was found to be much more rapid and the restoring effect of anodal hyperpolarization much less marked, and the author suggests that adrenalectomy may, in addition to its effects on electrolyte concentrations, give rise to metabolic disturbances in the nerve which render it more susceptible to the toxic action of the lithium ion.

Crescitelli (48) found that in de-sheathed bullfrog nerves the loss of excitability on removal of sodium from the medium took place within a few minutes, and an equally rapid recovery could be observed when the nerves were treated with Ringer solution or with 0.11 M (isotonic) lithium chloride. The rapidity of the changes was in contrast to the findings of Gallego and Lorente de Nó, and the author considered the diffusion barrier presented by the sheath the most likely cause of the difference. Crescitelli found the critical concentration of sodium and lithium, below which conduction failed, to be between 0.007 M and 0.011 M; prolonged exposure to lithium ions led to a depolarization of the nerves.

Grundfest and associates (107) observed that the general effect of intra-axonal injection of a series of cations was to cause a decrease of the spike amplitude, followed by propagation block; the resting potential decreased when the amplitude of the spike became low and block was incipient. The blocking effectiveness of potassium, sodium, and calcium, expressed as reciprocals of the relative amounts needed to cause block, was approximately 1:5:100. Rubidium had the same low effectiveness as potassium; lithium resembled sodium; while barium and magnesium were approximately as effective as calcium. These experiments demonstrate that Li^+ is also closely similar to Na^+ in its effects on the nerve, when applied to the cell interior. But it should be noted that whereas microinjection of sodium caused a marked prolongation of the spike at the injection site, this phenomenon was not seen after injection of lithium.

A discrepancy between the effects of sodium and lithium ions on nerve was observed by Ichioka (146), who measured the threshold and latency at single nodes of Ranvier of isolated toad nerve fibers. When isotonic sodium chloride was substituted for Ringer solution as external medium, a decrease of the threshold and a prolongation of the latency period could be observed. Application of isotonic lithium chloride, on the other hand, led to a slight increase of the threshold and a shortening of the latency period. From these and other observations the author concludes that the action current, the threshold, and the latency are based on separate processes, which are influenced differently by the ionic environment of the nerve fiber.

Lithium ions are not absolutely unique in their ability to replace sodium ions in the processes of excitation and conduction. Lorente de Nó (205) found that small frog nerve fibers continued to conduct impulses when the external sodium had been totally replaced by certain quaternary ammonium ions (R_4N^+). Crescitelli (48), who also worked with frog nerves, was unable to confirm this, and Burke, Katz and Machne (32) found that isolated crustacean axons became inexcitable when the external sodium was totally replaced by quaternary ammonium ions. However, in experiments with crab muscles Fatt and Katz (78) were able to show that not only could various R_4N ions replace sodium without loss of the

electrical activity, but the amplitude, rate of rise, and duration of the action potential became greater after the replacement. According to the latest report from Lorente de Nó's laboratory (175a) guanidinium ions are able to restore excitability in sodium-deficient A fibers from frog nerve.

Some scattered observations on the effect of lithium on nerve and muscle preparations may be listed; in the last chapter the findings summarized in this section are discussed further. Pieces of muscle (89) and brain (115) swell less in solutions of salts of sodium and lithium than in those of the other alkali metal ions. Other papers are concerned with the effect of lithium on the irritability of heart muscle (104, 124), on veratrine contraction in skeletal muscle (224, 225), on smooth muscle (26, 150, 233), and on invertebrate muscle (332).

Metabolic effects in embryos. The peculiar morphogenetic effects of lithium must probably be caused by an interference of this ion with metabolic processes that are responsible for the determination and differentiation of the developing embryo, and several reports have appeared on the influence of lithium on embryonic metabolism. In most of these studies the fertilized sea urchin egg has been chosen as the experimental organism.

Runnström observed in 1929 (278, footnote p. 261) that the oxygen consumption was decreased in lithium-treated sea urchin embryos, and Lindahl and associates have published further studies on this and related phenomena in a series of papers (188–194, 196). Their main observations may be summarized as follows: During the cleavage stages the respiration of the embryo increases exponentially, and it has been shown that the oxygen uptake is composed of two fractions, a constant and a growing one. If lithium is added at the time when respiration begins to increase, the growing fraction is selectively and reversibly inhibited, and the inhibition increases with increasing lithium concentration. If lithium is added at a somewhat later stage, only the further increase of the respiration is checked, while the respiration already established is uninfluenced. The embryos are particularly sensitive to the vegetalizing action of lithium during the period characterized by a steep rise of the respiratory rate, while earlier and later developmental phases are less sensitive to lithium. Addition of excess potassium to the medium counteracts both the morphological effects of lithium and the inhibitory action on the respiration.

These and other observations suggest a close—although perhaps not obligatory (196)—connection between the morphological events during the cleavage stages and that part of the respiration which is inhibited by lithium ions. What metabolic processes this fraction of the oxygen uptake represents is unknown, and it is probable that several mutually dependent metabolic chains are involved. It has been shown that lithium treatment of sea urchin embryos is accompanied by aberrations in carbohydrate (190, 192, 196), phosphate (194), and amino acid metabolism (110, 154) as well as in the rate of peptide and protein synthesis (5, 109, 111, 255). But it has not been possible in experiments with isolated animal and vegetal halves to demonstrate a preferential localization of certain metabolic types to the two centers of maximum morphogenetic influence (193). Studies of the metabolism of the developing sea urchin embryo under the in-

fluence of lithium and other agents have not yet led to a full understanding of the mechanism of action of these compounds. But work on this topic is of the greatest interest, because it represents a promising approach to the question of the connection between form and function in the living organism.

It must be added that in frog embryos, too, lithium treatment has been shown to cause parallel changes in morphology and metabolism (169, 170, 171).

Spermatozoa. A limited number of studies have been concerned with the effect of Li^+ and other alkali metal ions on spermatozoa. They have revealed the interesting fact that the sensitivity of spermatozoa to monovalent cations differs markedly from one group of animals to another.

Gellhorn (88) found that spermatozoa from *Rana temporaria* maintained their motility for the longest time in a solution of 0.025 M lithium chloride; cesium and sodium chloride in the same concentration were slightly more toxic, and potassium and rubidium chloride showed the highest toxicity. Spermatozoa from *Rana esculenta* were also least affected by lithium and cesium, but in this system sodium was more toxic than potassium and rubidium. When spermatozoa from mammals (guinea-pigs) were investigated, the picture was completely different. Now lithium was found to be the most toxic ion, and the toxicity of the other cations decreased in the following order: Cs, Na, Rb, K.

