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REVIEW ARTICLE

Pharmacokinetics and Temperature

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Keyphrases □ Pharmacokinetics—effects of body and environmental temperature on human physiological changes and physicochemical properties, absorption, distribution, and metabolism of drugs, review □ Temperature, human body and environmental —effects on physiology and physicochemical properties, absorption, distribution, and metabolism of drugs, review □ Drugs—effects of body and environmental temperature on physicochemical properties, absorption, distribution, and metabolism, review □ Environmental temperature—effect on drug pharmacokinetics, review □ Absorption and distribution, drug—effects of body and environmental temperature □ Elimination, drug and metabolite—effects of body and environmental temperature □ Metabolism, drug—effects of body and environmental temperature

The objective of this review is to discuss what effect body or environmental temperature variations might have on the physiological changes observed in humans, the physicochemical properties of a drug, drug absorption, drug distribution, drug metabolism, and drug or metabolite elimination. Information on this topic is widely scattered throughout the biological, medical, chemical, mathematical, pharmaceutical, pharmacokinetic, and related literature. As a consequence, it is highly probable that some key references may be inadvertently overlooked. It is beyond the scope of this review to consider in any great detail the possible effects that body or environmental temperature might have on a drug's pharmacological response.

The literature of pharmacokinetics has grown rapidly since the era of modern pharmacokinetics began in 1937 (1). The growth has been accelerated by the development of computers (2–7), which make the solution of pharmacokinetic and statistical equations a routine matter, and the development of sensitive analytical tools, which make the analysis of drug and metabolite concentrations in biological fluids less difficult than previously. The growth has also been accelerated because of an increased awareness among politicians and biomedical and pharmaceutical scientists that information derived from pharmacokinetic and biopharmaceutical studies may have an important bearing on patient care (8). Most pharmacokinetic studies have been conducted in animals and humans having "normal" temperatures. Several investigators have noted that pharmacokinetic and drug action studies in animals and particularly in humans under conditions of hypo- or hyperthermia are limited (9–11). Various review papers on pharmacokinetics have been presented (9, 12–23).

Humans have been known to survive when rectal temperatures have reached as low as 18° (24) and as high as 44.4° (25). Patients who are hypo- or hyperthermic may have received drugs prior to the onset of a body temperature change (26, 27) or after the body temperature change became evident (28–31).

Two groups in the general population are particularly sensitive to environmental temperature changes. They are the human newborn, whose body temperature under normal delivery room conditions may fall as much as 2–3° (32), and the elderly whose

home environments may put them "at risk" of developing hypothermia. The coldest elderly individuals tend to be the ones least aware of their problem. Fox *et al.* (33, 34) did not discuss drug utilization in the elderly population. Bender (35) and Hall (36) noted that the elderly tend to exhibit a decrease in both drug absorption and elimination, but they did not comment upon the possible effect of body temperature on these or other processes. The world energy crisis may make the home heating problem even more severe for the elderly and others in the near future. Weihe (10) stated that: "Once physicians as well as physiologists and pharmacologists become aware of the thermal environment, they will notice modifications of drug action in man and will be able to relate this data to ambient thermal conditions."

Buckley (37) indicated that a new facet in pharmacology, which could be called "environmental pharmacology," has emerged; it involves the possible alterations in drug action by environmental stimuli and the alteration of the response of the organism to its environment by drugs. A parallel field of "environmental (thermal) pharmacokinetics"[1] might also be emerging wherein conditions such as environmental or body temperature might affect the kinetics of drug absorption, distribution, metabolism, or elimination.

PHYSIOLOGICAL CHANGES

Temperature changes in the environment or within the animal may affect physiological functions and pharmacokinetic modeling. The literature in this field is extensive, and it is beyond the scope of this paper to review this topic. However, some major points should be mentioned. Many references cited in this section are review articles and should be consulted for references to the original work.

Some body reactions to high temperature have been summarized (38). The initial response to heat is peripheral vasodilatation followed by perspiration, which results in a large fraction of the total blood volume being circulated through the skin vessels for cooling. Venous return of blood to the heart is reduced, and a drop in blood pressure occurs. Compensatory mechanisms stimulate an increase in heart rate and cardiac output. External heat generally tends to lower blood pressure; however, the response is variable and depends upon the degree of vasodilatation, heart rate, cardiac output, pulse pressure, and body position. During artificial fever, the number and motility of leucocytes in blood are increased. High temperature increases respiratory rate, and a decrease in carbon dioxide alveolar tension results in a tendency for alkalosis to occur. In a hot environment, slight increases in rectal temperature are not accompanied by significant increases in renal blood flow.

Changing the environmental temperature influences the volume and composition of blood. Bass and Henschel (39) reviewed the effects of heat and cold on body fluid compartments and stated that one early response to abrupt heat exposure is the dilution of the plasma. This dilution is usually less than 5% and occurs during the first 30 min of exposure and before sweating occurs. The hemodilution is probably due to an influx of extravascular fluid as a result of peripheral vasodilation. There is also a decrease in urine flow and sodium- and chloride-ion excretion. After longer exposure to heat (49°) for up to 5 days, blood volume was shown to increase as a result of the addition of a fluid almost identical in composition to plasma. The increase in plasma volume was about 27% and the increase in interstitial fluid volume was about 14%. After 14 days at this environmental temperature, the total blood volume and circulating protein concentration returned nearly to control values.

One review (40) points out some physiological effects of environmental cold in humans. Initially, exposure to cold causes shivering, peripheral vasoconstriction, an increase in oxygen consumption, a fall in alveolar carbon dioxide, a fall in minute volume, an increase in respiratory rate, an increase in pulse rate, an elevation of blood pressure, an increase in cardiac output, and a progressive fall in blood pH. After the rectal temperature has fallen to about 35°, the metabolic rate begins to decline. Shivering usually ceases between 30 and 33°. After the initial increase in respiratory rate, a decrease in rate occurs, which is almost proportional to the fall in body temperature. Once rectal temperature begins to fall and cooling is continued, heart rate decreases. If the temperature falls below 28°, heart block may occur along with ventricular extrasystoles or nodal rhythm. Either ventricular fibrillation or cardiac asystole may occur if cooling is continued much below 28°.

After the initial rise in blood pressure and cardiac output, continued cooling causes a gradual decline in blood pressure due chiefly to a reduction of cardiac output. During deep hypothermia, blood viscosity increases. Cerebral blood flow and oxygen consumption both are reduced during hypothermia. Hypothermia causes a decrease in brain volume and an increase in extracerebral space volume. Splanchnic blood flow to the liver is decreased during hypothermia. The glomerular filtration rate, renal blood flow, and normal tubular reabsorptive capacity for glucose are decreased during hypothermia. Some acid–base and electrolyte disturbances observed in hypothermia have been reviewed (41).

