PERCUTANEOUS ABSORPTION OF TRITIUM OXIDE*

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TRITIUM, the mass 3 radioactive isotope of hydrogen, promises to become a widely used tracer for hydrogen in biological and chemical studies. Hazards attendant on the handling of this isotope are limited to those from internal radiation, the energy of its beta particle being so weak (maximum energy, 0.0185 mev.) as to constitute no external radiation hazard. In part, then, the problem of hazard evaluation becomes one of studying the various portals through which tritium, or compounds containing tritium, may gain entry to the body. The present paper is concerned with the hazards arising from a tritium oxide contaminated atmosphere.

The two main portals through which atmospheric tritium oxide may enter the body are presumed to be the lungs and the skin. The contribution of pulmonary absorption to the total body uptake from an atmosphere of known tritium oxide content can be readily calculated on the assumption that all tritium oxide entering the lungs is absorbed. This assumption has been experimentally verified by several investigators.[7,12,19] The contribution from absorption through the skin must be measured experimentally. The present investigation was made to determine the rate of percutaneous absorption of tritium oxide, to compare this with the rate of pulmonary absorption, and to investigate the factors which might be important in determining or changing the rate of absorption. While principal attention was focused on absorption from the vapor state, experiments were also performed to compare the rate of absorption of liquid water.

To the extent to which tritium may be considered a legitimate tracer for hydrogen, the results of this study contribute to the general problem of the permeability of the skin to water. Positive proof of the inward passage of liquid water has only recently been reported.[?] A preliminary note on our demonstration of the percutaneous absorption of water vapor has appeared in the literature,[9] and a recent review by Pinson[16] alludes to unpublished studies on percutaneous absorption of tritium oxide performed at the Los Alamos Scientific Laboratory.

METHODS

Subjects and Exposure Procedures. Subjects employed were CF-1 strain mice, rats of the Sprague-Dawley strain, and human, adult, white males. Except for a single total body exposure of a human subject, all exposures were to a circumscribed skin area. Unless otherwise specified, exposures were for one hour at 30° C. Animals were exposed under nembutal anesthesia.

Two systems were employed for exposure of the skin to the tritium oxide-labeled water vapor. The first of these, illustrated in Figure 1, consisted of a small cup containing tritium oxide in water* supported above the skin inside of a containing chamber. This apparatus will be subsequently referred to as the "static" system. Because of inadequate saturation of the air in the system and because of the danger of spilling liquid tritium oxide solution on the skin, a second type of apparatus, illustrated in Figure 2, was employed for the major portion of the investigation. This "dynamic" system consisted of a hydrator into which dried air was passed, via a sintered glass gas dispersion tube, through a water solution of tritium oxide and thence into a connected exposure chamber in which the saturated vapor was passed over the skin and out into a dry ice trap. Control experiments

* It will be recognized that the proportion of tritium oxide in the water solutions was, masswise, extremely small, and that the molecular species present which contained tritium was almost exclusively HTO.

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[illegible]ylene, which gas was then introduced into a[n] ionization chamber connected to a vibrating reed electrometer. The current produced was measured as a function of the length of time required to discharge a standard negative potential. Currently the hydrogen-filled Geiger counter has supplanted the vibrating reed electrometer because of ease and rapidity of operation and maintenance. Results obtained by either of these methods are reproducible with ±5 per cent. Absolute values may be subject to greater error due to uncertainties in the absolute calibration of the instruments and possibilities of slight isotopic fractionation in the generation of gas samples. Such absolute errors are not of significance in the present study, since all conclusions are based on comparisons of counts. Details of the counting procedure will be described by others.[10]

Expression of Results. Results are expressed in two forms. An absorption rate constant, K, is in units of μc tritium oxide absorbed per cm.² skin area per minute per μc/cc. of tritium oxide in the exposure atmosphere. In terms of experimentally determined quantities, this constant is calculated in the following manner:

$$K = \frac{UC_i}{AtC_e}$$

where U is the total volume of body water (liters), C_i is the activity of the body water (μc/liter), A is the area exposed (cm.²), t is the duration of exposure (minutes), and C_e is the activity of the exposure atmosphere (μc/cc.).

Results are also expressed as the quantity of water absorbed (in μg.) per minute per cm.² skin area. The symbol Δ is employed for this quantity which is calculated in the following manner:

$$\Delta = \frac{UC_i}{AtS}$$

where S is the concentration of tritium in the water employed, in μc/μg. This calculation, of course, assumes that tritium oxide functions as an ideal tracer for water, both in biological absorption and in the physical evaporation to form the saturated atmosphere. While this assumption cannot be strictly valid, error introduced by the assumption is no doubt smaller than other errors inherent in this type of study.