The high toxicity to mammalian spermatozoa was observed as early as 1909 by Hirokawa (131) in spermatozoa from the rat, and it has recently been confirmed by MacLeod and associates (210) in experiments on human spermatozoa. When lithium chloride was added to a suspension of human spermatozoa in an appropriate Ringer-glucose solution, only 36% of the spermatozoa were motile after four hours incubation (50% in the control suspension) when the final molarity of lithium in the medium was 0.006; if the lithium concentration was raised to 0.025 M, only 2% of the spermatozoa were active at the end of the experiment. The oxygen consumption was not influenced even by relatively high lithium concentrations, but the lactic acid production was markedly depressed. As little as 0.006 M lithium caused a measurable fall in glycolysis, and with a final lithium concentration of 0.025 M the lactic acid production was only 60% of the control value. Still higher lithium concentrations did not depress glycolysis further, so that a considerable glycolytic activity remained when virtually all motile activity had ceased. According to the graphs presented, inhibition set in almost immediately after the addition of lithium, a fact which indicates a rapid entrance of lithium ions into the spermatozoa. The authors point out that the lithium effect must be rather specific for this ion, since human spermatozoa are relatively resistant to large changes in their osmotic environment, and since the potassium concentration of the medium may be increased at least a hundredfold without affecting glycolysis or motility to any appreciable extent.

White (333a) observed that potassium ions exert a re-activating action on the motility of ram and bull spermatozoa that have been washed in a sodium-containing medium, whereas lithium ions are strongly toxic. It seems possible, therefore, that the effects of lithium on glycolysis and motility of mammalian spermatozoa may be due to a displacement of potassium from glycolytic en-

zymes that are involved in the mechanism or the energy requirements of spermatozoan motility.

Ciliary and amoeboid movement. Early in this century Lillie (185, 186) observed that the cilia of a number of marine animals (larvae of Arenicola and the gills of certain mussels) were extremely sensitive to pure solutions of single neutral salts. In solutions that were isotonic with sea water (about 0.5 M) the ciliary movement stopped and the cilia liquefied. Sodium and lithium salts were more toxic than other salts, while the addition of small amounts of certain divalent cations reduced the toxicity of the solutions considerably. Parker (251), on the other hand, found that the labial cilia of *Metridium marginata* (marine) maintained their mobility for a long time in sodium chloride, while the addition of $\frac{1}{6}$ M lithium chloride soon brought them to a standstill.

Höber (136), in continuation of the work by Weinland (330) and Maxwell (217), used pieces of mucosa from the frog pharynx and measured the duration of the ciliary activity in hypertonic and isotonic solutions of single neutral salts. If ciliary standstill was taken as an indicator of toxicity, the cations could be arranged in the following series: $Li > Cs = Na > NH_4 > Rb > K$, with Li^+ as the most toxic and K^+ as the least toxic cation. But it was observed that, when the rate of the ciliary movement was followed from minute to minute, the cations fell into two groups: in one, consisting of lithium and sodium, the cilia beat at a normal rate for a certain time and then stopped abruptly, while in solutions containing the other cations the ciliary movement slowed down gradually and finally ceased.

Gray (99–101) re-opened the question of the effect of ions on ciliary movement. He used gills of *Mytilus edulis* and was able to show that while solutions of single salts were toxic, the ciliary movement could be maintained for several days in sea water or in a "balanced" salt solution, *i.e.*, a solution with a controlled pH and containing proper amounts of sodium, potassium, magnesium, and calcium. Omission of potassium ions did not affect the cilia much, and the beat rate in these media was "normal", *i.e.*, equal to that observed in sea water. If ammonium or potassium ions were substituted for sodium ions, the rate of beat became quicker than normal, while the substitution of lithium for sodium ions stopped ciliary movement in less than two minutes. Friedrich (83) found that the ciliary movement of Nemertinea stopped when 0.5% lithium chloride was added to the sea water.

It appears that lithium is toxic to all cilia so far investigated and is unable to replace sodium in the medium; but Höber's findings indicate a qualitative difference between the effects of, on the one hand, sodium and lithium and, on the other, the remaining monovalent cations.

As mentioned previously, lithium treatment stimulates the amoeboid movements of Limnaea eggs. The action of ions on true amoebae was studied by Pantin (250), who found that the presence of calcium plus one of the alkali metals was essential for movement. The optimum alkali metal:calcium ratio for movement and the maximum velocity attained increased with the atomic weight of the alkali metal, *i.e.*, $Li < Na < K < Rb < Cs$. On the other hand, the viability

of the animals followed a different law, according to which the toxicity of the cations increased as follows: Rb = Li < Cs < K < Na. If the medium contained Ca^{++} plus two monovalent cations, the amoeboid movement could be maintained for a longer period, and the optimum conditions were reached with solutions containing sodium (or lithium) in large excess of potassium (or rubidium).

Bacteria, fungi, and higher plants. An analogy to the morphogenetic effects of lithium on animal embryos is observed in bacteria (125, 144, 163, 178, 245, 285, 294, 300) and fungi (76, 162, 223, 334). Exposure of these organisms to lithium ions may lead to anomalies of shape and of growth type.

During recent years it has been observed that lithium ions are toxic to various lactic acid bacteria (172, 211, 212, 283), and it has been proposed (172) to utilize the bacteriostatic effect of lithium in caries prophylaxis. A lithium-containing tooth paste has been marketed in Germany, but clinical experience so far gained does not permit an evaluation of its prophylactic or therapeutic value (287, 333). Advantage has also been taken of the different sensitivity of various yeast cells and bacteria to lithium ions in the preparation of differential isolation media (102, 123, 176).

Boas (23) found that glycolysis of bottom yeast was inhibited less by lithium than by sodium, ammonium, and potassium ions. Rothstein and Demis (275) were able to show that at low pH fermentation was markedly stimulated by potassium ions; rubidium ions had a moderate effect, and lithium, sodium, ammonium, and cesium ions had only a small stimulating capacity. None of the other ions reduced the stimulating action of potassium.

Lindahl (188, 189, 195) used bakers' yeast as a model system for the fertilized sea urchin egg. He demonstrated a lithium inhibition of glycolysis and respiration and an influence on phosphate metabolism.

The fate and function of lithium in plants are outside the scope of this paper. Scharrer (285) reviewed the field in 1941, and a few additional papers are listed here as clues to further reading: toxicity and influence on growth (1, 113, 209, 284, 304), influence on resistance to disease (156, 298, 326, 337), effect on vacuole contraction (25), absorption and distribution (24, 44, 45, 75, 157, 222, 284), and influence on bioelectrical potentials (50, 248).