The effects of cold on fluid compartments are not as clearcut as are the effects of heat. In an acute cold exposure experiment, nude reclining subjects exposed to cold (16°) for 2 hr showed a significant 7% decrease in plasma volume and an insignificant 1.6% decrease in circulating protein (39). In addition to hemoconcentration, acute cold frequently results in increased urine flow and increased sodium- and chloride-ion excretion. Prolonged exposure to cold, however, shows that blood volume is little affected. The composition of blood and plasma remains normal with respect to the concentration of plasma proteins, hematocrit, and plasma concentrations of sodium and chloride ions (39).

[1] The phrase "environmental pharmacokinetics" was defined more broadly by E. J. Ariëns, in "Drug Design," vol. I, E. J. Ariëns, Ed., Academic, New York, N.Y., 1971, p. 17.

Table I—Relationship between Gastric Emptying Time and Temperature

Species (Sex)	Number of Subjects	Age Range, Years	Experimental Conditions	Results	Reference
Human (♂)	9	—	Barium sulfate meal with 250 ml of ice water	Gastric emptying time for four subjects was increased by 15 min, for four subjects it was increased by 30 min, and for one subject there was no change	50
Dog	5	—	Barium sulfate meal; gastric emptying time measured in dogs exposed 20 days at −10°, room temperature (20–26°), and high temperature (32°) for 5 days	Gastric emptying time at −10° was shorter by 17%, and at 32° it increased about 10% compared to dogs at 20–26°	51
Dog	—	Puppies	Prolonged exposure to low environmental temperature	Increased rate of evacuation and decreased secretory activity of gastric glands	52
Human	24	—	Barium sulfate meal on fasting stomach; X-rays taken; first meal at about 37°, second at about 3°, and third at about 62°	Compared to 37° meal, the gastric emptying time for 3° meal was initially more rapid and the 62° meal was initially slower	53
Human (♂ and ♀)	—	—	Ingestion of 250 ml ice water (1.1–2.2°) on fasting stomach Ingestion of 90 g ice cream (−11.1–+6.7°)	Average gastric emptying time for water was delayed 30–45 min Gastric emptying time was delayed 30–45 min	54
Human (♂)	—	—	Irrigation of stomach with cold (9°) and hot (46°) water	Introduction of any fluid into stomach inhibited contractions temporarily; cold water had a longer inhibitory effect than hot water, and this effect did not occur when fluid was irrigated through in-lying balloon	55
Human (♂)	17	18–28	Barium sulfate meal on fasting stomach; X-rays taken; room temperatures of 25 and 49°	Gastric emptying time was faster in 16 subjects at 45° compared to that at 25°	56
Human (♂)	16	—	Barium sulfate and ice cream meal at −8, 26(32), or 65°; room temperature defined as 26 or 32°	Gastric emptying time was fastest with the 26° meal, slowest for the 65° meal, and intermediate for the −8° meal; no statistically significant relationship seen between gastric emptying time and meal temperature	57
Rat (♂)	54	Adult	*Acute studies:* rats ate a standard protein meal at 22° and then were transferred to a low (3°) or high (37°) environmental temperature *Chronic studies:* rats were maintained at 3, 22, or 37° for 6 days and then fed test meal	*Acute studies:* transfer of rats from 22 to 3 or 37° environment caused delays in gastric emptying time *Chronic studies:* gastric emptying time similar to that at 22°; sudden change of environmental temperature was responsible for delayed gastric emptying time	

In reviews on human circadian rhythms (42–44), studies were cited where a circadian rhythm has been observed in body temperature; circulatory function, such as pulse rate, blood and pulse pressures, stroke volume, and circulating blood volume; and renal function, such as urine volume, phosphate-, potassium-, sodium-, and chloride-ion excretion, and urine pH. At night, humans have a small flow of dark, acid urine, while in the morning, usually after awakening, both urine flow and urine pH increase. This phenomenon has been called the "alkaline tide" by some investigators.

The magnitude of human body temperature variations attributable to the normal circadian rhythm can be found in Blake's (45) work, which followed the sublingual body temperature in 74 humans. The lowest mean body temperature of about 36.2° occurred at 4 am and the highest mean body temperature of about 36.9° occurred near 8 pm. In this panel, approximately a 0.7° difference between maximum and minimum body temperatures was recorded.

Gastric Emptying Time—The duration of the gastric emptying time is a physiological variable that may influence the rate of drug absorption. This topic will be discussed later. The mechanics and regulation of gastric emptying have been reviewed (46, 47), as have factors affecting the regulation of gastric motility (48). Coates *et al.* (49) found that the gastric emptying time in human volunteers following the ingestion of a "standard egg sandwich" containing indium-113m chloride had a $t_{50\%}$ (time for half the radioactivity to leave the stomach) ranging from 42 to 95 min. Previous studies cited in the paper, using other radioactive elements, suggested that gastric emptying appears to follow a monoexponential curve. However, gastric emptying followed neither apparent first- nor zero-order kinetics. Table I summarizes chronologically some studies on the effects that meal temperature might have on gastric emptying.

Fordtran and Saltin (59) found that human gastric emptying of a solution containing 13.3% glucose, 1% polyethylene glycol (as a nonabsorbed marker), and 0.3% sodium chloride was not affected by severe ex-

ercise but the gastric emptying of a second solution of water with 1% polyethylene glycol was slightly inhibited by such exercise. Other factors affecting gastric emptying have been discussed (60). Elevation of body temperature above normal conditions resulted in an inhibition of gastric motility, but colonic motility was not altered (61).

Gastric pH and GI Transit Time—The pH of the gastric juice in the normal resting stomachs of dogs and of healthy male volunteers was measured (62). In 403 tests on 24 dogs, 77% had gastric pH values of 6.0 or above. In 1556 tests on 312 humans in four different geographical locations, the results from three locations showed a bimodal effect and one was unimodal. The gastric pH for 41% of all subjects was 3.5 or lower, 35% was 6.0 or greater, and 24% had pH values between 3.5 and 6.0. Among the normal humans studied, the gastric pH values ranged from 0.5 to 9.5.

For many years, it has been known that febrile patients may exhibit changes in gastric secretion patterns. Chang (63) studied 106 patients with various diseases having a temperature range of 37.4–41.3°. When using the histamine method, on an average there was a decrease in gastric acidity to about one-third that of normal. Chang noted that the decrease in gastric function was directly proportional to the magnitude of the fever temperature.

The reduction of gastric secretions in gastric pouch dogs given intravenous injections of a pyrogenic substance was measured (64). The gastric acid secretion was stimulated by subcutaneous injections of histamine solutions. The mean percent inhibition of gastric secretion was nearly proportional to the mean rise in body temperature or the log dose of the pyrogenic substance. These results were confirmed (65). Masuda *et al.* (66) found that the gastric free acidity in humans was significantly increased by immersing humans below the neck in a bath at 22–24°.

