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Effects of Cesium on Cellular Systems

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INTRODUCTION

Interest in cesium compounds and their behavior has been principally a result of the increasing exposure of living systems to radioactive Cs following increasing nuclear activity. The initial areas of investigation had been:

1. The general effects on metabolism, transport, and enzyme activation;
2. The toxicity, uptake, and retention of the radioactive forms of Cs in different organisms, their uptake, and passage through the food chain; and
3. Use of Cs compounds in treatment and therapy, particularly of mental disorders (*1*).

Later the work was extended to the effects of the stable forms and application of the interaction with other compounds in counteracting harmful effects.

The toxicology of Cs compounds has assumed importance owing to the observation that Cs^+, both in radioactive and nonradioactive forms, enters easily into the plant and animal system and finally the food chain. Cs^+ is then transferred to the human system and deposited in muscles and other soft tissues, giving a relatively long, although individually variable, half-life. A knowledge of the biochemistry of Cs^+ thus became necessary in devising methods for reducing the body content of radioactive Cs^+ (*2*).

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The radioactive forms, Cs^{134} and Cs^{137}, are produced in high-yield fission of uranium and plutonium from atomic fallouts. Stable Cs, on the other hand, is found in soil as well as in living organisms, in small and variable doses and is seen, in some cases, to control the uptake and distribution of the radioactive forms (*3*).

In assessing the transport of Cs^{137} in food chains, the amount of stable Cs available needs to be taken into account. Stable Cs determines to a large measure the rate of transport of Cs^{137} in systems where the radionuclide is sufficiently aged to be in equilibrium with stable Cs. Since soil is known to contain some stable Cs, small applications of stable Cs to the soil can greatly increase plant uptake of radioactive Cs, probably by carrier effect. Cs^{137} appears to get fixed on or in the clay lattice with time, becoming less available. These factors affect the cycling of Cs in the ecosystems (*3*).

The Chernobyl accident focused attention on the possible radiation hazards of radioactive Cs. Cs^{134} and Cs^{137} were located in dust samples in Thessaloniki (*4*); in rainwater collected in Nijmegen (*5*); and in grasslands at southwest England (*6*). High concentrations were measured in a number of species of fungi from Germany (*7,8*). Even after a year, the effective dose equivalents for $Cs^{137 + 134}$ ranged between 6 and 44Sv for workers in French nuclear installations. This amount is similar to the evaluation based on environmental measurements made within the first few weeks of Chernobyl accident (*9*). Direct exposure of two women in Kiev resulted in a committed effective dose equivalent of 0.4 mSv, the biological half-life of Cs being 60 d (*10*). In Sweden, a marginal increase of the existing dose from natural causes was recorded in farmers up to a year after the accident (*11*).

DISTRIBUTION

In Nature

Cesium occupies an intermediate place in the abundance table, as the 45th most abundant metal in the earth's crust. In soil, variable amounts of Cs have been reported from different parts of the world. In 22 samples of arable soils tested, the content ranged from 0.3 to 25.7 mg/kg of dry soil (*12*). The metal was located mostly in podzol soils on pegmatites, gneiss, and biotite, sulphate soils, and rendzines on andesite from Moravia. Only traces were found in certain black and brown soils (*13*). A sample of desert soil from Nevada, USA contained 4 μg/g soil (*14*).

In an assessment of perturbations of the geochemical cycles of metals, Cs is grouped with Li and Rb. The scale is zero at global level, but enhanced at regional and local levels because of mobilization of crustal metals like soil and dust. The most diagnostic environment is sediment

in coastal areas. The metals are soluble and toxic in excess but significant exposure is regarded as unlikely (*15*).

Neutron activation analysis of leached alkaline fly ash showed the presence of Cs, with Pb and other elements in the highly leached portions of residue sequences, suggesting an association with the resistant internal silicon-rich glass matrix of the ash particles (*16*). In two samples of loamy soil from India, Cs was more frequent in silty clay loam than in silty loam (*17*). Interestingly, the abundance of Cs in sea water is very nearly the same as in the earth's continental crust (*18*).

Cs content, estimated by flame photometry in 16 samples of surface water from four oceans was 0.37 microgram/L. The average concentration at 500–1500 m depth was about 14% higher than the surface average (*19*), suggesting that the metal may be transported downward by particulate matter. However, in the North Pacific, typically deep water contained 1.4% lower average concentration than the surface water (*20*). Analysis of 163 samples of mineral and thermal waters by electrothermal atomic absorption spectrophotometry showed the concentration of Cs to range between 4.5 and 148 $\mu g/L^{-1}$ (*21*). Information on the occurrence of Cs as a pollutant in air samples is meager, only one survey having been made in the United States. (*22*).

In Living Systems

The distribution of Cs in living systems depends on several factors. These include availability of Cs in the environment, like soil and water, and the presence of other elements, particularly potassium. The presence of stable Cs in the soil, in specific doses, also influences the uptake of radioactive Cs^{137} by plants. Simultaneous addition of stable and radioactive Cs to the soil increased the uptake of Cs^{137} by the bushbean, *Phaseolus vulgaris* (*23*). Large amounts of stable Cs, on the other hand, can also decrease uptake of Cs^{137} by isotope dilution.

Among algae, a detailed analysis of 14 species of the family Sargassaceae from four locations in Japan showed considerable variability in the content of Cs. *Sargassam thunbergii* accumulated a higher amount than the other species (*24*). Relatively detailed information is available on the occurrence of Cs in higher fungi (*25*). The content was determined in 433 species (1166 samples) of European wild fungi, including Ascomycetes and Basidiomycetes by flameless atomic absorption spectroscopy. It ranged from less than 0.1 to 308 mg/kg dry weight with an average of 7 mg/kg. The highest concentrations (308 mg/kg dry weight) were recorded in *Cortinarius alboviolaceus* (family Cortinariaceae) from Sweden, followed by Clavariaceae, Rhodophyllaceae, and Strophariaceae. The amounts in Helvellaceae and Lycoperdaceae were low. However, marked fluctuations were also recorded within the same species grown in the same location, indicating the modifying effects of other factors, probably climatic ones, on the uptake of this element. The higher content of Cs in the

fungi was to some extent related to the soil content. The distribution was related to the type of the tissue. In general, the amount of Cs was usually highest in the flesh of the cap in the fruit body and the lowest in the gills or more rarely in the stem. An earlier study of *Saccharomyces cerevisiae* (yeast) by energy dispersion X-ray microanalysis of thin sections had shown that the intracellular distribution of Cs and the allied elements K and Rb was similar. Their total concentration in the cytoplasm (190 mg/kg fresh weight) was about equal to that in the nucleus and twice that in the vacuole (*26*).

Neutron activation analysis was used to measure Cs in grass samples from mining districts (*27*) and rice species (*28*) marketed in Austria. The values did not show any significant variation in the latter, ranging from 0.016 to 0.032 ppm.