The values for total volume of body water were experimentally determined in the case of the rats and mice, and estimated at 61.8 per cent of total body weight in the case of the human subjects.[20]

The plus-or-minus limits listed with values of K and Δ are standard deviations of the mean at the 95 per cent confidence level.

RESULTS AND DISCUSSION

The results obtained from exposure of the various species to a saturated or near saturated water vapor atmosphere are recorded in Table I. Data for male and female rats and mice were calculated separately, but no sex difference was apparent and the results for both sexes were combined. The results obtained using the static exposure

TABLE I

PERCUTANEOUS ABSORPTION OF TRITIUM OXIDE FROM A SATURATED OR NEAR SATURATED WATER VAPOR ATMOSPHERE AT 30° C.

Subject	Method of Exposure	Site of Exposure	Pre-exposure Treatment	No. of Subjects Exposed	Absorption Rate Constant for Tritium Oxide = K (μc/cm.²/min./μc/cc.)		Water absorption rate = Δ (μg./cm.²/min.)	
					Based on cardiac blood sample	Based on sample of total body water	Based on cardiac blood sample	Based on sample of total body water
Rat	Static	Abdomen	Unshaved	21	.018 ± .003	.055 ± .010	.55 ± .07	1.6[illegible] ± .31
Rat	Static	Abdomen	Shaved	25	.082 ± .017	.141 ± .026	2.29 ± .45	4.06 ± .[illegible]4
Rat	Dynamic	Abdomen	Cloth covering (shaved)	24	.175 ± .029	.189 ± .035	5.31 ± .87	5.[illegible] ± 1.06
Rat	Dynamic	Abdomen	Shaved	30	.134 ± .015	.188 ± .018	4.[illegible] ± .46	[illegible] ± .[illegible]3
Mouse	Dynamic	Abdomen	Shaved	29	—	.6[illegible] ± .16	—	[illegible]
Man	Dynamic	Forearm	Unshaved	[illegible]	—	.28 ± .05	—	8.6 ± 1.[illegible]
Man	Static	Abdomen	Unshaved	2	—	.34	—	[illegible]
Man	Dynamic	Total body	Unshaved	1	—	.84	—	[illegible]

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system are low t[...] reasons previous[...] included in Tabl[...] qualitative comp[...] that data publish[...] inary note[9] were[...] method [...]ad are t[...] with the best va[...] "static" data fron[...] do indicate quite[...] sorption occasion[...] area.

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system are low to an uncertain degree for reasons previously discussed. They are included in Table I only for purposes of qualitative comparison. It should be noted that data published previously in a preliminary note[9] were obtained by the static method and are therefore not in agreement with the best values here reported. The "static" data from rats included in Table I do indicate quite clearly the enhanced absorption occasioned by shaving the exposed area.

In all cases the values of K and Δ calculated from cardiac blood samples are lower than the corresponding values calculated from samples of the total body water, indicating a lag in the distribution of the absorbed water. This effect was noted and studied more extensively with short-term exposures by Pinson.[18] With respect to the eventual body burden, however, the values based on samples of total body water are of primary significance, since uniform distribution of the absorbed activity must certainly occur within a period of time which is short compared with the biological half-life of tritium oxide in the body.

The experiment in which a series of rats were exposed with a layer of cloth covering the skin area was designed to evaluate possible effects of clothing on percutaneous absorption. The cloth employed was heavy cotton material of the type commonly found in laboratory coats and coveralls. No effect was observed on total absorption, as indicated by the K values calculated from total body water samples. There does appear to be an increase in the rate at which the absorbed activity appears in the circulation as evidenced by the values of K calculated from the cardiac blood samples.

The data from human subjects are characterized by a lack of agreement between the results obtained for different exposure sites. The agreement between the data from 12 subjects exposed on the forearm was quite good, considering the disparity in physiques and the consequent error in assuming a constant proportion of body water in all subjects. While the two exposures to the abdomen were made using the static system, the results are of qualitative interest, since they indicate a higher rate constant for the abdomen than for the forearm. The quantitative difference is undoubtedly greater than that indicated, since all of the data obtained with the static system were low compared with results obtained using the dynamic system.

The single total body exposure experiment indicates an absorption rate constant about three times as great as the constants calculated from forearm exposures. Several factors must be considered in evaluating this result. First, it is obviously unsafe to generalize too extensively from the results of a single exposure. Second, the conditions of this total body exposure were somewhat different from those which existed in the forearm exposures. While the forearm exposures were performed in an essentially saturated water vapor atmosphere, the average per cent saturation during the total body exposure was only 70 per cent. This difference, while influencing Δ values, should not affect K values, as will be shown in later discussion. Third, the subject involved in the total body exposure was one of the subjects included in the forearm exposure group, the K value from his forearm exposure being 0.23, thus strengthening the evidence for a real difference in absorption rate between different skin areas.