Beresford *et al.* (67) noted that it is a common clinical observation that febrile illness in humans generally resulted in reduced transit time through the GI tract. Reviews on the digestive system and GI tract motility have been presented (68–73).

Selected Organs and Organ Systems—Beltz and Reineke (74) showed that the heart rate of neonatal rats increased with an increase in intraperitoneal temperature in accordance with the Arrhenius equation over a 16–29° range. They cited evidence that the heart beat rate in other animal species is similarly affected by temperature change.

Merrill and Pelletier (75) studied the rheological properties of human blood over a range of shear rates from 0.1 to 100 sec^{-1} and over a temperature range from 10 to 37°. At a constant hematocrit level, the relative viscosity of whole blood (viscosity of blood/viscosity of water) remained nearly constant at shear rates between 1 and 100 sec^{-1} over the temperature range. At shear rates below 1 down to 0.1 sec^{-1}, the relative viscosity increased slightly with increasing temperature.

Reemtsma and Creech (76) measured the viscosity of dog blood at various hematocrit levels, dog plasma, and some plasma substitutes over a temperature range of 5–40°. As the temperature was lowered from 40 to 5°, *(a)* the blood viscosity increased more steeply at the higher hematocrit levels, *(b)* the viscosity of plasma more than doubled, and *(c)* the viscosity of dextran solutions of various molecular weights increased more sharply as molecular weight increased.

The apparent pK′ value or a "complex constant-of-convenience" (77, 78) for carbonic acid in serum was determined (79, 80) at various pH and temperature values. The pK′ value is a mixed constant involving the pKa for carbonic acid (81), the hydration of carbon dioxide in solution to form carbonic acid, and the activity and degree of dissociation of bicarbonate ion. While the thermodynamic pKa of carbonic acid is probably not affected by pH, the value for pK′ is. Both pKa and pK′ are influenced by temperature.

The rate of bile flow in isolated liver preparations and in intact animals has been shown to decrease with a reduction in liver temperature (82–84).

Individuals exposed to extremes of cold or heat or who are febrile are usually treated in part by varying periods of bed rest. Even among normal subjects, prolonged bed rest can affect certain physiological functions. Vogt *et al.* (85) found that blood volume changes during bed rest were variable, possibly because they used the radioiodinated serum albumin plasma volume method for their assay. However, with bed rest, diuresis was observed and there was an increase in both sodium- and potassium-ion excretion over control values. These and other physiological effects to cold and heat have been reviewed in detail (86–96).

PHYSICAL AND CHEMICAL PROPERTIES OF DRUGS

While changes in environmental and body temperature have important bearings on many physiological functions, one cannot ignore possible changes in the physical and chemical properties of the drug with temperature, which also may be important in the pharmacokinetic modeling process.

Solubility—As a general rule, the aqueous solubility of inorganic and organic solid drugs increases with increasing temperature (Table II). Different polymorphic forms of the same drug can exhibit this type of solubility behavior (105). Exceptions to this rule include calcium acetate and calcium hydroxide (106). In contrast, the aqueous solubility of gaseous drugs decreases with increasing water temperature (107). For nitrous oxide dissolved in water, the Ostwald solubility coefficient (the ratio of the volume of the absorbed gas to that of water) decreases from 0.693 at 20° to 0.435 at 40° (108). The Ostwald solubility coefficient for halothane in water, human blood, and plasma all decrease over the 25–37° temperature range (109). In plasma, the solubility, S, of carbon dioxide equals $[H_2CO_3$ (mmoles/liter)]/$[P(CO_2)$(mm Hg)], and increases from 0.0288 at 40° to 0.0554 at 15° (110).

pKa—Over the range of temperatures compatible with living organisms, the pKa of drugs in water generally decreases with increasing temperature

Table II—Solubility and pKa Values of Selected Weak Acids in Aqueous Solution at Different Temperatures

Drug	Temperature	Solubility, g/100 ml	Reference	pKa	Reference
Barbital	20°	0.629	97	8.06	98
	37°	0.949	97	7.82	98
Phenobarbital	20°	0.088	97	7.60	99
	37°	0.184	97	7.2	100
Sulfadiazine	20°	0.00616	101	6.35	102
	38°	0.0099	101	6.28	101
Tolbutamide	25°	—	—	5.42	103
	27°	0.0077	104	—	—
	37.5°	0.0142	103	5.32	103

(Table II). The pKa for water is also temperature dependent and follows the equation (81):

$$\mathrm{pKa}(H_2O) = \frac{4471.33}{T} - 6.0846 + 0.017053T \qquad \text{(Eq. 1)}$$

where T is the absolute temperature. The pKa for water is 14.17 at 20° and decreases to 13.63 at 37°.

Partition Coefficient—Renkin (111, 112) measured the olive oil–water partition coefficients of antipyrine and other 5-pyrazolone derivatives at various temperatures. Within the 2–31° range, the logarithm of the partition coefficient of a particular compound was a linear function of temperature. Munson and Eger (113) summarized the blood–gas and oil–gas partition coefficients of the anesthetic agents cyclopropane, fluroxene, halothane, and methoxyflurane over the 27–42° temperature range. The partition coefficients all decreased as the temperature of the *in vitro* system increased.

Diffusion Coefficient—For the majority of drugs, data on the aqueous diffusion coefficients are not known as a function of temperature, and the temperature dependency of the diffusion coefficient of drugs in biological fluids is virtually nonexistent. To circumvent the problem, the following equation was derived (114):

$$D_r = \frac{T}{T^0}\left(\frac{\eta r^0}{\eta r}\right)_{H_2O} \cong \frac{T}{T^0}\left(\frac{\eta r^0}{\eta r}\right)_f \qquad \text{(Eq. 2)}$$

where D_r is the relative diffusion coefficient, T and T^0 are two absolute temperatures (T^0 being the reference temperature), $(\eta r^0/\eta r)_{H_2O}$ is the ratio of the relative viscosities of water at temperatures T^0 and T, and $(\eta r^0/\eta r)_f$ is the ratio of the relative viscosities of body fluids such as blood serum or plasma at temperatures T^0 and T.

Over a 1–37° temperature range, the aqueous relative diffusion coefficient for dextrose calculated from Eq. 2 differed by less than 3% from the experimental relative diffusion coefficient calculated from Longsworth's data (114, 115).

Dissolution Rate and Tablet Disintegration—Wurster and Taylor (116) reviewed the many factors affecting solid dissolution rate. Generally, the rate of dissolution of solid drugs in water at a constant agitation rate increased with increasing temperature. The dissolution rate of 80–100-mesh crystals of benzoic acid from 25 to 40° was greater at the higher temperature (117). Gibaldi (118) showed that the dissolution rates of salicylic acid, benzoic acid, and phenobarbital all increased as the pH of the system increased from 1.5 to 9.0. In his review, Lowenthal (119) cited cases where the tablet disintegration rate in water was generally greater at 37° than at 18–20° (120–123); however, in one study, no difference in disintegration rate was noted between 20 and 40° (124).