The occurrence of Cs, as with other trace elements, differs in parasites. For example, helminths like *Fasciola hepatica* growing on different hosts show different amounts, possibly belonging to different taxonomic groups, related to the specific metabolism of both the host and the parasite and also the biogeochemical environment (*29,30*). Larvae of class Trematoda were seen to accumulate Cs and the amount was correspondingly reduced in the invaded host freshwater snails, like *Lymnaea stagnalis* (*31*). Other metals also affect the Cs content in the body wall of *Ascaris suum*, notably Na and K (*32*). A comparative study of the distribution of the alkali group metals in marine animals had shown that muscle cells selectively absorbed K, Rb, and Cs from extracellular fluids. Distribution of Rb and Cs in these cells was related to a certain extent to the specialization of muscle fibers for the performance of phasic activity (*33*). In the North Pacific albacore, concentration of Cs was 26.75–2.35 in liver and 37.10–0.72 in muscle respectively (*34*). Detailed investigations on distribution of Rb and Cs in fresh water migrating marine fishes shows a relationship with the type of the tissue (*35*). The value of Rb/Cs in the muscle tissue of fishes is usually almost the same as in the preceding link of the food chain (*36*).

A direct relationship was noted between food intake and Cs concentration in yellow-fin tuna (*Thunnus albacares*) (*37*). Significant positive correlation was observed between K and Cs concentrations in all tissues studied excluding kidney (*38*).

In laboratory bred rats, given 0.025 ppm Cs dry weight in diet, the amounts present in the different organs (as ppm dry weight) were trace in lung, 0.028 in brain, 0.036 in liver, 0.043 in spleen, 0.069 in heart, and 0.062 in kidney (*39*). In an earlier experiment, where the diet contained 0.032 Cs (ppm dry weight), Cs values for kidney and liver were higher but for the heart were lower (*40*) indicating that the amount accumulated is associated closely with the amount in the diet. Cs content of blood (as μg/kg) was 0.42 in plasma and 1.82 in erythrocytes in another set of rats on diet similar to the first one. The amounts of Cs in kidney and liver were, however, much lower (*41*), indicating the role of factors other than

dietary ones in retention of the metal. Analysis of bovine tissues shows the highest concentration of Cs in the forepart of the animal body (buccal and shoulder muscles, tongue, esophagus) (*42*).

In human systems, as in other higher animals, Cs is a biologically important trace element owing to its relationship with K in different biochemical and physiological processes. The amounts detected in serum and packed blood cells were about 0.74 and 4.82 μg/kg net weight respectively (*43*). The relative quantities in pure and impure platelets were 54.8 ± 19.2 and 35.2 ± 13.8 respectively (*44*). In an earlier study of human tissues of cadavers in England, stable Cs in the bone occurred in the same proportion as in soft tissues (9–20 ng/g wet weight). The estimated amount of body Cs located in calcified bone was 2–7% (*45*). Cs was observed to be widely distributed throughout the human body, mainly in the soft tissues (*46*). Uptake from gastrointestinal tract was rapid and essentially complete. Excretion was principally by the urine, but there was a continuing loss through the feces, irrespective of the mode of exposure. The whole body retention of the element can be expressed by a two-component exponential function of time. An average of 10% of a single oral dose is excreted within 1–2 d, but the major part has a half-life of 50–150 d. This variability may explain the wide range of Cs^{137} contents reported from fallouts. More recent studies give a median value of 3.7×10^{-8} ppm for Cs in human bone, which is uniform for both sexes but varies significantly between child and adult (*47*). A single report is available on the presence of Cs in trace amounts in human milk from Australian women (*48*). The amount of Cs in human tissues has been associated with the age of the donor in some cases. It has been shown to increase with progressing age in nearly all organs, except the skin (*49*). In brain, however, the proportion of Cs shows no consistent relationship with age, unlike K, P, and Rb (*50*).

The levels of Cs have, in certain cases, been associated with disease conditions. In brain tissues from schizophrenic cadavers, an increase in Cs has been reported (*51*). Significant difference ($p \leq 0.05$) has been observed in concentrations of Cs from 40 bulk samples, from patients with Alzheimer's disease, as compared to controls (*52*). In addition, persistent imbalances are seen for the univalent cations Na, K, Rb, and Cs, supporting the hypothesis that Alzheimer's disease is caused by membrane abnormality (*53*). Patients with major depressive disorder had reduced blood levels of Cs, which increased to normal levels on recovery (*54*). Contrary to earlier reports, no difference in Cs concentration was recorded in urine, serum, and blood samples between manic, depressed, recovered manic, recovered depressed patients, and normal controls, by neuron activation analysis (*55*). Cs content of blood plasma (+73%) and erythrocytes (+51%) was enhanced in persons with renal disorders during the first stages of the disease. This suggests an effect of renal insufficiency on the Cs load of these patients (*43*). In 10 patients treated with chronic dialysis, Cs amount in serum was high before dialysis but

decreased afterwards. There was no change in RBC (*56*). Total opaque (mature) cataractous lenses from 51 patients with senile cataract showed amounts of Cs related to the age of the donor (*57*). In a group of 40–59 yr-old males from Leningrad with histories of ischemic heart disease, a correlation was found between the content of trace elements, including Cs, in serum and levels of cholesterol, triglycerides, and α - lipoprotein cholesterol in the blood (*58*). Only one report is available of variation in blood Cs content between cancer patients and control, but the data is inconclusive (*59*).

The half period of retention of radioactive Cs^{137} in the human body has been variously given as 80–130 d with an average urinary excretion of 0.6% of the body burden (*60*). In some pregnant women, the biological half-life was seen to be 30 d and in their infants after birth of only 25 d (*61*).

UPTAKE AND TRANSPORT

Soil-Plant-Animal-Human Chain

The exposure of human systems to Cs is considerably influenced by its incorporation into the food chain, which, in part, is determined by the transfer from soil to plants (*62*). The extent of transfer depends on a number of factors. Some are well-known, like the species of the plant, growing conditions, soil properties, and agricultural methods (*63*). Other aspects have not been studied in such detail (*64*). Fixation in the lattice structure of clay minerals is the most important factor for the biochemical cycling of Cs in terrestrial ecosystems (*65,66*). The degree of fixation influences the subsequent longterm availability of Cs to plants and depends on the type and portion of clay minerals (*67*). Agricultural methods also affect the uptake of Cs by roots (*68–71*). Plowing of the soil, for example, mixes the superficially deposited Cs into subsoil layers. The transfer of Cs is similar between different marshy soils but is almost twice or more on podzol, which contains low total K, low clay, and fine silt (*62*). The degree of transfer also decreases with the age of the Cs deposit in the soil (*72*). In permanent pastures, the pH and amounts of organic carbon, exchangeable K and total Ca do not affect the Cs transfer significantly (*62*). The entry into the food chain and finally into the human system may be directly through fodder into animals used for meat and milk.