Pinson[18] has suggested that percutaneous absorption of water vapor could be looked upon simply as the reverse phase of the physiological phenomenon of insensible perspiration. If this is the case, and it appears entirely reasonable, then the extensive data previously collected on insensible perspiration should be pertinent to an understanding of percutaneous absorption. Table II lists some of the results obtained over the past thirty-five years, recalculated where necessary to a common basis of μg. water loss per cm.^{2} per minute. Where original data were given in terms of the total body surface an average skin area of 1.8 M.^{2} was assumed, and it was further

TABLE II

INSENSIBLE WATER LOSS THROUGH THE SKIN
LITERATURE VALUES

Portion of Body	State of Skin	Rate of Loss (μg. cm.² min.)	Environment	Reference	Year
Total body	Living	13	-	(21)	1917
Total body	Living	25-30	-	(15)	1931
Total body	Living	25	Liquid, 72° F.	(23)	1932
Index finger tip	Living	120	75° F.	(14)	1941
2nd toe tip	Living	79	50% rel. hum.		
Pinna	Living	32			
Leg	Living	15-20	28° C.	(17)	1942
Ball of foot	Living	180	75° F.	(3)	1943
Plantar surface, heel	Living	160	50% rel. hum.		
Palm	Living	150			
Index finger tip	Living	150			
Lateral surface, arm	Living	140			
Mid plantar, foot	Living	120			
2nd toe tip	Living	88			
Cheek	Living	71			
Mid forehead	Living	70			
Axilla	Living	62			
Posterior surface, leg	Living	53			
Thigh and flank	Living	41			
Mid epigastrium	Living	37			
Volar surface forearm	Living	29			
Epigastrium	Living and dead	100*	75° F.	(2)	1944
Epigastrium	Living and dead	100*	75° F.	(4)	1944
Total body	Living	16	75° F.	(5)	1945
Total body	Dead	9	50% rel. hum.		
Palm	Dead	29	24° C.	(6)	1946
Sole	Dead	18	70% rel. hum.		
Axilla	Dead	10			
Epigastrium	Dead	3.3			
Total body	Living	13	23° C. 51% rel. hum.	(8)	1948
Palm	Living	70-150	27° C.	(16)	1951
Sole	Living	50			
Face	Living	40			
Arm, leg and trunk	Living	7			

* These studies indicate a maximum rate, since dried O_2 was passed over the skin.

assumed that 52 per cent of the total insensible water loss was via the lungs.[3] These figures represent net water loss and constitute the balance between the outward and inward movement of water through the skin. As such, they bear no necessary relationship to the magnitude of either of these individual processes. If, however, the

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TABLE III

EFFECT OF WATER VAPOR PRESSURE ON PERCUTANEOUS ABSORPTION OF TRITIUM OXIDE

Expt. No.	NaOH Molarity	Theoretical: Vapor pressure (mm. Hg)	Theoretical: Conc. of $T=C_e$ (μc/cc.)	Experimental: Vapor Pressure (mm. Hg)	Experimental: Conc. of $T=C_e$ (μc/cc.)	No. of rats exposed	K (μc/cm.² min./μc/cc.)	Δ (μg./cm.²/min.)
1	[illegible]	31.8	[illegible]	30.5	7.28	30	.188 ± .018	5.70 ± .53
2	8	19.4	4.44	20.3	4.65	11	.186 ± .033	3.30 ± .59
3	13	12.7	2.39	10.8	2.34	11	.158 ± .044	1.51 ± .42
4	16	7.2	1.38	7.47	1.4	11	.199 ± .033	1.26 ± .20
5	18	5.6	1.09	5.85	1.31	10	.135 ± .024	.705 ± .124
6	20.4	.9	.18	1.73	.347	11	.245 ± .048	.340 ± .067

mechanism of inward and outward passage of water through the skin is identical or closely similar, one would expect that high net water movement would be associated with high rates of movement in both directions. It is evident from an inspection of the data of Table II that the rate of net water loss varies considerably in different skin areas. The one series of studies which included the volar surface of the forearm shows a lower rate for this area than for any other area measured. It thus appears not unreasonable that the average total body rate of percutaneous absorption should exceed the forearm rate by several fold; and, although based on a single determination, the value of 0.84 μc/cm²/min/μc/cm.³ atmosphere is probably a reasonably accurate measure of the total body percutaneous absorption rate constant.