Drug Stability—Garrett (125) pointed out that "... kinetic and predictive studies of drugs in the pharmaceutical literature are of relatively recent vintage. In fact, *ca.* 1950 can be considered the start of the modern era in the quantitative comprehension and prediction of drug stability." Some factors that may affect a drug's *in vitro* stability in aqueous systems include the concentrations or activities of hydrogen ion, hydroxide ion, and other charged species present, which may be components of buffers or excipients. The ionic strength and temperature of the system may also affect the observed velocity of the drug degradation reaction. For example, at pH 7.2, the apparent half-life of fluprednisolone acetate in aqueous solution is approximately 85.6 days at 25° and 27.7 days at 40° (126). From a manufacturer's standpoint, this drug was not considered sufficiently stable to be a component in ophthalmic solutions.

The stability of drugs in aqueous solutions that are introduced into body compartments having various temperatures within the physiological range could create pharmacokinetic modeling problems, particularly if the *in vitro* half-lives are short. Indeed, such drug degradation might be misinterpreted as being attributed to drug metabolism.

ABSORPTION

A few papers dealing with the effect of temperature of drug solutions and pellet implants from a number of anatomical sites have appeared, including intramuscular, subcutaneous, lymph sac, intraperitoneal, and GI sites.

A problem encountered in the early days of penicillin therapy occurred when the aqueous drug solution was administered intramuscularly. The drug tended to disappear rapidly from both the injection site and the bloodstream. If the drug was to be effective, it had to be administered at frequent intervals. One method of prolonging the action of a single dose of penicillin administered intramuscularly was to cool the injection site with an ice bag (127–129). Trumper and Hutter (128) suggested that the absorption rate of the penicillin solution was retarded by slowing the circulation around the injection site.

McInally *et al.* (130) studied the clearance of $^{24}NA^+$ following an injection of isotonic saline into the subcutaneous tissue of the legs of normal humans. The clearance of $^{24}Na^+$ from the injection site was increased in the subjects whose trunk and upper extremities were heated by an electric blanket compared to the clearance observed when the same subjects were tested at a room temperature of 18–20°. The investigators concluded that the clearance of $^{24}Na^+$ from the subcutaneous tissues is largely

governed by the blood flow surrounding the injection region, which is presumably greater in the heated subjects.

Franke *et al.* (131) injected $^{24}Na^+$ in physiological saline intramuscularly and subcutaneously into dogs and followed the rate of drug clearance. A decrease in the drug clearance rate over controls was observed both when an ice–salt pack was placed over the injection site and when radiant heat from an IR source was directed toward the injection site. In the latter experiment, the skin surface temperature was 55° and hyperemia was evident, which might explain the decreased clearance rate observed over controls.

The effect that body temperature has on pellet implant absorption was studied (114). Pellets of acetanilid and sulfanilamide were placed on separate occasions in the dorsal lymph sac of frogs, which had been paralyzed by an injection of tubocurarine chloride. Frogs were selected because it was possible to study drug absorption over a 0–29° range while the paralyzed animals were able to respire through their moist skin. The investigators showed that if the absorption rate per unit area of a pellet were known at one reference temperature, say 0°, it would be possible to predict the absorption rate of the same drug at any other temperature up to 29° by use of the equation:

$$(\bar{R}/\bar{A})_r = (K_r)(D_r)[(Ss)_r/\delta_r] \qquad \text{(Eq. 3)}$$

where $(\bar{R}/\bar{A})_r$ is the mean pellet absorption rate per mean area at a given temperature relative to that at 0°, K_r is a proportionality constant, D_r is the relative diffusion coefficient, $(Ss)_r$ is the relative solubility of drug, and δ_r is the relative diffusion layer thickness. A plot of $(\bar{R}/\bar{A})_r$ *versus* (D_r) $[(Ss)_r/\delta_r]$ yielded a straight line with a slope, K_r, of 1.09 for the two compounds. Theory would predict a value of 1.0 if the heart beat rate could be reduced to a hypothetical zero value. The advantages of using pellets for studying the effect of temperature on the drug absorption rate from this absorption site are that a quantitative estimate of the amount of drug remaining at the absorption site can be made at any time by removing and weighing the dried pellets and that the area of the tissue or membrane across which the drug molecules diffuse is maintained almost constant. In contrast, when drugs are administered orally, rectally, or parenterally (not intravenously), it is difficult and often impossible or impractical to maintain the area of the biological membrane in contact with the drug molecules constant or to recover the unabsorbed drug quantitatively from the absorption site.

Kalser *et al.* (132) found, by LD_{50} measurements, that rats exposed for 49 days to 5° were able to tolerate twice the amount of intraperitoneally administered atropine sulfate compared to rats exposed to 5° for only 1 day. This tolerance to atropine in the chronically cold-exposed rats was attributed to a slower absorption rate of drug from the peritoneal cavity compared to the absorption rates of acutely cold-exposed rats or controls maintained at 25°. The authors concluded that the cold-acclimated rat exhibited a decreased toxicity to atropine due to a limiting of atropine absorption *via* the portal circulation rather than due to an increase in drug excretion.

GI Absorption—There has been a paucity of experimental information regarding the effect of body or environmental temperature on the rate of drug absorption from the GI region. Several reviews included the many factors affecting the GI absorption of drugs and other substances (133–137). These factors generally have been classified under the broad headings of the physicochemical properties of the drug and the dosage form, the physiological functions of the GI tract, the metabolic activities of the GI epithelium, and the structure of the intestinal epithelium as an absorbing surface.

Levy (133) pointed out that the absorption of drugs administered as solid dosage forms (*e.g.*, tablets) can be described as a two-step process. The solid dosage form must disintegrate into its primary particles, followed by dissolution of the drug in the particles into the fluids present in the GI tract. Once the drug is in solution, it passes through the GI epithelium by one or more absorption mechanisms into the fluids of distribution in the body. In many cases, the dissolution or disintegration step, which depends upon the physicochemical properties of the drug and dosage form, is the rate-limiting factor in the absorption process. When this step is rate limiting, one might predict that the drug absorption rate would be reduced at lower temperatures compared to higher temperatures, because the rate of dissolution or disintegration of solid dosage forms is generally slower at the lower temperatures at constant pH and velocity of agitation. The *in vivo* testing of this hypothesis, however, has not been performed to date.

The physiological factors having a possible effect on the GI drug absorption rate include the gastric emptying rate, GI pH, intestinal motility, and GI blood flow.