Uptake and Transport in Plants

In algae (*Chlorella kessleri* and *Scendesmus obliquus*), the value for accumulation of Cs was found to be 2.9 (*73*). In various hydrophytes, including plankton and benthic algae and some members of Potamogetonaceae, from the Lithunian freshwater basin, the process of absorp-

tion of various radionuclides, including Cs^{137} by different cell components, was studied with reference to the role of the plant in radionuclide migration (*74*). In yeast cells, the translocation of Cs at low pH is by three sites across the cell membrane, of which the interaction of Cs is only with the double electrical layer (*75*). The amount of Cs uptake by mushroom is higher because of the large surface of the mycelium. The absorption of Cs by lichen, being probably by the mycobiont, is less than that of the fungi (*76*). A more efficient retention of Cs^{137} was recorded in lichens from Brunswick, Canada, probably owing to its physiological uptake as a proxy for K. An inverse relationship between Cs^{137} and K^{40} activities is seen in lichen (*77*). The accumulation of alkali metals, including Cs, showed a high level of correlation with taxonomic characteristics of 62 plant species collected from 9 sites in the temperate forests of Japan. A marked association of Cs (8.2 ppm) was detected in leaves of *Lastrea japonica*, which was 6 times higher than species with the lowest concentrations (*78*).

In bean plants, Cs enters the roots and reaches the protoplasts of the epidermal cells, the speed of penetration being increased in the presence of K (*79*). The concentration ratio for Cs in trifoliate leaves of bush beans (*Phaseolus vulgaris*) varied from 8.67 (in presence of high K) to 0.96 (low K). The Y values (effect of concentration vs uptake) for Cs in plant parts were consistently near one, indicating Cs uptake to be directly proportional to its concentration in the nutrient solution. Roots accumulated 6 times more Cs than did leaves (*80*). The penetration of Cs through isolated *Prunus aremeniaca* leaf cuticles takes place by diffusion and is impeded by charge interaction between the solute and charge sites in the penetration pathway (*81*). The upward movement of Cs in the xylem and redistribution from the leaves of *Lycopersicon esculentum* (tomato plants) showed a delay with respect to the redistribution of newly imported Cs from the source leaf, of about 16–20 hs. The net Cs delivery into the leaves was considerably altered in the presence of fruits (*81,82*). The lateral escape of Cs from the xylem seems to be proportional to the surface area of the xylem vessels and is apparently controlled by its transport across the cell walls of the transport channels (*83*). Cs uptake in roots of winter wheat was found to follow a dual pattern similar to K in barley. The soil-to-root transfer factor decreases in relation to an increase in the substrate concentration of the metal. At substrate concentrations equivalent to carrier-free Cs concentration, however, the soil-to-root transfer factor is linear (*84*). The movement of Cs from the parent trees to the seedlings of *Liriodendron tulipifera* was followed from floral parts of inoculated trees, through seed maturation, and into the components of germinated seedlings. Cs^{137}, in both fruit and seedlings (cotyledons), followed pathways paralleling those of sugars and other translocated organic substances that may be stored in the tissues and later used to sustain early seedling growth. This shows that Cs may be transferred from the parent trees to second generation plants (*85*).

Uptake and Transport in Animals

Transport of Cs in animals is actively dependent on the intracellular concentration of K ions.

Invertebrates

The ability of single neurons of the snail, *Planobarius corneus*, to accumulate Rb and Cs varies in the presence of ouabain in vitro. In such cases, the passive uptake of these two metals is related to intracellular K concentration and the K diffusion potential plays a major role (*86*). The short circuited midgut from the larvae of *Hyalophora oecropia* can actively transport Cs, together with Rb and K from blood to lumen. Cs and K compete in the transport mechanism. High Cs:K values facilitate active transport of Cs (*87*). The application of Cs (2000 ppm) to tobacco budworms, *Heliothis virescens* eggs, revealed that individual eggs contained detectable levels of Cs (68%) alone. The latter was reduced by 10% over a 7-d period. Cs concentration could be detected in whole bodies, wings, and head capsules of both treated males and females (*88*). The uptake of Cs by beetle larvae (*Chrysomela knabi*) feeding on willows was estimated to be 7–16 mg dry weight of plant/larvae/d under field and 9–10 under laboratory measurements (*89*). The accumulation of Cs in the muscle tissues of perch (*Perca fluviatilis*) was found to be slightly higher than for roach (*Rutilus rutilus*) (*90*).

Lower Vertebrates

When embedded frog muscles are exposed to various concentrations of Cs, the deposition of Cs occurs in specific protein sites in the A-bands and Z-lines of myofibrils (*91*). It is suggested that Cs ions, like other alkali metals, are not free in cell but are absorbed on α -carboxyl side chains of cell proteins (*92,93*). Administration of 40 m*M* CsCl in drinking water to rats for periods up to 15 d led to rapid uptake of Cs into fibers in red soleus and in pale vastus lateralis muscles. When Cs rich muscles were immersed in plasma for 30 min, from the same animal containing ouabain, and bubbled with N and the membrane potentials were measured, very striking accumulation of Cs was seen in red muscles in contrast to pale ones. This effect was probably not owing to slower efflux of Cs but to a much faster influx of cation (*94,95*).

Mammals

Following intravenous administration of CsCl to laboratory rats, the total excretion of Cs was cumulative, between 50 and 20% of the dosage in 4 d. Fecal excretion was relatively slow and urinary between 2 and 7% of the dosage in 4 d. The maximum excretion was in the first 24 h. The fraction of the metal excreted into bile did not depend on the dose administered. The bile/plasma concentration ratio was close to 1, and for liver/plasma above 1, indicating that the metal was concentrated in the

Table 1
Distribution of Cs (% of dose/10 g or mL tissue)

Dosages (mg/kg)	3	10	30	100
Liver	4.00	3.76	4.20	4.06
Kidney	7.43	7.28	6.13	5.90
Spleen	2.52	2.57	2.62	2.51
Heart	6.41	6.39	6.00	6.16
Lung	2.61	2.60	2.69	2.78
Pancreas	3.35	2.77	3.53	2.89
Intestine	5.08	5.10	5.40	5.26
Stomach	2.31	2.18	2.09	2.15
Testes	0.441	0.394	0.383	0.459
Muscle	0.536	0.573	0.607	0.656
Bone	1.08	1.06	1.02	0.802
Brain	0.130	0.127	0.122	0.146
Blood	0.158	0.164	0.162	0.186
Plasma	0.141	0.132	0.127	0.136

liver. The tissue distribution of Cs 2 h after administration is given in Table 1 (*96*).

Administration of semichronic (repeated) and acute injections of CsCl to mice and subsequent study of brain tissue showed that the accumulation was considerably higher with repeated treatment. The concentration in the brain remained elevated up to 6 d after the termination of treatment. The course was biphasic with the highest levels obtained 48 h after treatment. Treatment with Rb gives similar results but Li reached a peak much earlier and decreased progressively. These differences might be related to the duration of action of these three elements (*97*). Cs accumulation in brain slices had been earlier suggested to depend on energy metabolism, similar to the accumulation of K (*98*). The absorption of Cs in the gastrointestinal tract was found to be 6.4–79% of the daily intake. When bentonite (a clay mineral belonging to the filicilicates) was added to the diet, the intestinal absorption of Cs was drastically reduced (*99*).

Specific activities of Cs^{137} and Cs^{133} were found to be similar in brain and muscle of the reindeer, *Rangifer tarandus*, although the concentration was higher in the latter issue (*100*). In dairy cows, fed with Cs-contaminated hay for 5 wk, the concentration in milk followed the Cs-intake rather quickly during the first week. After 5 wk, the specific activity of Cs in the milk reached a level of 10.9 nLi and attained equilibrium. In general, 60% of the Cs uptake was excreted with the feces, 20% with urine, and 5.0–8.8% with the milk (*101*).