Miscellaneous. Chèvremont-Comhaire (40) studied the effect of lithium on *in vitro* cultures of fibroblasts and myoblasts from chick embryos. The presence of lithium in the medium (0.002–0.025 M) caused changes of the growth curves, the occurrence of multinucleated giant cells or large nuclei with an abnormal number of nucleoli, and a change of the relative length of the various mitotic phases.

It was shown by Dogiel (65) that the excretion of neutral red from infusorians was stimulated by lithium sulphate, and Mörch (231) found that very low concentrations of lithium stimulated the phagocytic power of leucocytes *in vitro*. Lithium chloride inhibits the response of frog skin melanocytes to adrenaline and noradrenaline (66).

VI. ABSORPTION, DISTRIBUTION, AND ELIMINATION

Absorption. Lithium ions are readily absorbed from the intestine and from subcutaneous, intramuscular, and intraperitoneal depots, and lithium may be detected in tissue fluids and organs within a few minutes after administration (9, 97, 152, 305). Kent and McCance's (158) data suggest that the lithium occurring naturally in bread is less readily absorbed than soluble lithium salts added to the diet. This cannot be due to a precipitation as phytate, since lithium phytate is soluble, and the authors suggest that lithium in bread may be enclosed in cellulose particles and thus escape absorption.

Hüfner (141) was unable to demonstrate absorption of lithium through the human skin, but percutaneous administration of lithium may be accomplished by iontophoresis (72, 167).

Distribution. Lithium is distributed in the animal organism differently from both sodium and potassium. Whereas sodium is located mainly outside the cells and potassium mainly inside, lithium appears to be rather evenly distributed throughout the water phase of the body. However, small differences do exist between the lithium concentrations in the various organs and between these and the concentration in the extracellular fluid, but the concentration gradients across the cellular membrane are much smaller than those observed for sodium and potassium.

The entrance of lithium into organs was demonstrated by the early investigators (97, 152), but their methods of analysis did not permit any exact measurement of the concentrations. Later investigators computed the apparent volume of distribution of lithium after intravenous injection of lithium chloride from the amount of lithium injected, the amount excreted during the experiment, and the serum lithium concentration. It had been ascertained by preliminary experiments that lithium ions are not bound to the plasma proteins. Radomski and associates (257), in experiments on dogs, rats, and monkeys, found that the lithium space calculated in this manner approached the volume of the total body water (49–65 % of the body weight). Talso and Clarke (315) reached similar values; in nephrectomized dogs the serum concentration became stabilized about eight hours after injection, and at this time the calculated volume of distribution of lithium was about 67 % of the body volume. Foulks and associates (81) also found that the apparent volume occupied by lithium regularly exceeded that of the extracellular fluid, but the lithium space measured depended largely on the rate and duration of the infusion. Equilibrium between rate of infusion, cellular uptake, and excretion was generally achieved when the calculated volume of distribution of lithium was 40–60 % of the body weight. If the intravenous infusion was interrupted or markedly reduced in rate, or if a rapid injection of a single, large priming dose had been given, the lithium space expanded to values as great as 95 % of the body weight, *i.e.*, more than the total body water volume. The authors considered this an indication of a cellular accumulation of lithium against a concentration gradient; but it seems obvious that the calculation was invalidated by the falling serum lithium concentration, because

the release of lithium from certain tissues may have been slower than the removal of lithium from the blood stream by the kidneys.

Direct tissue analyses after lithium administration have given more reliable information. Davenport (53) injected 6 mM lithium chloride per kg body weight intraperitoneally into rats and determined the lithium concentrations in blood plasma, brain, and muscle at various times after injection. One hour after injection the lithium concentrations were 7.6 mequiv./l, 0.7 mequiv./kg wet tissue, and 3.3 mequiv./kg wet, fat-free tissue, respectively. Twenty-four hours after injection the corresponding values were 2.0, 2.0, and 2.6; after 96 hours the lithium concentrations were below the level detectable by analysis. The experiments show that lithium ions pass rather rapidly from the extracellular fluid into muscle. The blood-brain barrier is considerably less permeable to lithium, which is not astonishing in view of its low permeability to sodium and potassium.

An almost even distribution of lithium in all organs analyzed was found by Radomski and associates (257), who determined the lithium concentration in tissues from dogs that had received lithium chloride by mouth for some time. In heart, muscle, kidney, liver, brain, and adrenals the lithium content per kg water ranged between 0.52 and 1.25 times the serum concentration. No information was given about the time interval between the administration of the last lithium dose and the death of the animals. Sivadon and Chanoit (297) and Trautner and associates (319) found lithium evenly distributed between a number of organs in lithium-treated dogs and in a case of fatal lithium poisoning in man, respectively.

Detailed studies on rats treated with intraperitoneal injections of isotonic lithium chloride have established that lithium ions enter rapidly into liver, kidney, and skin, somewhat more slowly into muscle and bone, and very slowly into brain (289). Tissue analyses performed twenty-four hours or more after the last injection showed that, although the lithium concentrations in extracellular and intracellular fluid do not differ greatly, there is for each organ a distinct concentration gradient across the cell wall.

Bertrand (14) determined the small amounts of lithium occurring naturally in whole blood and in serum. Calculations show that the lithium concentrations in serum and in erythrocytes were of the same order of magnitude.

In several *in vitro* studies on red blood cells lithium has been used as a substitute for sodium to maintain the tonicity of the medium when the effect of a low external sodium concentration was being investigated. In these experiments the observations on lithium transfer and distribution were largely incidental, and it is not always evident whether the effects observed were due to the low sodium concentration or to the lithium present.

Lithium appears to enter the erythrocyte with a transfer constant of about 0.02 hr^{-1} (214), *i.e.*, of the same order as the passive transfer rates of sodium and potassium. The outward transfer constant for lithium is of the same low magnitude (214), and the data suggest that there is no active efflux of lithium comparable to that of sodium. In accordance with this are the distribution data, which all show a tendency for lithium to reach almost even concentrations in

the intracellular and the extracellular fluid, and the fact that a transport of lithium against a concentration gradient has not been observed in erythrocytes.

According to Solomon (299), lithium and cesium, in contrast to rubidium, do not appear to compete with potassium for entry into the red blood cell, and the reduced potassium influx observed in sodium-poor, lithium-rich media (80, 256) may be a result of the lowering of the sodium concentration (119, 214). A certain competition between lithium and sodium for inward transfer was indicated by Solomon's data, but Harris and Maizels (120) and Maizels (214) found that both inward and outward transfer constants of sodium were unaffected by high concentrations of lithium.