The gastric emptying rate often affects the drug absorption rate in normal subjects, whether the drug is administered in solution or as a solid dosage form, because of the pH–partition effects (138) in the stomach and intestine and the relative differences in the areas of the two absorbing membranes. The effect of the gastric emptying rate on the drug absorption rate is usually more pronounced with solid drugs that are organic weak acids or bases. The dissolution rate of organic weak bases is enhanced in the low pH of the gastric fluids, while the dissolution rate of solid organic acids is not. Because of pH–partition considerations, the absorption rate of organic weak base molecules in solution per unit area of absorbing membrane is enhanced in the fluids of the intestinal tract that generally have a higher pH than the stomach fluids, while the absorption rate of organic weak acid molecules in solution is retarded in the intestine. A detailed treatment of this topic was presented (133).

The effects of hot and cold test liquids and meals on gastric emptying time are shown in Table I. Inspection of Table I shows that it is difficult to make

generalizations from animal and human data, which would be useful in pharmacokinetic modeling. Nonetheless, liquid and meal temperatures seem to have an effect on gastric emptying time even though the effect appears to be mixed, possibly depending upon the population studied and/or the experimental conditions used.

In the *Physiological Changes* section, it was noted that the gastric pH of "normal" humans had a range of 9 pH units in a large population. In febrile subjects, the pH tended to increase; subjects exposed to cold showed a decrease in gastric pH compared to the normal subjects in the studies cited. How important these gastric pH changes due to body or environmental temperature changes are seems to be unclear at present in terms of the pharmacokinetic modeling process.

As pointed out previously, during febrile illness the transit time through the GI tract is generally reduced. Beresford *et al.* (139) noted that ^{59}Fe-labeled ferrous ascorbate absorption was profoundly depressed in Jamaican children who had a febrile illness or a febrile response to diphtheria–pertussis–tetanus immunization. They proposed several mechanisms that might explain the decrease in iron absorption. One explanation was that pyrexia increases small bowel motility, so iron salts pass more rapidly through the duodenum and have less time for absorption. Cortell and Conrad (140) found that rats injected intraperitoneally with an endotoxin derived from *Escherichia coli* showed 12 hr later a decreased intestinal absorption of ^{59}Fe as ferrous citrate, an accelerated clearance of iron from the plasma, and a decreased serum iron concentration when compared to controls.

In a review on factors affecting drug absorption, the influence of blood flow on the intestinal absorption of drugs was noted (136). For example, the absorption of tritiated water is nearly blood flow limited, while that of adonitol (ribitol) is nearly independent of blood flow. Thus, any change in blood flow to the intestinal region due to hypo- or hyperthermic conditions may affect the absorption rate of drugs that are partially or totally affected by blood flow rate. Cordier *et al.* (141) found for the fish, *Tinca vulgaris*, that the percent intestinal absorption after 17 hr increased as temperature increased over the 2–20° range. For any given temperature, the rate of intestinal absorption for various sugars was: glucose $\geq$ galactose > fructose > xylose.

Block and Corbin (142) administered 300 mg of acetaminophen in aqueous solution orally to healthy subjects; this solution was followed by the ingestion of water at 4, 25, 37, or 50° in a complete crossover study. The urinary excretion of free acetaminophen and its metabolites was measured as a function of time. They concluded that changes in intragastric temperature resulting from the ingestion of water over a 4–50° range had no effect on acetaminophen absorption.

The everted intestinal closed sac technique has been widely used for studying *in vitro* drug absorption. The observations of Levine (134) indicate that at 37° such preparations may undergo serious morphological changes as a function of incubation time. For example, after 30 min of incubation, between 50 and 75% of the normal epithelial tissue had disappeared, and there was total destruction of the epithelial borders after 1 hr. The only intact structures present were at the deepest regions of the crypts where no drug absorption takes place. When the everted sac preparation was incubated at 23°, the tissue damage appeared more slowly than at 37°. According to Levine (134), the morphological changes were probably due to an excess accumulation of fluids in the intestinal tissue of the everted sac, which normally would have been removed *via* the lymphatic or blood drainage under *in vivo* conditions. The slower rate of appearance of damage at 23° compared to that at 37° was attributed to a slowing in the metabolic processes that transfer water and salts from the mucosal to the serosal intestinal surfaces.

DISTRIBUTION

Shortly after a drug is injected or absorbed into the general circulation, the drug molecules tend to distribute among many tissues, organs, and compartments. Changes in body or environmental temperature may influence the rate and extent of drug distribution.

Protein Binding—A great many drugs interact or bind to proteins. The interaction between drugs and serum albumin probably has been studied most extensively (143–146). Drug molecules are in a rapidly reversible dynamic equilibrium between the free molecules in solution and those occupying the several binding sites on the protein. The unbound drug molecules are the species that are diffusable through membranes and are believed responsible for eliciting the pharmacological effects for drugs in which a correlation between serum drug concentration and intensity of a given pharmacological response has been established. Thus, any factor, such as an increase in body temperature over normal, that tends to weaken the various bonds involved in the formation of the drug–protein species would result in a shift in equilibrium so that a greater fraction of free or unbound drug is present for any given total drug and protein concentration. With increasing temperature, the fraction of drug bound to proteins and the binding constants tend to decrease for a number of drugs including ampicillin (147), benzylpenicillin (148), diazepam (149), diphenylhydantoin (150), phenoxymethyl penicillin (penicillin V) (147), propicillin (147), sulfadiazine (151), sulfaethidole (152), sulfamethoxypyridazine (153), urate ion (154), and warfarin (155, 156).

Schoenemann *et al.* (157) considered the pharmacokinetic consequences of plasma protein binding of drugs and developed equations appropriate for both one- and two-compartment open models. In the theoretical examples, the number of binding sites on the protein was varied from one to 10 and the percent plasma or tissue binding was varied from 9 to 90%. One implicit assumption in their equations is

that the temperature of the system is constant or has no effect.

Plasma Clearance—After intravenous injections of sulfobromophthalein into anesthetized dogs, the disappearance of sulfobromophthalein from the plasma was followed as a function of time (158). Hypothermic dogs having a rectal temperature of 30° showed the slowest disappearance rate; those having a rectal temperature of 35° showed a slightly faster rate. It was postulated that the reduced sulfobromophthalein disappearance rate in the hypothermic dogs could be due to a decrease in metabolic activity at the removal site and/or reduced hepatic blood flow.