In different mammals, including rats, the absorption of Cs^{137} from the gastrointestinal system is rapid and its movement is affected by the

presence of food (*102*). Excretion increases with reduction of environmental temperature, probably owing to increased metabolic rate (*103*). Enhanced K intake above requirement reduced the half-retention time for Cs^{134} at a decreasing rate (*104*). Increased age influenced retention of Cs^{137}, but not uniformly (*105*). Chronic exposure of more than 400 d gave the highest levels in muscle and the lowest in fat. Concentration in the whole bone is related to the quantity and the state of the bone marrow (*106*). It appeared rapidly in the fetus after oral administration to pregnant mice (*107*). Supplementation of diet with high levels of KCl and NaCl increased the rate of excretion of Cs^{137}, possibly owing to diuretic action (*108*). Intraperitoneal administration of Cs^{134} as chloride to mice induced the maximum Cs level in the kidneys, heart, lungs, and liver in the first hour, in the muscle after 8 h, and in brain and blood after 24 h. Transport is not wholly dependent on the ATPase system (*109*).

Human System

Because of the health hazard for radio-isotopes of Cs, interest was initially focused mainly on whole body retention of radionuclides and their elimination (*1,41*). The main pathway of excretion was considered to be through the kidney, the ratio of urinary-to-fecal absorption being 10:1. Orally administered Cs^{137} is rapidly and almost completely absorbed and is taken up by red cells from the plasma. The distribution in tissues decreases with time and the biological halflife was found, from analysis of excreta, to be 50–60 d. The rate of excretion could not be enhanced by diuretics, corticosteroids, or ion-exchange resins (*110*).

Both diet and environment are responsible for the accumulation of Cs in the human body. In 10 families from Japan the estimated daily intake of Cs in diet was 0.01 mg (*111*). The metal can also be deposited in the lung from inhaled particulate matter (*112*). Scalp hair was found to contain traces of Cs (*113*). In samples from Italy, Cs contents in human milk could be related to Cs concentration in diet and drinking water (*114*). Various factors have been offered to explain or predict such wide variation in the retention of Cs among humans.

The model for the retention of Cs in human internal organs was derived from the rat model by modifying the rate constants to fit human data (*115*). The retention pattern of Cs in adult humans may vary widely with age, sex, and state of health, and may also show substantial variations for healthy persons of the same age and sex. McCraw (*116*) developed a model that expresses the biological half times of Cs as an increasing function of age throughout life. Total body K appears to be a reliable index to estimate retention of Cs. Cs follows the movement of K in the body and competes with K for transport across cell membranes, but substantial differences in the distribution and retention of Cs develop because of differences in transport rate across membranes (*1*).

Cs^+ is known to activate Na/K-dependent ATPases in the absence of K^+ (*117–120*). It is transported into cells through pathways sensitive to

ouabain inhibition. The amount of Cs^+ needed to activate Na/K-ATPase and the transport rate varies depending on the system studied. Usually Cs^+ is less effective than the other alkali metal, Rb^+, in substituting for K^+. In specimens with excitable membranes, Cs^+ blocks the voltage-dependent channels that normally conduct Na^+ or K^+ ions. The resting permeability of Cs^+ is, however, 0.3–0.1 times the K^+ permeability (*121*).

EFFECTS OF CS ON PLANTS AND LOWER ORGANISMS

Lower Organisms

The growth of spiroplasma is inhibited by CsCl, the effect being inversely proportional to the concentration. At 150 m*M*, growth of *Spiroplasma floricola* was inhibited totally, whereas limited growth was observed for *S. melliferum* (*122*). The bottom component of B_{1a} of turnip yellow virus with a buoyant density of 1.45–1.43 g/mL is converted to a more dense particle B_{2a} following CsCl density gradient centrifugation. This conversion is enhanced by incubating the virus in CsCl solution at elevated temperature, which may be because of the exchange of polyvalent cations like Mg^{2+} and spermine with Cs ions (*123*). When propagated in Cs-rich medium, poliovirus incorporates enough Cs atoms to shift its buoyant density from 1.34 to an upper limit corresponding to about 4200 Cs atoms/virion. The Cs-loaded virions were normal with respect to specific infectivity, neuralizability by specific antisera, and electrophoretic profile of coat protein. If the RNA of the virus is exposed to Cs ions while the virus is being assembled, the poliovirus binds approximately the same number of Cs ions as human rhinovirus (*124*). Cs ions bind to the cell wall of psychrophylic microorganism (*Flavobacterium*) at different temperatures (*125*). Cs was seen to be a noncompetitive activator of the enzyme tyrosine-phenol lyase present in *Citrobacter intermedius*. It affects the absorption and LD spectra of the enzyme and its complex with the quasi-substrate-alanine. The activation of tyrosine-phenol-lyase by Cs was connected with the increase of the active protonated form of the holoenzyme (λ max 420 mm) induced by Cs activators (*126*) owing to conformational rearrangements of the protein molecules (*127*). Even in *Bacillus cereus*, the enzyme adenosine deaminase (EC 3.5.4.4) that is quite unstable, is stabilized by Cs, indicating that Cs influences the reactivity of some SH groups of the enzyme (*128*). Ribosomal proteins of *E. coli* are dissociated under the influence of high CsCl concentrations from the ribosomes, turning normal 50S and 30S ribosomal subunits (37% protein) into protein-deficient 43S and 28S particles called A particles (30% protein). Centrifugation of these A particles in CsCl leads to the formation of ribonucleoprotein particles even deficient in protein (20% protein). However, the dissociation of proteins from

ribosomal particles under the action of high CsCl concentration appears to be reversible (*129*). Another report suggests a competition between streptomycin and Cs uptake by *E. coli* B cells. Cs ions however, were more weakly bound than streptomycin (*130*). *E. coli* cells that contain a functional Kup (TrKD) system took up Cs^+ with a moderate rate and affinity. Kup (TrKD) is a separate K^+ uptake system with relatively little discrimination in the transport of the cation Cs. Regardless of the presence or absence of Kup, K^+ replete cells took up Cs primarily by a very low affinity mode, proportional to the ratio of the Cs and K concentrations in the medium (*131*). Cs (0.01*M*) is observed to increase the rate of hydrolysis of ortho-nitropheno-β -D-galactosidase in *E. coli*, although higher concentrations are inhibitory. Cs induces inductive changes on the active site through binding with the substrate (*132*). Acyl-coenzyme A carboxylase from *Streptomyces erythraeus* was activated by Cs (*133*). *Holococcus morrhuae* and *Halobacterium vallismortis* assimilated succinate in the formation of dicarboxylic acids and the rate of assimilation was hindered by CsCl (*134*). Growth yield of halotolerant bacterium A505 was inhibited by Cs and Li, unlike the other alkali metals; including Rb (*135*). When bacteria were irradiated in a solution of Cs salts, the lethal action was significantly higher than that obtained by irradiating the bacteria alone. Bacterial denatured DNA increased in buoyant density by about 0.045 density units in alkaline CsCl solution. Loss of water occurred from the hydrated Cs-DNA complex. One-third of the water was liberated by the DNA per degree elevation in temperature (*136,137*).