When lithium enters the erythrocyte, it displaces sodium (until the ratio of external to internal sodium is re-established) as well as potassium (80, 119, 120, 214). A displacement by lithium of both sodium and potassium inside the cell was also found by Taggart and associates (311) in kidney cortex slices.

The entrance of lithium into special body fluids, *e.g.*, aqueous humor of the eye, saliva, gastric juice, and cerebrospinal fluid, was established by qualitative methods at an early date (9, 97, 152, 246). Oberhard and Sserafimow (244) even claimed that permeability changes of the blood-spinal fluid barrier to lithium could be used as an aid in the diagnosis of various neurological and psychiatric diseases, but no documentation was presented. Leusen and Demeester (181) found lithium in the cerebrospinal fluid two hours after intravenous injection of lithium chloride in dogs, and in a case of lithium poisoning in man Hanlon and associates (116) found 1.5 mequiv. lithium per l spinal fluid two days after lithium administration was stopped; at this time the serum lithium concentration was 2.6 mequiv./l. Schou and associates (290) determined the lithium concentration in cerebrospinal fluid in six manic patients who had been treated with lithium salts for one to two weeks; in all cases the lithium content was lower in the spinal fluid than in the serum, the average ratio being 0.47. In both of the last-mentioned studies the spinal fluid and serum analyses were made during a period of falling serum lithium concentration; accordingly, the data indicate that even in a steady state the spinal fluid lithium concentration is lower than the lithium level in the serum.

Elimination. When a single dose of a lithium salt is administered to an intact animal, a large part of the lithium is eliminated from the organism during the first few days, mainly through the kidneys. But small amounts of lithium may still be found in the urine after one to two weeks, presumably because the release from certain tissues is rather slow (9, 97, 152, 243, 319). During the continuous lithium treatment of psychotic patients with doses of 0.5–1.0 mequiv./kg body weight per day, the serum lithium concentration usually ranged between 0.5 and 2.0 mequiv./l, although higher values were occasionally observed (290). Trautner and associates (243, 319) claim that at the beginning of the treatment manic patients appear to excrete considerably less lithium than do normal controls; after some days a profuse elution of lithium coincides with a reduction of the manic symptoms. Further documentation of this interesting observation must be awaited.

The amount of lithium excreted in the feces is usually a small fraction of the dose given (97, 158, 257, 315), but the loss through gastrointestinal secretion may increase in case of vomiting and diarrhea (97). Some lithium may also be excreted through the sweat (243).

The unhappy experience gained by the administration of lithium chloride as a taste substitute for sodium chloride (47, 103, 116, 253, 306, 328) showed clearly that lithium is much more toxic if the administration is combined with a low sodium intake. Less lithium is then excreted through the kidneys, and the lithium concentration in tissue fluids and cells may reach toxic levels. If the lithium dosage is increased, a similar accumulation with symptoms of poisoning may be observed with a normal or high sodium intake (257, 289). This indicates strongly that lithium ions are to some extent treated like sodium ions in the kidney, and one might propose the hypothesis that the reabsorption of lithium in the tubules, although much less efficient than the reabsorption of sodium, is influenced by the same factors that regulate the renal excretion of that ion. None of the available experimental data are incompatible with this hypothesis, and some appear to support it indirectly.

Radomski and associates (257) gave a single intravenous injection of lithium chloride to three normal dogs and found lithium-creatinine clearance ratios of 0.45, 0.38, and 0.43. No similar studies were performed on dogs with different levels of sodium intake. The lithium-creatinine clearance ratios observed by Talso and Clarke (315) ranged between 0.01 and 0.43, and it was noted that dogs on a high sodium diet had higher excretion fractions of lithium than had those on a low sodium diet at corresponding levels of serum lithium. The correlation between lithium and sodium excretion fractions was not studied systematically. The tubular reabsorption of sodium was not significantly altered by the presence of lithium, but the serum lithium level in these experiments did not exceed 9 mequiv./l. The correlation between the excretion fractions of lithium and potassium was rather poor.

The renal excretion of lithium in relation to sodium and potassium was studied by Foulks and associates (81). The lithium-creatinine clearance ratios ranged from 0.18 to 0.45 and averaged 0.30, showing that approximately 70% of the filtered lithium was reabsorbed. In a typical experiment isotonic lithium chloride was infused intravenously; this led to a marked elevation of potassuim excretion, and the authors suggested that an accumulation of lithium in the cells of the renal tubule might act as a stimulus to potassium secretion. (Berliner (10) and Orloff and Kennedy (247) made similar observations.) In the same expriment the excretion fraction of sodium rose from 0.0017 to 0.0135 while that of lithium changed only from 0.25 to 0.28. The lithium excretion was not modified by simultaneous potassium loading, and the administration of a mercurial diuretic was also without significant effect on the lithium excretion (according to the data presented, the excretion of sodium was also very little affected by the diuretic used). The effect of sodium loading was not studied. The authors were inclined to think that the lithium reabsorption is accomplished by a process of passive back diffusion. They rightly pointed out, however, that this

would be a rather unusual behavior for a cation, and they suggested as an alternative hypothesis that the peculiar excretory pattern of lithium could be attributed to inefficient competition for a transport system shared with another cation. The latter hypothesis appears to the present reviewer to be in agreement with the behavior of lithium in a number of other biological systems.

VII. TOXIC EFFECTS IN ANIMALS AND MAN

Lithium is relatively toxic to the animal organism. This had already been demonstrated in the 19th century, but nevertheless lithium salts have been used in human therapy for the last hundred years, sometimes in dangerously high doses. The slow realization of the toxicity of lithium salts may be due to several reasons, but the most important is presumably the fact that the accumulation of lithium and hence its toxicity is determined not only by the amount of lithium given but also to some extent by the sodium intake. Lack of knowledge on this point led to several severe intoxications some years ago when lithium chloride was given as a taste substitute to patients on a salt-free diet.

The relation between lithium toxicity and sodium intake renders most statements of minimum toxic and lethal doses of lithium almost valueless, unless they are combined with information concerning the amount of sodium given with the food. Unfortunately, very little systematic work has been done to determine the acute and chronic toxicity of lithium salts on varying and known levels of sodium intake.

The clinical picture of lithium intoxication is rather complex and involves several organs and organ systems, but symptoms from the gastrointestinal tract, the kidneys and the central nervous system are usually prominent. Neither in animal experiments nor in the fatal cases of lithium poisoning in man has it been possible to establish the cause of death with certainty, but a number of reports point to the kidney as the *locus minoris resistentiae*.