Brain and Cerebrospinal Fluid—The rate of penetration of drugs into the central nervous system (CNS) at a constant blood flow rate seems to depend mainly upon the magnitude of the lipid–water partition coefficient of the unionized form of the drug and upon the degree of ionization at a physiological pH (159, 160). Kurz (161) perfused the heads of dogs at a constant flow rate *via* the carotid arteries with an isotonic drug solution saturated with oxygen and at pH 7.4. The perfusion fluid was held at 0 or 37°. Some drugs studied were aniline, antipyrine, and barbital. Samples of the cerebrospinal fluid were collected from the cisterna magna after the perfusion began. Aniline had the greatest heptane–water (pH 7.4) partition coefficient at a given temperature and tended to penetrate the cerebrospinal fluid most quickly, while barbital had the lowest partition coefficient at a given temperature and tended to penetrate most slowly. Antipyrine occupied an intermediate position. At 37°, all three drugs had greater rates of penetration than they did at 0°. A decrease in temperature appeared to cause a greater decrease in the rate of drug diffusion through a lipid layer than was found for an aqueous phase (agar–gel). Renkin (112) noted that the temperature coefficients of lipids must be considered in discussions of the diffusion of lipid-soluble molecules. The temperature coefficients of viscosity for lipids tend to be greater than those for water. The results just described (161) for the *in vitro* dog's head preparation should be viewed with some caution, since in the intact dog it is unlikely that the perfusion rate of drug through the carotid arteries would remain constant at two widely different temperatures because of functional changes in the cardiovascular system.

One area of research largely ignored by those interested in drug distribution involves the possible role of the process of phagocytosis. Gomez-Luz (162) injected microcrystals of oxytetracycline subcutaneously into humans and shortly thereafter found crystals of the drug in peripheral blood, some intracellular and some free. Microcrystals, both inside and outside of leucocytes, were found in the exudates of patients suffering from osteomyelitis and urethritis due to gonococcus or staphylococcus and were also found in human bone marrow. The effect of temperature on the rate of phagocytosis by leucocytes of several animal species on a variety of inorganic particles and microorganisms has been reviewed (163, 164). McCutcheon (165) showed that the velocity of locomotion of human neutrophilic polymorphonuclear leucocytes appeared to double *in vitro* by a 10° rise in temperature up to about 40°, but at 42° there was a depression of locomotion.

Noordhoek (166) studied the pharmacokinetics and dose *versus* sleeping times of mice administered hexobarbital. He found that at low doses (80 mg/kg) the elimination of hexobarbital from the brain was monoexponential 10 min after intravenous administration of the drug. At 48 mg/kg, the sleeping time was 11.8 min at 23° and 9.6 min at 37°. At 75 mg/kg, the sleeping time was 28.9 min at 23° and 27.5 min at 37°. Statistically, the differences in the duration of sleeping time at a given dose were not significant at the two temperatures. The sleeping time is determined by the rate at which the drug is eliminated from the brain and the brain level of drug at the time of awakening. During the first 10 min after intravenous injection of hexobarbital in mice, the drug equilibrates among the plasma, brain, and other tissue compartments. Afterward, the decrease in drug concentration in the brain parallels the decrease in drug plasma concentration, which is affected by metabolism, renal excretion, and diffusion of drug from the plasma to the fat depots. No attempt was made to explain why temperature appeared to have little effect on sleeping times for a particular dose of hexobarbital.

Urinary Bladder—Borzelleca and Lowenthal (167) considered several factors that might influence the rate of movement of drugs across the isolated urinary bladder of the rabbit. A nicotine solution at pH 8.1 disappeared from the bladder in an apparent first-order manner. At 27, 32, 37, and 42°, the apparent first-order rate constants were 0.117, 0.177, 0.266, and 0.139 hr^{-1}, respectively. Thus, the rate of drug movement was greatest at 37° and decreased as the temperature of the bath either increased or decreased from 37°.

Heat and Exercise—Swartz and Sidell (168) injected pyridine-2-aldoxime methochloride and the sodium salt of *p*-aminohippuric acid intravenously into male volunteers and followed the plasma concentrations of both substances as a function of time. The disappearance of pyridine-2-aldoxime methochloride and *p*-aminohippuric acid from the plasma could be described by the biexponential equation:

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 4)}$$

where C_1 is the plasma concentration of drug at any time t; β is -2.303 times the negative slope of the terminal linear segment of the plot of the logarithm of the plasma concentration *versus* time, with the half-life $(t_{1/2})_\beta$ for this segment equaling $\ln 2/\beta$; B is the extrapolated zero-time intercept of this line; α is -2.303 times the negative slope of a line plotted by the method of residuals from the initial plasma level values; A is the extrapolated zero-time intercept of this line; and α and β are hybrid rate constants for the distribution and metabolism or excretion in and out of the central (plasma) and peripheral (tissue) compartments, respectively. At time zero after the

Table III—Pharmacokinetic Constants following Intravenous Administration of Pyridine-2-aldoxime Methochloride (5 mg/kg) and Sodium *p*-Aminohippurate (900 mg Total Dose) into Human Males (168)

Condition[a]	V_1, ml/kg	V_2, ml/kg	$(t_{1/2})_\beta$, min	Percent Dose Recovered 0–3 hr	Percent Dose Recovered 0–24 hr
		Pyridine-2-aldoxime Methochloride			
R	369	393	71.2	84.3	85.3
E	425	481	87.7	74.6	84.5
H	444	475	71.1	73.2	82.6
HE	404	476	86.2	73.6	84.2
		Sodium *p*-Aminohippurate			
R	261	165	43.8	77.5	78.8
E	294	214	50.9	69.9	71.1
H	334	214	42.9	71.6	73.0
HE	298	193	41.1	66.5	67.3

[a] For pyridine-2-aldoxime methochloride and sodium *p*-aminohippurate *R* = resting for 3 hr at 21.1°, *E* = exercise consisting of walking on a treadmill at 4.83 km/hr for 20 min of each half-hour for 3 hr at 23.9°, *H* = resting for 3 hr at 40.6° dry bulb/23.9° wet-bulb, and *HE* = walking at 40.6°/23.9° for 3 hr.

intravenous injection, all of the dose is in plasma Compartment 1 at an initial concentration of $C_1^{(0)}$, and V_1 is the volume constant for Compartment 1. The concentration of drug in Compartment 2, or the tissue compartment, at any time is C_2. The term V_2 is the volume constant for Compartment 2.

Each of the six subjects in this study experienced nonstress or rest *(R)* conditions and three "stress" conditions including walking exercise *(E)*, environmental heat *(H)*, and simultaneous heat and exercise *(HE)* (Table III). For both drugs, the V_1 and V_2 terms all increased when going from *R* conditions to a stress condition, although the level of statistical significance varied. For both drugs, the plasma half-lives, $(t_{1/2})_\beta$, increased significantly when going from *R* to *E* conditions. For both drugs, the percent of dose recovered in the urine after the first 3 hr following administration was two-thirds or greater, and there was a significantly lower 3-hr recovery under all stress conditions compared to *R* conditions. As estimated by *p*-aminohippuric acid clearance, exercise decreased renal plasma flow, and this decrease may affect pyridine-2-aldoxime methochloride elimination, which is excreted 80% or more unchanged *via* the kidney. The increases in V_1 and V_2 during stress conditions compared to *R* conditions suggest that the two drugs are distributed to tissues not receiving as much drug at rest conditions. It is possible that drug metabolism may also occur in the newly perfused areas. The results of this study provide the best quantitative evidence so far to suggest that environmental or body temperature may affect the pharmacokinetics of drugs. It is of interest to know how the body temperature under conditions of exercise, heat, or both compares to that under conditions of rest.