Growth of the algae *Chara fragilis* and *C. vulgaris* was increased in the presence of small amounts of Cs and Rb (*138*). Outer membranes of the cells of *C. corollina* contain channels that are highly selective for K^+. Cs is seen to reduce K currents in *Chara* at high C_DK^+ (Ca^{2+}) channels. It mainly inhibited K^+ inward current, in a strong voltage-dependent manner. The effective valence of the blocking reaction was often greater than one, increasing with higher external Cs and lower K^+ concentrations. Selectivity of the channel to Cs varied, depending on the method of measurement, suggesting that ion movement through K-selective channels may not be independent (*139–141*). Cs was observed to activate glutamate dehydrogenase of *Chlorella pyrenoidosa* (*142*). Cs ions affected growth and induced lock-like banding in wild strains of *Podospora anserina* at low concentrations (0.04 mol/L) (*143*).

In yeast, Cs stimulated the depression of phosphate transport produced by glucose to a lower extent than K (*144*). Toxicity of organotins towards the marine yeast *Debaryomyces hansenii* has been observed to be reduced by CsCl (*145*). Cs also inhibited the enzyme Δ24 sterol methyltransferase present in mitochondria of yeast (*146*). Cs is considered to be the most toxic among the alkali chlorides and inhibits growth of *Aspergillus niger* and *A. oryzae* (*147*). It reduced the levels of the enzymes acetamidase, histidase, nitrate reductase, and urate oxidase in *A. nidulans* (*148*) and inhibited ribonuclease present in *Ustilago sphaerogena* (*149*). On

the other hand, mutants of *Micrococcus varians* ssp. *halophilus* were able to grow in CsCl when isolated from a complex medium (*150*).

Higher Plants

The toxic effect of Cs studied on tomato plants was seen to depend on two parameters: reaction affinity of the element to the organic fraction of the cell and the accumulation coefficient (*151*). Hypocotyls of tomato seedlings, germinated both in light and dark with CsCl, appeared as though they had been attacked by a virulent pathogen or wilt disease (*152*). CsCl when given at concentrations of 0.1–100 mm reduced the amounts of amino acid and ammonium nitrogen in tomato leaves (*153*). The metal accumulated in leaf, stem, root, and apical points, suggesting the presence of constant absorption sites for Cs in these tissues (*154*). Although the germination frequency of tomato seedlings was high when CsCl solution was added, root growth was inhibited. In addition, the hypocotyl hook region became adversely sensitive to white or red light. Hypocotyl hook was suggested to be the primary site of Cs-induced photosensitivity (*155–157*).

The mean dry matter content and drying rates of alfalfa (*Medicago sativa*) were increased by 0.2*M* of Cs solution (*158,159*). Similar to other alkali metals, CS was observed to prolong the period of the leaf movement in *Oxalis regnellii*, depending on the ion concentration when applied continuously (*160*). Different concentrations of Cs were measured in the leaves of *Sapindus mukorosis*, *Alstonia scholaris*, and *Diospyros embryopteris* following airborne emission (*161*). The uptake of Na in the presence of Cs was enhanced at lower concentration and inhibited at higher concentrations in pea, cucumber, and wheat plants. Stimulation was strong in wheat, less pronounced in cucumber, and weak in pea plants (*162*). Zn absorption in wheat was depressed by Cs (*163*). Germination frequency and germination energy of cucumber seeds were enhanced when grown in Cs. Activities of catalase and peroxidase were also enhanced, but not of phenoloxidase (*164*). Wheat germ acetyl CoA carboxylase (*165*), peroxidase, and isocitric dehydrogenase were all activated by Cs. Cs affected the protein metabolism of sprouting seeds of wheat, intensifying the conversion of stored protein and the accumulation of structural and catalytic proteins (*166*). Chlorophyll synthesis was hampered, followed by shoot damage, when etiolated barley seedlings received Cs nutrition exposed to radiant energy (*167*). Cs in nutrition inhibited chlorophyll development and accumulation of protochlorophyllide in the following dark period. These changes in the chlorophyll development caused by Cs were closely related to changes in the fine structure of the plastids in the plants. The arrangement of the thylakoids in the typical grana structure could be scarcely detected in the plastids, and most thylakoids were swollen, associated with strongly depressed chlorophyll synthesis. Changes in the structural protein of the plastids,

resulting from Cs nutrition, were primarily responsible for the decreased chlorophyll synthesis. The total pigment disintegrated and the barley sprouts died. Such harmful effects of Cs are mediated through photoinduced absorption of Cs ions, which change the conformation of protein molecules and disturb their normal functioning or convert porphyrins to protochlorophyllide (*168–170*). The presence of Cs has also been observed to increase the intensity of two fluorescence bands of pigment system I at 735 nm in spinach chloroplasts (*171*).

EFFECTS OF CS ON ANIMAL SYSTEMS

Lower Animals

The damage induced by Cs could be related to the concentration to which the system was exposed. Recessive mutants of *Paramecium tetraaurelia* have been shown to be sensitive to CsCl in higher doses, together with RbCl and KCl (*172*). In the septal membranes of the median and giant axons of earthworm, which contain gap junctions, two types of channels were seen. One type, apparently a K^+ channel, was blocked by Cs^+ and had a unitary conductance of 30–40 ps. The other, with a unitary conductance of 90–110 ps, could conduct Cs^+ even in the presence of other divalent cations (*173*). In single neurons of the snail, *Helix aspera*, the A-current K^+ channels are permeable to Cs^+ (*174*). When external K^+ ions are replaced by Cs^+, the outward currents are reduced (*175*). A similar high permeability was seen for single glutamate-gated channels in locust skeletal muscle (*176*). The blockade of snail neuron K^+ channels by other alkali metals, including Cs^+, was found to depend on the voltage (*177*). Internal Cs, relative to internal K, altered Na current time course in *Myxicola* giant axons (*178*). Application of Cs^+ to the basal face of sensory epithelium of Lorenzinian ampullae of the Black sea skate, *Raja clavata*, suppressed spike response adaptation (*179*). Similar to K^+, Cs^+ can also produce a reversible abolition of the action current in the nerve of *Maia squinado*, but 3.2 Cs ions are needed to give the effect of one K ion (*180*). Large concentrations of Cs ions could block a small, but statistically significant, fraction of outward K current for potentials < 50 mV positive to reversal potential in axons of the squid, *Loligo pealei* (*181*). The isolated gill cuticle of the shore crab *Carcinus maenas* showed a level of permeability to Cs^+ that was higher than Rb but lower than K^+ (*182*). A single report is available of the induction of metamorphosis of *Phronis psammophila* larvae (Phoronia, Tentaculata) by CsCl (*183*). Pink bollworm, *Pectinophora gossypiella*, raised on artificial diet containing Cs or on cotton plants sprayed with different doses of CsCl, showed the presence of Cs in the adults. Higher doses (5×10^{-2}) of CsCl were, however, lethal (*184*).