General effects. Some effects of lithium poisoning are rather vague and cannot be attributed to any single organ system. These are anorexia, weight loss amounting to extreme emaciation, general weakness and fatigue, dehydration, thirst and dryness of the mouth, and a fall of body temperature; the last symptom has been observed only in animals.

Gastrointestinal tract. Among the most frequent toxic signs observed in both animals and man are nausea, salivation, vomiting, and diarrhea, sometimes amounting to loose, watery, bloody stools (34, 52, 53, 61, 64, 68, 81, 95, 97, 116, 129, 166, 181, 210, 243, 257, 267, 271, 290, 291, 297, 306, 315, 317). The effect of lithium on the gastrointestinal tract is not due to its absorption through the intestinal wall, since the symptoms mentioned appear just as readily when lithium is administered parenterally. Talso and Clarke (315) observed that when a single dose of a 10% lithium chloride solution was injected intravenously into dogs, the animals all vomited during the rapid rise of serum lithium concentration, except when they were anesthetized. Most of the gastrointestinal symptoms observed in animals may be counteracted by the administration of atropine (1–2 mg atropine sulphate per kg body weight) (53, 143); this therapy has not

been tried systematically in man. The mechanism by which the irritation is produced is not evident. One of the few macroscopic findings in lithium-killed animals is a strong hyperemia of the intestinal mucosa, occasionally with small ulcers and free blood in the lumen.

Nervous system and muscles. The signs from these organs are many and varied, and so far they cannot be ascribed to a single pathogenic mechanism. They are presented here in their approximate order of frequency, as recorded by numerous authors (31, 34, 42, 47, 52, 53, 61, 68, 95, 103, 116, 129, 164, 174, 181, 210, 243, 253, 257, 267, 268, 271, 290, 291, 293, 297, 306, 315, 317, 319, 328).

Even with relatively moderate doses a fine tremor of the hands may be seen, sometimes also of the lips and lower jaw. In more severe cases the following signs appear: muscular weakness with ataxia and a positive Romberg sign, giddiness and tinnitus, drowsiness and sleepiness, slurred speech, and blurred vision. At a more advanced stage one may observe muscular hyperirritability with hyperactive deep reflexes, muscular fasciculations, especially in the face, skin hyperirritability, lethargy and stupor, nystagmus, and paralysis of the limbs; the last sign has been observed only in frogs (31). In a few cases (103, 297) mental confusion has developed with delirium and anxiety, which necessitated the admission of the patient to a mental hospital. In other instances, reversible chorea-athetotic and Parkinson-like syndromes have been observed (68, 253, 297). The gravest cases of lithium intoxication were characterized by coma and epileptic seizures, and some of them ended fatally (47, 103, 116, 257, 271). The type and sequence of toxic signs are, on the whole, identical in animals and in man.

Brains from lithium-killed animals have revealed no anomalies, but systematic investigations have not been performed. In the fatal cases of lithium intoxication reported by Roberts (271), by Trautner and associates (319) and by Duc and Maurel (68), the necropsy did not give indication of structural brain damage. One of Glesinger's (95) patients died during lithium treatment with signs of ataxia, incoordination of the muscles and general weakness. The post-mortem findings indicated a "query encephalitis type", but the causal relation to the lithium administration seems open to question.

Electroencephalographic changes were observed by Corcoran and associates (47) in a severe case of lithium poisoning; the electroencephalogram (EEG) showed a severe, generalized, slow dysrhythmia with frequencies of four to six per second and voltages up to 150 mV. Somewhat similar changes, only less pronounced, were found by Schou and associates (290, 291) in a number of lithium-treated psychotic patients with no signs or only slight signs of clinical intoxication. The changes consisted of the appearance of frequencies of six to seven c/s, and the voltage was increased but did not exceed 100 mV. The EEG changes appeared after one to two weeks of treatment with moderate lithium doses and disappeared about a week after lithium administration was stopped. Lithium-induced EEG changes have also been observed by Daumézon and associates (52), by Duc and Maurel (68) and by Reyss-Brion and Grambert (267).

Comparatively little experimental work has been concerned primarily with

the effect of lithium on the central nervous system. A certain apathy and slowness of reaction have been frequent symptoms in the experimental animals, but evidence is lacking to indicate whether this is a result of the general intoxication or due to a more direct action on the brain. Application of lithium chloride directly on the spinal cord of the toad resulted in paralysis of the muscles (230). This led Kotzoglu (165) to administer solutions of lithium or magnesium salts or mixtures of these to dogs and humans by the rectal route; in several cases universal analgesia was obtained, but the author considered the procedure too dangerous for practical use.

In contrast to these findings are the observations by Moracci (234), who applied various salts to the exposed motor area of the dog cortex. While sodium and potassium salts were without noticeable effect, the application of lithium salts resulted in tonic and clonic seizures localized to the corresponding muscles, but with a tendency to become generalized. Davenport (53) demonstrated that rats treated with intraperitoneal injections of lithium chloride had lower seizure thresholds to electrical stimulation than the control animals.

Heart and circulation. Toxic symptoms from these systems are usually not prominent in spite of early observations of cardiac arrest after intravenous injection of lithium chloride into frogs, pigeons, and rabbits (129, 142, 293) and of "cardiac depression, and even dilatation, as the result of the excessive and continued consumption of lithia-tablets" (206). Later experience with lithium administration to animals and man has been less drastic, although there is ample evidence of an effect on the heart even when lithium is given in comparatively small doses.

A decrease of the heart rate has been observed in experimental animals (129, 142, 166, 268, 293) and in a lithium-poisoned cardiac patient (306). Leusen and Demeester (181) were able to raise the arterial blood pressure in animals by intracisternal injection of lithium chloride. On the other hand, lithium administration caused a lowered blood pressure in some of the cases described by Corcoran and associates (47) and Glesinger (95). Schou and associates (291) were unable to find blood pressure changes during lithium treatment of psychotic patients.

The most regular sign of a toxic effect on the heart consists in changes in the electrocardiogram (ECG). Schou and associates (291) observed during treatment of psychotic patients with moderate doses of lithium (25–50 mequiv. per day) that after one to two weeks about one fifth of the patients had ECG changes: flattening or isoelectricity and in a few cases inversion of the T waves. The changes were in all cases reversible and disappeared a few weeks after the lithium medication was stopped. In none of these cases was the serum potassium concentration outside the normal range. Experiments on animals have shown similar (and opposite) changes of the T waves in addition to numerous other anomalies of the ECG. McKusick (218) administered lithium chloride intravenously or intraperitoneally to dogs, cats, rabbits, and guinea-pigs and found a consistent series of ECG events: amplification of the T waves, auricular standstill or fibrillation, widening of the QRS complex, and appearance of bizarre, biphasic QRS-T

complexes. The author points out that the hyperlithemia was accompanied by a progressive increase in serum potassium and is inclined to consider this the cause of the ECG changes.