Data on the effect of water vapor pressure on the percutaneous absorption of tritium oxide in rats are summarized in Table III. These experiments were conducted in a manner exactly similar to the other exposures, except that the water vapor pressure in the exposure atmosphere was controlled by addition of sodium hydroxide in various concentrations to the tritium oxide solution in the hydrating chamber of the "dynamic" exposure apparatus. Table III lists both the calculated vapor pressure and tritium concentration of the atmosphere[1,13] and their values as determined experimentally by sampling the atmosphere. Satisfactory agreement was obtained, except for the two highest sodium hydroxide concentrations. In these two cases the theoretical values were based on extrapolation, and the experimental figures are undoubtedly the more accurate of the two. In calculating values of K, theoretical C_e values were used for experiments 1–4 and experimental values for experiments 5 and 6. Values of K and Δ in Table III were based on tritium determinations on the total body water from the exposed animals. Blood samples were also analyzed and led to values of K and Δ which were consistently about 70 per cent of the total body water values, indicating again a time lag in the equilibration of absorbed tritium oxide with the total body water.

It is evident from Table III that the rate of water absorption (Δ) is directly proportional to water vapor pressure. It is also clear that the absorption of tritium oxide from an atmosphere of constant tritium oxide content (K) is independent of total water vapor pressure. The direct proportionality between water absorption and water vapor pressure supports the hypothesis of a simple diffusion mechanism for percutaneous absorption. From the hazard standpoint, the results indicate that humidity is not a factor to be considered in exposure considerations.

The results of liquid water absorption studies on the rat are shown in Table IV. Absorption rates were calculated from analyses on total body water. The much higher values obtained from unshaved animals must be attributed to tritium-labeled

TABLE IV

PERCUTANEOUS ABSORPTION OF LIQUID WATER BY THE RAT

Expt. No.	No. of Rats	Auxiliary Treatment	(μg./cm.²/min.)
1	17	Shaved prior to exposure	15.2 ± 3.0
2	5	Unshaved	31.3 ± 4.7
3	5	Shaved subsequent to exposure	10.6 ± 3.5

water adsorbed on the hair and included in the total body water determinations. Shaving either before or after exposure reduced the values. The results of experiments 1 and 3 are not significantly different considering the small number of animals in experiment 3. The absorption rate appears to be two to three times larger for liquid water than for saturated water vapor. These results on liquid water should be considered only as preliminary findings; and the possibility of extensive adsorption on the skin, resistant to thorough washing, should not be overlooked. So far as the eventual body burden is concerned, however, any such tightly adsorbed water is practically equivalent to absorption. Pinson[10] has reported no difference in the absorption rate from liquid water or a saturated water vapor atmosphere.

RELATIVE HAZARDS OF PERCUTANEOUS VERSUS PULMONARY ABSORPTION OF TRITIUM OXIDE VAPOR

Using the value of 0.84 for the absorption rate constant for human total body exposure (Table I), a "standard man"[11] during an eight hour period of exposure to the presently established permissible maximum[11] will absorb 360 μc through his skin:

Absorption rate constant (0.84) × total skin area (1.8×10^4 cm.²)* × time (480 min.) × tritium oxide concentration in atmosphere (5×10^{-6} μc/cc.) = 360 μc.

Similarly, for pulmonary absorption, assuming complete retention of inhaled tritium oxide, a value of 500 μc is obtained:

Volume inspired (10^7 cc.) × tritium oxide concentration in atmosphere (5×10^{-5} μc/cc.) = 500 μc.

From these calculations it is apparent that percutaneous absorption and pulmonary absorption contribute approximately equally to the total body burden of tritium oxide acquired through exposure to an atmosphere contaminated with tritium oxide.

The present permissible maximum level for atmospheric tritium oxide contamination was established without consideration of percutaneous absorption. A reduction in the permissible maximum by a factor of two is therefore suggested by the results of the present investigation. The establishment of percutaneous absorption as a significant hazard also emphasizes the inadequacy of respiratory protection alone in tritium oxide contaminated atmospheres.

SUMMARY

The percutaneous absorption of tritium oxide-labeled water vapor was studied in mice, rats and man. In terms of μg. water absorbed/cm.²/min. from a saturated water vapor atmosphere, the rates found were: for mice (abdomen), 20 ± 5; rats (abdomen) 5.7 ± 1.1; man (forearm) 8.6 ± 1.7. A single total body exposure to a human at 70 per cent relative humidity gave a rate of 18 μg/cm²/min. The rate of water vapor absorption in the rat was found to be directly proportional to water vapor pressure. For a constant level of atmospheric tritium oxide, absorption of tritium oxide was independent of total water vapor pressure.

It was shown that for humans the rate of percutaneous absorption of tritium from a tritium oxide contaminated atmosphere is about the same as the rate of pulmonary absorption from the same atmosphere.

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* This represents the total skin area of a 70 kg. and 170 cm. man.[1]

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