METABOLISM

The conversion of drugs to one or more active or inactive metabolites is usually controlled by various enzymes found in many organs. A drug that is an ester may undergo both enzymatic and nonenzymatic hydrolysis in the body (169). Temperature changes may have major effects upon the rates of enzyme-catalyzed reactions and of inactivation of the enzyme (170). There has been a long-standing debate concerning the most appropriate method of plotting the rates of enzymatic reactions or biological processes *versus* temperature (171–173); however, the Arrhenius equation is most commonly employed:

$$k = Ae^{-E/RT} \qquad \text{(Eq. 5)}$$

where k is the reaction rate, A is a constant, E is the activation energy, and R and T are the gas constant and absolute temperature, respectively (174). Thus, a plot of $\log_{10} k$ *versus* $1/T$ usually yields a straight line over a limited temperature range with the slope equal to $-E/2.303\,R$.

During hyperthermia, organ damage may occur and enzymes may "leak" into the blood. Burger *et al.* (175) maintained groups of rats at a room temperature of 18° and in water baths at 37.5 and 42°. After hyperthermia, the serum of rats showed an increase over controls in the levels of alkaline phosphatase, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, and lactate dehydrogenase. The serum levels of glutamate dehydrogenase and sorbitol dehydrogenase at first increased and then decreased.

The effect of temperature on drug metabolism in the intact animal is poorly understood for most drugs. A few studies should illustrate the present state of the art. Cottle and Veress (176) measured the total urinary glucuronide excretion from two groups of rats acclimated to 5 or 25° for 1 month. After a 1-day control urine collection, both groups were injected intraperitoneally with a solution containing 50 mg of sodium benzoate. Urine was collected for 2 days. Table IV shows that cold-acclimated rats excreted more total glucuronide in the urine compared to control values than did rats living under the 25° conditions. The capacity of the conjugation mechanism appears to be increased in the cold-acclimated animals compared to those at 25°.

Rink *et al.* (177) and Gray *et al.* (178) utilized a perfusion technique in the isolated rabbit liver to study morphine and thiopental metabolism at 24 and 37°. The biological half-life for the loss of free morphine from the plasma was 94 min at 24° and 3.7

Table IV—Excretion of Glucuronides in Urine of Wistar Rats (176)

	Rats Acclimated to 25°, mg/day	Rats Acclimated to 5°, mg/day
Control period	10.3	15.6
0–24 hr after sodium benzoate	13.2	21.1
24–48 hr after sodium benzoate	12.6	22.3

min at 37°. The biological half-life for the loss of free thiopental from the plasma was 185–530 min at 24° and 46 min at 37°.

A series of papers (179–182) was published on drug metabolism under hypothermic conditions using a perfused rat liver preparation. The acetylation of sulfanilamide by the liver was temperature sensitive. Most acetylated drug appeared in the blood, and the half-lives for the metabolite's appearance were 70 min at 37° and 750 min at 15° (179). In a similar study with pentobarbital, the half-lives for the disappearance of unchanged drug from the blood were 315 min at 37° and 1325 min at 20° (180). Hydrolysis of procaine in this perfusion system occurred only in the liver and not in rat plasma. Procaine disappearance from the blood at 37° had a half-life of 3 min; at 17°, it had a half-life of 35 min (181). In the perfused rat liver system, a ^{14}C-label on atropine disappeared from the plasma in an apparent polyexponential manner. The half-lives for the fastest component were 6 min at 37° and 20 min at 17° (182).

Creaven *et al.* (183) showed that the 10,000×*g* supernate of rainbow trout liver homogenate was able to *O*-dealkylate six 2- and 4-alkoxy-substituted biphenyls. The dealkylating activity in the trout preparations was more active at around 20° than at 37°. Frog liver preparations, *Rana temporaria,* also dealkylated the same substrates, but the optimum enzyme activity was at 37° instead of at 20°.

Following oral drug administration, extrahepatic drug metabolism may occur with normal intestinal microorganisms. As Scheline (184) pointed out, drugs may undergo reduction in molecular size and change their physicochemical properties. Goldman (185) recently reviewed the therapeutic implications of the metabolism of such drugs as salicylazosulfapyridine and levodopa by intestinal microflora. Neither investigator mentioned how changes in intestinal temperature might influence the rate of such drug metabolism.

Drug (or foreign chemical) metabolism has been shown to occur within various segments of the GI tract wall (186–188). Levy (189) found that hydrolysis of aspirin occurred in everted segments of the rat small intestine and that the percent hydrolysis decreased with increasing aspirin concentration. A linear relationship between the reciprocal of the aspirin hydrolysis rate and the reciprocal of the initial aspirin concentration was found on a Lineweaver–Burk-type plot. Possible temperature effects on metabolism were not studied by these investigators.

Extrahepatic metabolism occurred with some ester-type drugs in the serum or plasma of the rabbit (169) and the human (190–193). Both enzymatic and nonenzymatic hydrolysis of atropine occurred in rabbit serum and was affected by serum pH and temperature. At pH 8.4, the optimum activity of the tropine esterase occurred at 38° (169), and the hydrolysis was an apparent zero-order reaction.

Wislicki (194) studied the blocking action of succinylcholine on the gastrocnemius muscle in anesthetized cats during artificial hypo- and hyperthermia. Following a lowering of rectal temperature to 30°, the duration and magnitude of the neuromuscular blocking effect of succinylcholine were about double compared to animals at normal body temperature. The artificial warming of animals lessened the response of the gastrocnemius muscle to succinylcholine. The *in vitro* activity of succinylcholine incubated in cat plasma was measured using frog recti abdominis muscles to detect drug activity over a 30–45° temperature range. The rate of inactivation of succinylcholine increased from 30 to 40°, reached a maximum between 40 and 42.5°, and then decreased at 45°. The correlation between the *in vivo* and *in vitro* experiments suggests that the temperature dependence of enzymatic hydrolysis of succinylcholine may play an important role in determining the magnitude and duration of the neuromuscular block at various body temperatures. However, other factors might also be involved; for example, variations in blood circulation to muscle tissue at different temperatures could affect the results.

ELIMINATION

Although drug and metabolite elimination can occur *via* many routes, only the effect of temperature on renal and biliary elimination will be considered in this report. Several reviews discussed factors affecting drug excretion by the kidney (195–197) and the bile (195–200), but temperature effects were usually omitted.