Similar ECG changes were found by Radomski and associates (257) after oral administration of lithium to dogs. The changes became marked in the terminal stages of intoxication and included T wave inversion and an increase of T wave amplitude, widening of the QRS complex, depression of the S-T segment, a-v block, and disappearance of the P waves. These authors, too, ascribed the changes solely to the accompanying rise of serum potassium. Roberts and Magida (272) injected lithium chloride intravenously into dogs and noted tachycardia, increase of T wave amplitude, obliteration of the S-T segment, and finally bradycardia with disappearance of P waves, development of nodal rhythm, and ventricular complexes. Some of the ECG changes could be seen before the serum potassium concentration was measurably increased.

In the isolated heart considerably higher lithium concentrations are required to provoke ECG changes. Butcher and associates (33) recorded simultaneously from the cavity and the epicardium of the isolated perfused heart of the dog and the turtle before and after alteration of the cation concentration in the perfusate. A high concentration of lithium (more than 50 mequiv./l) led to a decreased heart rate, a prolonged S-T interval, and a decreased voltage of the QRS complex. Stein and associates (303), in experiments with isolated frog hearts, found similarly that if lithium chloride was added to the Ringer solution, ECG changes could be observed only when the lithium concentration exceeded about 50 mequiv. per liter; however, in sodium-poor solutions ECG changes were produced by as little as 30 mequiv. lithium per l perfusate.

It may be concluded that the lithium ion appears to exert a specific influence on the heart, which may manifest itself in ECG changes even when lithium is administered in moderate doses. In graver cases of intoxication a rise of the serum potassium concentration, possibly due to renal failure, may complicate the picture, and in acute animal experiments the cause of death often appears to be cardiac arrest. It should be noted, however, that in the cases of fatal lithium intoxication observed in man, cardiac symptoms have not been conspicuous.

Blood and blood-forming organs. Rissetto and Gazzano (269) investigated the cytology of the peripheral blood after intramuscular injection of lithium salts into guinea-pigs. The administration of 15 mequiv. lithium per kg per day for two days led to a small rise of the red blood cell count and a moderate increase of the white blood cell count with granulocytosis. When the animals had received 6 mequiv. lithium per kg per day for 20 days, the number of red blood cells and the hemoglobin content were decreased by about 10–20 %, and the white blood cell count was moderately increased with lymphocytosis. Radomski and associates (257) noted a gradually developing lymphocytopenia in dogs treated for a long time with somewhat high lithium doses.

During lithium treatment of manic patients Bille and Plum (19) found in three cases indication of toxic changes of the bone marrow, whereas Schou and

Kissmeyer-Nielsen (292), who studied 12 patients under lithium treatment with a view to hematotoxic reactions, were unable to discover any significant anomalies. It should be noted that a few observations (256, 319) indicate a slightly increased fragility of erythrocytes in lithium-containing media.

Kidneys. Several authors have noted oliguria and an elevation of the blood nonprotein nitrogen in the terminal stages of lithium poisoning in animals and in man (47, 52, 257, 289). Microscopic investigation of the kidneys from lithium-killed animals show degenerative changes of the tubular epithelium (257, 289, 297), and renal failure is considered the principal cause of death by Radomski and associates (257).

During lithium treatment of psychotic patients, Glesinger (95) and Trautner and associates (319) observed transient proteinuria in a number of cases, and Duc and Maurel (68) and Giustino (94) found hematuria in a few cases. Other workers have not found any evidence of renal damage under similar conditions (243, 290, 291).

Some studies have indicated changes of the urinary excretion of various electrolytes after lithium administration (220, 297, 319), but the food intake of the experimental subjects was not controlled during the experiments, and exact balance sheets could accordingly not be made.

It has occasionally been observed that lithium administration may be accompanied by an increase of the urine volume (219, 220, 317, 319). Recent experiments on rats (289) have established that a conspicuous feature of chronic lithium intoxication is the development of a state resembling diabetes insipidus, during which the animals excrete a very large volume of hypotonic urine. If the lithium dosage is increased or the sodium intake reduced, the condition changes rapidly into the picture of renal failure described above.

Other organs. In animals treated with moderate to large doses of lithium salts, the adrenals become slightly hyperplastic (257, 289, 297), and iron-containing material is deposited in the spleen (289). Radomski and associates (257) also observed "a very slight degree of focal necrosis of the voluntary muscles".

Blood and tissue chemistry. Administration of therapeutic doses of lithium salts to patients with a proper sodium intake does not lead to any measurable change of the blood chemistry (118, 290, 291), but in cases of lithium intoxication in patients on a low sodium diet the following anomalies have been observed: a lowered serum sodium concentration, a slight increase of hematocrit values and plasma chloride, and a decrease of the serum carbon dioxide-combining power (47, 116, 306, 314).

Davenport (53), in experiments on rats, observed various changes in the water and electrolyte content of plasma, brain, and muscle. The most significant change was a decrease of the sodium concentration in the extracellular fluid, and the author suggests that this, perhaps in combination with the presence of lithium in the brain, may explain why lithium-treated rats had lower seizure thresholds than did the pair-fed controls. Radomski and associates (257) were able to show that subacute doses of lithium chloride in dogs on a low sodium diet and also larger doses in dogs on a normal diet produced a marked loss of sodium in the

urine, which in some cases was accompanied by a fall in the serum sodium level towards the end of the survival period. There was furthermore a retention of potassium and, terminally, azotemia and an increase of serum potassium to cardiotoxic levels.

Rissetto and Gazzano (270) found a slight rise of serum nonprotein nitrogen and cholesterol in lithium-treated guinea-pigs.

Treatment of lithium intoxication. It seems certain that a proper intake of sodium salts is of prophylactic value against lithium intoxication. It has furthermore been observed (289) that excretion of the lithium remaining in the body after a treatment period may be significantly accelerated by the administration of liberal amounts of sodium chloride. However, these experiments were performed on animals and patients who were, at most, only slightly intoxicated, and it is still an open question whether sodium chloride administration is of therapeutic value in cases of severe intoxication with incipient or manifest kidney damage.