External Cs blocks the adenosine 5′-triphosphate-dependent K channels in sarcolemma vesicles from frog skeletal muscle in a voltage depen-

dent fashion, the degree of blockage increasing with hyperpolarization (*185*). Similar results were obtained from frog sinus venosus trabeculae (*186*). In frog skeletal muscle cells, Cs competed for the absorption sites normally occupied by K^+ (*187*) and strongly reduced K conductance in atrial trabeculae (*188*). External Cs ions reduced K efflux in muscles incubated in Na containing medium, apparently by inhibiting the K:K exchange mechanism (*189*). Cs ions are possibly transported inwardly by an active process after first accumulating in a superficial reservoir (*190*). Gradual increase of miniature end plate potentials was observed in frog neuromuscular junction, which decreased when low concentrations of CsCl were applied (*191,192*). Cs has been observed to increase the osmotic fragility of erythrocytes in dehydrated frogs (*Rana temporavia*) by affecting the water balance of the animal (*193*). Cs depressed pacemaker activity, conductivity, contractility, and vagal stimulation of frog hearts by replacing K (*194*). In frog skin, Cs blocked K transport by binding to site within the channel (*195*). Analysis of the Na^+ kinetics shows that K^+ and Cs^+ participate in a Na^+ exchange mechanism in direct proportion to their penetration across the cell membrane (*196*). *Bufo arenarum* eggs reared in Cs solution showed maximum anomalies at the blastula stage (*197*).

Cs polarizes the skin of the fish *Kryptopterus*, producing a specific skin potential, but a dependence characteristic of its own. Both the skin potential and the potential of the sensitivity maximum are nearly equal (*198*). Summated neurol responses were observed from the peripheral nerves of the lateral line organs in the goby, *Gobius giorinus*, in the presence of a threshold of $-\ 10^{-3}M$ Cs solution (*199*). Most of the intracellular K^+ in the turtle, *Testudo hermani*, can be replaced by Cs^+. The intracellular accumulation of Cs possibly occurs via an active inward transport system that operates with the simultaneous efflux of Na (*200*). Isotonic Cs solutions depressed outward current of acetycholine-activated channels of chick myotubes. Dilution of internal Cs increased the permeability of the channel (*201*).

Mammals

Since Cs is an industrially important element and exhibits properties similar to the other alkali metals, a large amount of information is available on the toxic effects of Cs compounds, using mammalian test systems.

Interperitoneal injection and oral administration in both rats and mice gave moderately toxic effects, except the hydroxide of Cs compounds (*202,203*). Even the hydroxide and iodide were less toxic than the corresponding salts of Rb and K. In most reports Rb compounds were found to be more potent than Cs compounds in bioactivity and toxicity. However in one case greater chronic toxicity was reported for CsCl in rats than the other two elements (*204*). Higher amounts of CsCl and RbCl

reduced the voluntary intake of alcohol by rats (*205*). Toxicity of chloride, sulphate, carbonate, and nitrate of Cs was observed to be relatively low in all laboratory animals following all modes of administration. Of these the first two salts were even less toxic than the two latter (*206*). When Cs was given intragastrically, subcutaneously, or intraperitoneally to mice and rats, no signs of distress or of poisoning could be seen. In fact, some rise in the resistance of the animals to the repeated administration of Cs was observed. Subcutaneous injection of 26 mg $CaCl_2$ resulted in excretion of 17.5–20% of the Cs in the first 24 h, and 3% in the next 24 h. The urine eliminated 84–85% of the Cs and the remaining in the feces. Rundo (*207,208*) later carried out elaborate experiments on the effects of Cs salts on frog, mice, guinea pigs, pigeons, rabbits, and cats. All the salts were found to be toxic in higher doses. Following IV injection, the toxicity was twice that after oral route and 1.5 times that after subcutaneous route. Direct harmful effects of Cs compounds on mammals observed included acute and chronic poisoning and irritation of skin and mucous membrane. Cs_3AsO_4 was seen to be embryotoxic. Permissible levels in the air were suggested to be 0.03 mg/m^3 for Cs_3AsO_4 and 0.3 mg/m^3 for CsOH (*209*).

Despite such mild toxic effects, Cs has been clinically used as an antidepressant of motor activity in mice (*210*). CsCl shows the lowest toxicity. It reduces isolation-induced aggression (*210*) and decreases the analgesic action of morphine (*211*). Multiple ip injections of sc doses of CsCl to rats and mice daily for 4–56 d showed no significant difference from controls in tissues from lung, brain, liver, kidney, and spleen of mice. In ileal tissue only, prominent lymphoid follicles were seen. A single high acute dose induced effects more or less similar to the chronic one. Ca accumulates rapidly in both rat liver and kidney (*212*). NaDH in rat liver was inhibited when CsCl was added to submitochondrial particles (*213*) and the 60s ribosomal subunits of rat liver were inactivated at a relatively low concentration (*214*). The levels of lipoperoxidation and glutathione were altered in livers of mice and rats, following application of 40 mol/kg of Cs; related to dose and time of exposure (*215*). In a study of different animal circulatory systems, in vivo and in vitro, CsCl and Cs_2SO_4 were observed to cause negative chrono-, ino, and dromotrophic reactions and at high doses, disturbance of rhythm and stoppage. The mechanism of Cs action is composed of direct and reflex effects on the vasomotor nerves, central and peripheral cholinergic components, adrenergin component, and direct effect on the vascular system musculature (*208*).

Cs has no known vital function. However, since the concentrations of Rb and Cs appear to show a similar level in rats, depending on the organ and the postnatal age, and Rb is known to possess unique neurophysiological characteristics in animal systems (*216*), it was suggested that these two elements are essential to life (*217*). Cs ions activate chloride channels in cultured rat spinal cord neurons, possibly by acting

directly on the extracellular surface of the neurons. The channels activated are of the same type as are activated by GABA and the inhibitory neurotransmitter glycine (*218,219*). The locus ceruleus neurons of rat showed anomalous rectification strongly dependent on the external K^+ concentration, which could be blocked by external Cs^+ (*220*). External Cs ions also depressed the acetycholine (Ach) induced inward current in rat adrenal chromaffin cells in culture (*221*). Cs^+ is also shown to disturb the normal neuromuscular transmission of stimulus in rats (*222*). In cats immobilized by myorelaxants intracellular injection of Cs^+ ions in pyramidal neurons of sensorimotor blocked inward current (*223*). Similar blockade of various K conductances by internal Cs^+ ions was also recorded in cat motoneurons (*224*).

Regional changes were induced in brain glutamic acid and α-aminobutyric acid when rats were injected with CsCl (*225*). The effect on creatine kinase, 5'-nucleotidase, phosphodiesterase, and deaminase was very low. AMP protein kinase was inhibited in brain (*226*). Binding of rRNAse to Cs occurs only when the nucleic acid is sufficiently deionized (*227*). Acute action leads to autonomic upset in mice and multiphasic excitant–depressant effects on the central nervous system (*228*). Excitant effects of Cs ion had been described in the central nervous systems of mammals (229–233).

A depressant component of CNS responses and a possible antipsychotic-like activity were postulated (*234–236*). Cs was also seen to interfere with acquisition of pole-climbing conditioned avoidance response (CAR) and showed a mutual synergism of CAR suppression with chlorpromazine and haloperiod (*237*).