Page (201) studied the effects of progressive hypothermia on the renal function of dogs maintained at a 20° room temperature for at least 5 days. After sodium pentobarbital anesthesia, intravenous infusions of *p*-aminohippurate and creatinine were initiated. At 20°, control values for the glomerular filtration rate were measured using exogenous creatinine clearance, the effective renal plasma flow was calculated from *p*-aminohippurate clearance, and the maximum tubular secretory capacity for *p*-aminohippurate, ^{Tm}p-aminohippurate, was determined. The dogs were then transferred to a cold room held at about −25° where urine and blood samples were collected and rectal temperatures were recorded. During progressive hypothermia, the glomerular filtration rate and effective renal plasma flow decreased in a linear manner with decreasing rectal temperature. An Arrhenius plot of the logarithm of ^{Tm}p-aminohippurate *versus* the reciprocal of the absolute rectal temperature yielded a linear plot with a negative slope. The average activation energy, *E,* for four normal dogs was 23.5 kcal/mole.

Previously, it was mentioned that there are many human circadian rhythms including those related to urine and plasma pH and body temperature. During sleep, urine and plasma pH values are lower than after awakening. Body temperature tends to be lowest 4 hr after midnight and highest at about 8 pm. An error in logic would occur if it were stated that just because two events occur simultaneously, or nearly so, one event was the cause of the other. However, the possibility of causal relationships between urine pH and body temperature cannot be ruled out pending the completion of suitable experiments.

When the urine pH is shifted from low to higher values, or the reverse, due to normal processes such as the circadian rhythm or due to the oral administration of acidifying agents (*e.g.*, ammonium chloride) or alkalinizing agents (*e.g.*, sodium bicarbonate), the rate of urine excretion and the biological half-life of some weak organic acids and bases may be altered. The physical properties of the drug, such as the pKa and the lipid–water partition coefficient, may determine whether the biological half-life of an organic weak acid or base will be affected by changes in urinary pH. For example, Dettli *et al.* (202) conducted a crossover study with human volunteers using two sulfonamides. The urine pH was not controlled in one test period ("spontaneous period"), and in the other test period ("alkali period") the urine pH was maintained at 8 with sodium bicarbonate. The mean serum biological half-lives of unchanged sulfalene (pKa′ = 6.1) were 7.3 hr for the alkali period and 14.0 hr for the spontaneous period, and the mean half-lives for sulfasymazine (pKa′ = 5.5) were 32.46 hr for the alkali period and 71.58 hr for the spontaneous period. Thus, for both drugs the biological half-life during the alkali period was approximately half that for the spontaneous period.

Dettli and Spring (203) found that the mean biological half-life of sulfasymazine (pKa′ = 5.5) in humans at night was about 2.6 times longer (35.0 hr) than that found during the day (13.5 hr). The mean biological half-life for sulfanilamide (pKa′ = 10.5) at night (12.7 hr) was nearly the same as that found during the day (11.1 hr). Spring *et al.* (204) noted that the biological half-life of sulfalene (pKa′ = 6.1) in human plasma was about three times longer at night (145.7 hr) than it was during the day (46.2 hr).

According to the pH–partition hypothesis (205), the unionized form of lipid-soluble drugs that are organic weak acids or bases can diffuse passively through cell membranes within the body. At any given physiological pH and temperature, the degree of ionization, α, of an organic weak acid, for example, is:

$$\alpha = \frac{1}{1 + 10^{pKa' - pH}} \qquad \text{(Eq. 6)}$$

Thus, sulfanilamide is nearly completely unionized at any physiological pH, while the sulfonamides having pKa′ values of 5.5 and 6.1 have a large fraction of the total sulfonamide present in the ionized form at pH 8 and less in the ionized form at lower pH values, the actual fraction being determined by pH.

Sulfonamides having pKa′ values of 5.5 and 6.1 would not tend to be as readily reabsorbed into the tubular cells from an alkaline urine as an acidic one. Dettli *et al.* (202) suggested that the decrease in biological half-life of an acidic drug in serum during an alkalization of urine is partly due to a diminished nonionic tubular reabsorption of drug and may be partly due to nonionic redistribution of drug within the organism. If the intracellular pH is less affected than the pH of the extracellular fluid due to the administration of alkali, then the fraction of unionized molecules of drug will decrease in the extracellular fluid. Unionized molecules will tend to diffuse from the cells into the extracellular fluid. Since the amount of sulfonamide eliminated per unit of time equals the product of the renal clearance and the plasma concentration, an increase in drug elimination rate would result as the plasma concentration increases. Thus, the observed increase in elimination rate following alkali administration could be due to diminished nonionic tubular reabsorption as well as to nonionic redistribution within the organism. A drug like sulfanilamide, which is nearly completely in the unionized form at all physiological pH values, would exhibit little increase in its elimination rate following administration of alkali.

The effects that body or environmental temperature may have on the biliary elimination or excretion of drugs has been investigated for such substances or drugs as bilirubin, sulfobromophthalein, glycerol, ethanol, liothyronine, and thyroxine. Roberts *et al.* (206) studied the influence of temperature on the maximum biliary excretion (T_m) of bilirubin and sulfobromophthalein in anesthetized rats and mice. A decrease in rectal temperature from 39 to 31° reduced both bilirubin and sulfobromophthalein T_m values in a linear manner. Bile flow in both species decreased linearly with a decrease in rectal temperature.

Larsen (207) measured the effect of body cooling on the liver function of anesthetized cats. Liver function was measured by following the elimination rate of glycerol and ethanol and the hepatic uptake of indocyanine green which were infused into the femoral vein. A 1–2° reduction of the body temperature reduced the elimination rate of glycerol and ethanol and the hepatic uptake of indocyanine green by about 40%. The changes in liver function following a slight decrease in liver temperature might be explained by a reduction in the interhepatic circulation and reduction in functional capacity of the liver in the anesthetized animal.

Cottle (208) found that the biliary clearance of liothyronine in rats acclimated at 5° was greater than in rats acclimated at 25°. Hillier (209) confirmed these results and also showed that the biological half-life of thyroxine in the blood following an intravenous injection was shorter for cold-adapted rats (4°) than for warm-adapted rats (22°).

CONCLUSIONS

The fragmentary evidence presented in this review

suggests that environmental or body temperature may influence the pharmacokinetic behavior of a drug. The magnitude or importance of this role for any one particular drug in intact animals or humans under hypo- or hyperthermic conditions cannot be defined precisely, because in nearly all instances the critical experiments needed to define pharmacokinetic constants have yet to be performed under controlled conditions. The potential for research in the area of temperature and pharmacokinetics is great and may prove to have valuable therapeutic consequences in determining dosages and dosing regimens in patients whose body temperature is not within the "normal" range throughout the day.

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