In the literature the following therapeutic procedures against lithium intoxication have been suggested: intravenous injection of isotonic or hypertonic sodium chloride or glucose, and the administration of adrenocortical extracts, barbiturates and other sedatives, diuretics, laxatives, sodium thiosulphate, BAL, crude liver extract, vitamins, and "Cylotropin" (which contains 40 % hexamethylenetetramine, 16 % sodium salicylate, and 1 % caffeine) (47, 52, 95, 116, 271, 306, 317). Some of these procedures seem to lack any rational foundation, and none of them is based on experimental or clinical data.

VIII. MEDICAL USES OF LITHIUM SALTS

Gout and urinary calculi. Lithium was introduced into medicine about a hundred years ago. Lipowitz (200) had shown in 1841 that the lithium salt of uric acid was soluble in water, and Ure (320) found in 1844 that a urinary calculus containing uric acid was slowly dissolved when placed in a warm solution of lithium carbonate. These observations led Garrod (87) to administer lithium salts to gouty patients and patients with urinary calculi in the hope that the lithium would dissolve the uric acid deposits around the joints and in the urinary tract. During the following years numerous *in vitro* experiments were carried out to demonstrate the "solubilizing" effect of lithium salts on uric acid (21, 149, 166, 213, 232, 273, 301), and a number of enthusiastic therapeutic reports appeared (64, 173, 184, 309, 336). The lithium salts, mostly the carbonate or the citrate, were given in doses containing from 12 to 80 mequiv. lithium per day. They were usually administered by mouth, but administration by iontophoresis has also been employed (72, 130, 167, 183). However, since sodium and potassium form insoluble salts with uric acid, and since these ions are always present in the organism, lithium cannot possibly have any "solubilizing" effect on the uric acid deposits. Subsequent clinical and biochemical work has given completely negative results (51, 68, 118, 221, 274, 314), and lithium salts are no longer used against these diseases.

Taste substitute for sodium chloride. Some years ago lithium chloride was rather

widely used as a taste substitute for sodium chloride for patients with cardiac diseases who had to live on a salt-free diet. Although no untoward reactions were observed in a clinical trial with controlled doses (314), several severe lithium intoxications and a few deaths from lithium poisoning were observed (47, 103, 116, 253, 306, 328), and the use of lithium chloride as a taste substitute was discontinued.

Various medical uses. In 1864 Gibb (93) advocated the use of lithium bromide as a mild tonic, while Lévy (184) administered it as a sedative. Mitchell (229) used lithium bromide against epilepsy in doses containing from 4 to 45 mequiv. lithium per day, but the alleged superiority of the lithium salt over other bromides does not appear to have been demonstrated. Carrère and Pochard (36) have recently used lithium citrate as a supplement to the barbiturate therapy of epilepsy, but they do not present any documentation of its effectiveness, and a certain reservation concerning this use seems indicated by Davenport's observation of a lowered seizure threshold in lithium-treated rats (53).

Lithium salts have been employed in the treatment of diabetes mellitus, because it was thought that uric acid metabolism might be altered in this disease (331, see also, however, 54, 147). Their use against various infectious diseases appears to rest on an equally weak foundation (143, 254). The addition of lithium salts to tooth paste has already been mentioned.

Zahl and Cooper (339) made preliminary experiments on the accumulation of lithium in tumor tissue after intravenous injection of lithium salts of certain acid dyes. The authors propose that this procedure might be developed into a technique for the treatment of tumors that lie near the surface; if these areas are irradiated with slow neutrons, nuclear capture reactions will occur, which release energetic particles and result in local destruction of tumor tissue. Further work is needed before the possible usefulness of this procedure can be evaluated.

Use in psychiatry. Lange (173) gave lithium salts to patients with gout and mental depression; he claimed beneficial results in both diseases, but did not present any documentation.

In 1949, Cade (34) made an accidental observation of a sedative-like action of lithium salts when administered to guinea-pigs. After a latent period of about two hours, the animals, although fully conscious, became lethargic and unresponsive to stimuli for one or two hours before once again becoming normally active and timid. Cade then administered lithium carbonate and citrate to ten manic patients, and the condition of all the patients improved during the treatment. Since then lithium treatment of mania has been tried in a number of mental hospitals, primarily Australian and French, and mainly with good results (4, 36, 55, 60, 61, 68, 94, 95, 168, 215, 243, 267, 297, 317).

These reports often comprise rather large numbers of patients, but they are all based on clinical "impressions" rather than on controlled therapeutic experiments. In 1954, Schou and associates (290, 291) made a more systematic study of the effectiveness of lithium treatment of manic phases of manic-depressive psychosis. They used a "double-blind" technique so that neither the patients, nor the ward personnel, nor the psychiatrists knew whether the tablets given

contained lithium or were placebos, and the medication was shifted in a random manner between lithium and placebo at intervals of two weeks. The effect of the treatment was evaluated with due consideration of the spontaneous course of the disease in each case.

Of 48 manic patients treated with lithium salts, 18 could be classified as "+ effect". In these cases it was highly improbable that the improvement observed during the treatment had been due to inaccuracies in clinical assessment, suggestibility, or spontaneous variation. Twenty-one patients were grouped under the heading "possible effect". Their condition was clearly improved during the treatment, but a spontaneous cessation of the mania could not be excluded. In 9 patients the lithium treatment did not influence the mania; these were classified as "− effect". In the "+ effect" and "possible effect" groups the patients were almost or completely relieved of manic symptoms, and several patients could be discharged from the mental hospital, some after having stayed there for many years. The authors conclude that even if lithium is too toxic to be an ideal therapeutic agent, the lithium treatment of mania represents a very welcome addition to the therapeutic measures against a disease that is very resistant to most types of treatment or in which the improvement after treatment is frequently rather short-lived.

In a recent publication (288) the experience from lithium treatment of manic patients during three years is reviewed; out of 85 manic patients 16 did not show any improvement, while in 69 patients the manic symptoms abated or disappeared during the treatment. It is pointed out that chronic, *i.e.*, protracted or frequently recurring, manias constitute the main indication for treatment with lithium salts. Kidney and heart diseases and conditions leading to a low salt intake must be regarded as contraindications. No late toxic manifestations were observed in patients who had received lithium carbonate continuously for three years.

Psychic exaltation in other psychotic patients, *e.g.*, in schizophrenics, has also been treated with lithium salts, but the effect in these cases appears to be more questionable (34, 36, 55, 61, 68, 95, 243, 267, 297), and controlled therapeutic experiments have not been performed. Cade (34) and Noack and Trautner (243) found that the depressive phases of manic-depressive psychoses were unaffected or in some cases aggravated by treatment with lithium salts, but the question of a possible therapeutic action of lithium in these states does not appear to have been fully explored yet.