Irradiation with Cs^{137} induced additional DNA synthesis in the neocortex tissue and the neurons of the cerebral cortex of rats. In 14-day-old animals, the induced synthesis stopped 2 h after irradiation whereas in the cortex of 60-d old rats and in neurons of rats of both age groups, it proceeded for 3–3.5 h (*238*).

In rat erythrocytes, the affinity of Cs to the binding sites is decreased by Cs (*239*). Cs produced extrusion of Na in the rat myometrium (*240*). In isolated rat osteoclasts, Cs could suppress the inward currents activated by hyperpolarizing voltage commands (*241*). Differences were reported in the retention of Cs^{137} and Cs^{144} in male and female rats following ip injections. The differences were related to the age of the animal, but not to a significant level. The retention in the skeleton was most affected (*242*). A combination of Cs salts (carbonate or chloride), zinc gluconate, and vitamin A showed repression of tumor growth in colon carcinoma implanted in BDF_1 mice (*243*).

In cats, Cs salts at doses from 5 mg/kg to the lethal dose (160 mg/kg) initiated a bi-phasic action, with an initial brief hypotension followed by moderate hypertension, bradycardia, and weakening of the cardiac contractions (*244*). Diastolic depolarization is caused by a Cs-sensitive component (*245*). The most striking effect of internal Cs on cats was a marked

prolongation of the falling phase of action potentials, a large reduction in the amplitude after hyperpolarization, and a considerable increase in the size of the delayed depolarization. Similar effects were observed in dogs (*246,247*). Internal Cs apparently blocks voltage dependent K conductance of spike repolarization (*224*). Cs induced early and delayed after depolarization, ventricular arrhythmia, and atrioventricular blocks in feline, canine, and sheep Purkinje fibers (*248,249*).

Cs is adsorbed on cell membranes in guinea pig hearts (*250*) and protects against myocardial ischemia in guinea pigs by facilitating restoration of developing pressure and reducing the "reperfusion contracture" (*251*). It releases superoxide from guinea pig peritoneal neutrophils (*252*). The addition of Cs to brain cortex of guinea pigs led to considerable increase in the respiration of the brain mitochondria, optimally at 10–50 m*M* (*253*). Cs ions allowed Purkinje cell dendrites to depolarize to a range of 20–30mV, and to reverse both climbing and parallel fiber responses (*254*). Cs increases excitability in the left atria but in lower concentrations it decreases excitability in the papillary muscles (*255*). The cochlear function of guinea pigs showed toxic effects related to Cs ion concentration (*256*). On the other hand, guinea pig spermatozoa were unable to fuse with eggs unless exposed to a millimolar concentration of extracellular Cs (*257*).

Cs was insensitive to ouabain when isolated rabbit hearts were artificially induced complete atrioventricular block (*258*). Cs salts stimulated immunobiological properties and promoted mobilization of adaptive, protective, and compensatory reactions (*259*). In rabbit sarcoplasmic reticulum vesicles, Cs reacted with the cation transport system only from the outside (*260*). ATP diphosphohydrolase from the sarcoplasmic reticulum increased bimolecular lipid membrane (oxidized cholesterol) conductance several hundredfold in the presence of Cs (*261*). Enolases were also activated in rabbit by Cs (*262*). Rates of Ca transport and Ca^{2+} dependent ATP hydrolysis of the reticulum of rabbit and dog cardiac membrane were stimulated by Cs (*263*). The magnitude of Na pump current in sheep is an S shaped saturating function of Cs. Hill coefficient of the current was 1.73 for Cs and the pumps were activated by external Cs (*264*). Survival rate of cultures from monkey heart cells was increased by the action of CsC1 and taurine given together in equimolar concentrations (*265*). Cs replaced intracellular K in the bovine heart mitochondria (*266*).

EFFECTS OF CESIUM ON HUMAN SYSTEMS

One of the earliest works on human systems was by Girard and Peyre (*267*), who claimed that injection of Cs eosinate salt would protect against anaphylactic shock when given intravenously. In general, Cs ions block K channel in biological membranes in a voltage-dependent

manner. For example, external Cs blocks inward current with little or no effect on outward current (*268*).

Experiments using in vivo NMR studies have shown that in biological samples:

1. Intra and extracellular Cs^+ ions have different chemical shifts that are readily resolved;
2. Spin-lattice relaxation times for intracellular Cs^+ ions are significantly shorter than values of extracellular ions;
3. In red blood cells Cs^+ ions are taken up at approximately one third the rate of K^+ ions; and
4. This rate is decreased in the presence of the cardiac glycoside ouabain (*1*).

The mechanism for volume regulation in hypotonic media was analyzed in human peripheral mononuclear (PBM) cells. Generally hypotonic swelling was followed by regulatory volume decrease. In high K^+ hypotonic media, shrinkage was absent and a second swelling phase was observed. With Cs^+, shrinkage was observed at lower dilutions and secondary swelling at higher ones (*269*). Alpha-amylase activity of dialyzed and nondialyzed human granulocytes was activated by 0.02*M* Cs (*270*). The volume of human red cells contracted on administration of Cs (*271*).

The effects of Cs on the rate of ouabain binding and of the Na-K pump were examined in human red blood cells. In Na-containing solutions, Cs decreased the rate of ouabain binding. The kinetics of these effects were similar to those of the activation of the pump. In Na-free (choline substituted) solutions, the rate of ouabain binding was increased by Cs (*272*). The concentrations of Cs were found to be highest in the lungs of the oldest individuals in a sample of 8. It was assumed that the element was enriched in the tissue by inhaled dust accumulated and deposited in an insoluble form (*273*). The ability of the cations Cs^+ and Rb^+ to substitute for K^+ as agents for causing contraction was studied in segments of human uterine muscle. The tension produced by Cs^+ was identical to that produced by K^+ (*274*). In human granulocytes, CsCl increased the activity of alpha-amylase to the same level as chlorides of Na, K, and NH_4 (*270*). Unlike Li and Rb, however, the stabilizing effect of Cs on the cell membrane of human erythrocytes, following electric field-mediated hemolysis, is rather insignificant (*275*). During studies on Cs blockade in a calcium-activated potassium channel from smooth muscle, internal blockade was found to be voltage-dependent and could be explained on the basis of a Cs^+ binding to a site that senses 54% of the applied voltage. External Cs^+ however, blocks the channel in micromolecular amounts and the voltage dependence of the blockade is a function of Cs^+ concentration. The channel itself behaves as a multi-ion pore. External Cs^+ blockade can be relieved by increasing the internal K^+

concentration, but can be enhanced by increasing the external K^+. A model is suggested incorporating a "knock on" of Cs^+ by K^+ (*276*). Functional changes in the cardiovascular and nervous systems were reported in workers employed in the production of Cs and Rb (*277*).

Cs levels were reduced in blood from depressive patients, which increased toward normal on recovery (*254*). The response to Cs is altered in disease conditions, as per example, in streptozotocin—induced diabetic mice (*278*). In a group of 29 patients with brain neoplasms, leukemia, and other noncerebral malignancies and 32 nonmalignant control patients, some with neurological and others with nonneurological conditions, the mean Cs value in the control group was 3.8 g/L. There was no difference in the value between the groups investigated (*279*). This result is of interest in view of the fact that Cs, although not directly involved in the causation of cancer, is reported to be an activator of one or more enzymes (*280*). It has been measured in brain tumor tissue (*281*) and in the cerebrospinal fluid of patients with motor neuron disease (*282*) or amytrophic lateral sclerosis (*283*). In patients with Alzheimer's disease, as mentioned earlier, persistent imbalance of univalent cations like Na, K, Rb, and Cs has been reported in the brain, particularly in amygdala and hippocampus, and this observation suggests a membrane abnormality related to the disease (*53*).

Cs did not alter brain superoxide dismutase (SOD) both in vivo and in vitro. In this behavior it resembled K but not Li (*284*). Cs also differs in other behavioral patterns from alkali group metals. For example, in binding with membrane phospholipids, the binding forces decrease in the order $Cs^+ \rightarrow Rb^+ \rightarrow K^+ \rightarrow Na^+$ (*285*). The binding selectivity of heparin for alkali cations increases with an increase in the radius of the hydrated cation form, namely, $Li^+ \rightarrow Na^+ \rightarrow K^+ \rightarrow Cs^+$ (*286*).

Cs has been used as a substitute for radium in the treatment of carcinoma of the cervix. In overall patterns, the results of the two are very similar (*287*). However, in some cases, it has been to show anticancer properties (*288*).

Animal models have been extensively employed in studying effects of Cs, but in some cases caution is needed in interpreting the results as related to the human systems. For example, the transient nature of the arrhythogenic action of CsCl injection in dogs make a systematic study of the acquired long QT syndrome observed in man difficult (*289*).

EFFECTS ON CELL DIVISION

Relatively little information is available on the clastogenic effects of Cs. Oral administration of different doses of CsCl to mice in vivo (125,250, and 500 mg/kg body weight) induced chromosomal aberrations in the bone marrow cells, when observed 6,12,18, and 24 h after exposure. The frequency of aberrations increased linearly with increasing

concentrations of the chemical. The frequency of cell division was initially enhanced by the lower concentrations but higher ones were mitostatic (*290,291*). The degree of toxicity, as shown by the clastogenic effects, was reduced significantly by dietary supplements. Calcium chloride decreased the frequency of chromosomal aberrations significantly when it was given simultaneously with CsCl or 2 *before* the administration of CsCl, indicating that $CaCl_2$ possibly acts through occupying the cellular sites rather than by binding with CsCl (*292*). Ca had been shown to reverse the antimicrobial effects of Cs (*147*). Similar protection against clastogenicity was afforded by crude aqueous extract of fruit of *Phyllanthus emblica* L., which contains an appreciable amount of vitamin C. When mice were fed the extract or an equivalent amount of vitamin C daily for 7 d and then exposed to CsCl for 24 h, the frequency of chromosomal aberrations was reduced to a significant level (*293,294*). Chlorophyllin, a known component of green plant parts, could also decrease the percentage of chromosomal aberrations to a marked extent when administered either simultaneously with, or 2 h before, exposure to CsCl (*295*). These observations are of importance since these indicate that dietary supplements may be effectively employed to reduce the toxic effects of acute exposure of CsCl, in populations at risk.

Chronic exposure of *Allium sativum* bulbs to CsCl induced aberrant cells in proportions directly related to the concentration of the chemical and the period of exposure. Higher concentrations and prolonged exposure led finally to lethality of the cells, possibly owing to physical toxicity rather than any specific action on the cell components (*296,297*). The only report of the action of radioactive Cs is that of Cs^{137} gamma radiation in human lymphocytes in culture. The chromosomal aberrations followed a Poisson distribution and the frequency was related to the dosage administered (*298*).

CONCLUSIONS

Cesium is produced in high amounts during radioactive fallout and hence is potentially a major contamination problem. The isotopes Cs^{134} and Cs^{137} belong to the main longterm radiactive pollutants resulting from nuclear fission. During the 1960s, most publications dealing with cesium were involved with determination of whole body retention of the radionuclides and methods for their elimination. Only later was attention given to the behavior and analysis of stable cesium in biological systems.

The most important factor in revival of interest in Cs toxicity was that Cs is an industrially important element and is being increasingly introduced in new materials. In addition, it closely approximates the biologically active alkali earth metals, Na, K, Li, and Rb. Cs is present in air, soil, and water in various concentrations, permitting an efficient

transfer through the soil-plant-food chain to the human system. It has been recorded in different organs of plants, animals, and human systems. Since Cs can act as an analog for potassium, it can also be potentially harmful.

Cs has been shown to be toxic in higher doses to lower organisms, like viruses, bacteria, spiroplasmas, and to some extent, to some higher plants. The effect was pronounced on chlorophyll synthesis and activity of certain enzymes. The uptake of Cs by roots from the soil was markedly influenced by the presence of stable Cs in the soil itself.

In animals, in common with other alkali metals, Cs affected various central nervous functions, mainly involved with K^+ transfer. The level of toxicity, was, however, lower than that of Rb and Li. The effect was predominantly depressant, leading finally to respiratory problems. The organs most affected were the liver, heart, kidney and intestine, indicating a generalized toxicity of the element. An increase of metal in the organs is seen with age, in common with other nonessential elements. Repeated administration of CsCl resulted in considerably higher accumulation in the tissues.

In human systems, Cs is widely distributed throughout the body, mainly in the soft tissues. Uptake from the gastrointestinal tract is rapid and almost complete. An average of 10% of a single oral dose is excreted within 48 h, but the major part has a half-life of 50–150 d. Levels of Cs have been seen to be altered in certain disease conditions, especially Alzheimer's disease, but no consistent relationship can be drawn.

Both diet and environment influence the accumulation of Cs in the human body. Cs^+ follows the movement of K^+ in the body and competes for transport across cell membranes. Usually Cs^+ is less effective than Rb^+ in sustituting for K^+. It has no known vital function, although the simultaneous occurrence of equal amounts of Cs and Rb in rat organs, suggests that Cs might be involved, like Rb, in neurophysiological functions.

Oral administration of CsCl to mice in vivo induced clastogenic effect on the chromosomes in the bone marrow cells in a degree directly proportional to the dosage applied. In plants, the effects mainly involve spindle disturbances whereas in leukocyte cultures, acentrics and dicentrics were recorded.

There appears to be a maximum threshold for cesium in blood. Cs has a long half-life and the greater the amount given, the longer it stays in the blood. Additional cesium, given above the threshold, would be excreted at a more rapid rate. Therefore, if the threshold level of Cs is maintained, it can protect against the uptake of radioactive Cs from nuclear activities. Cs probably adheres to the red blood cell and hence saturation of these sites by normal Cs may prevent binding of Cs^{137}, so that the latter is excreted. The prospects of protection against radioactive Cs exposure through addition of nontoxic doses of stable Cs are feasible. Cs toxicity can also be minimized by dietary factors, like Ca, plant

extracts and vitamins. The entry of Cs^{137} into the plants through soil can be modulated by changing stable Cs in the soil.

Apparently, therefore, cesium, although a major contaminant from nuclear fallout and industrial efflents, can be easily contained within the soil and within the biological systems, so that the toxic effects are mostly eliminated.

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