Most workers in the field agree that the therapeutic index of lithium is rather low. Many of the patients suffer from mild gastrointestinal distress and tremor of the hands during treatment with therapeutic doses, and in a few cases grave intoxications have been observed during lithium treatment of psychotic patients. The cause of these isolated cases of lowered tolerance to lithium is not evident, but a low sodium intake may have been a contributory factor in at least some of them.

The lithium salts, mostly the carbonate or the citrate, are given to the patients in tablets, and the dosage is usually around 40–60 mequiv. lithium per day (cor-

responding to 1.5–2.3 g lithium carbonate per day), although somewhat higher doses have been used occasionally. Frequently the dosage may be reduced after treatment for one to two weeks, and in many cases a maintenance dose of about 20–30 mequiv. lithium (0.8–1.1 g lithium carbonate) per day suffices to keep the patient in a normal state.

The effect of lithium salts in cases of mania differs markedly from the results of treatment with barbiturates and with "tranquilizing" agents. The patients do not generally give the impression of being "drugged"; they are quiet and cooperative, but usually not drowsy, and in many cases they are able to attend to their work quite normally while on a maintenance treatment. Apparently the lithium ions counteract the manic symptoms in a rather specific way.

IX. COMMENTS

The biology and pharmacology of the lithium ion present a highly complex picture, and it is as yet not possible to arrange the many morphological, biochemical, and clinical data in a coherent pattern. Still, a bird's-eye view of the lithium literature reveals a number of general trends; most of these have been discussed in previous chapters, and only a few comments on certain aspects are added here.

The most striking feature of the biology of the lithium ion seems to be its partial similarity to the sodium ion. This resemblance is indicated by experiments with a number of biological systems, but is most clearly shown by the demonstration of an active transport of lithium, similar to that of sodium, through the isolated, short-circuited frog skin and through the gills of goldfish. It seems reasonable to assume that lithium ions are treated, at least partly, like sodium ions also in other tissues in which a "sodium pump" mechanism has been demonstrated or is supposed to be at work, and an active, but inefficient, outward transport of lithium would appear to be a satisfactory explanation of the distribution of this ion between the extracellular and intracellular water phases of the body.

A further significant point of similarity is the apparent inability of the impulse mechanism to distinguish between lithium and sodium. A large number of studies have shown that Li^+, as the only inorganic ion, may be substituted for Na^+ in the medium surrounding nerves and muscles without loss of excitability; preparations rendered inexcitable by exposure to sodium-free media regain their activity by being placed in a solution containing lithium ions above a certain concentration. The resting membrane potential is influenced only to a slight extent by lithium ions; in this respect also the effect of lithium is much closer to that of sodium than to that of potassium.

On the other hand, a number of distinct differences exist between the effects of sodium and lithium on these preparations. Although in experiments of short duration *the resting membrane potential* is little affected by the addition of lithium ions to the medium or by substitution of lithium for sodium in the medium, there is ample evidence to show that on prolonged exposure of the preparations to lithium-containing solutions the resting potential (in several studies followed

as the demarcation potential) undergoes first a slight increase and later a decrease; the depolarization eventually becomes irreversible. In nerves that have previously been kept in a sodium-free solution or in nerves excised from adrenalectomized frogs, the phase of hyperpolarization is absent.

In nerves made inexcitable by exposure to a sodium-free solution, *the action potential* is restored by a lithium-containing medium. In isotonic lithium chloride the immediate restoration is complete, but eventually the amplitude of the action potential decreases. The decrease may, according to Cerf and to Ramos and Calva, be counteracted by anodal hyperpolarization; Gallego and Lorente de Nó were unable to show this.

Various *other indices of nerve function* also react differently to sodium and lithium: while sodium ions increase the "L fraction" of the membrane potential in nerves made inexcitable in a sodium-free medium, lithium ions decrease it and reduce the effectiveness of the nerve reaction; the threshold and the latency of a single node of Ranvier change in opposite directions by exposure to isotonic solutions of sodium chloride and of lithium chloride; a prolongation of the action potential can be observed at the injection site after intra-axonal injection of sodium ions, whereas this is not seen when lithium ions are injected; and the substitution of lithium for sodium in the medium may lead to changes of tonus and of contraction frequency in preparations of smooth muscle and heart muscle.

Our present knowledge of the role played by the monovalent cations in nerve and muscle function does not enable us to explain the similarities and dissimilarities between the effects of sodium and lithium. One would like to bring into relation the sodium-replacing ability of Li^+, unique for an inorganic ion, and the observation of an active transport of lithium ions by the "sodium pump" in an isolated frog skin and in goldfish gills, a phenomenon also not observed for any other inorganic ion. The resemblance of lithium with sodium, rather than with potassium, in a number of enzyme systems might also be relevant in this connection.

The peculiar, almost even, distribution of lithium ions across the cell membrane should undoubtedly be taken into consideration in a study of the effects of lithium. It does not appear farfetched to regard the gradual decrease of the spike height in lithium-containing media as due, at least partly, to an entrance of lithium ions into the axon. If, as some data indicate, lithium ions retain their similarity to sodium ions inside the nerve fiber, a gradual equilibration between the extracellular and the intracellular lithium concentrations must lead to a decrease of the "sodium" gradient across the nerve membrane and consequently to a decrease of the amplitude of the action potential. But it is evident that such a course of events can not explain all the effects of the lithium ion, and one must also consider other possible mechanisms, *e.g.*, a displacement of intracellular potassium, an inhibition of enzyme reactions, an alteration of the structure of the axonal membrane, *etc.* It seems likely that experiments in which nerve and brain preparations are exposed to sodium-containing media with a low lithium content, rather than to pure lithium chloride in high concentration, might serve to elucidate the relative importance of these processes.

It should finally be pointed out that nothing is known about the mechanism of the therapeutic action of lithium salts in certain psychotic states. We do not know whether we are dealing with a general influence on the entire nervous system or with an action on circumscribed regions in the brain. We are equally ignorant of whether the effect is due to a stimulation or to an inhibition of cerebral processes. And it is not even certain that the lithium ion acts primarily on the brain in these cases. Still, it seems natural to look primarily for an effect on the nervous system, and it may be speculated whether the therapeutic action of lithium in psychotic states will not find its explanation in the effects of this ion on the transmission of nervous impulses along the lines discussed above.

Many questions are thus left unanswered about both the pharmacology and the general biology of the lithium ion. Further systematic studies are needed of the fate and function of lithium in a number of experimental systems, and one cannot help feeling that work in this field may lead to a better understanding not only of the specific properties of the lithium ion but also of the fundamental biological processes in which its chemical relatives, sodium and potassium, are involved.

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