Dissolution Profile of Log-Normal Powders: Exact Expression

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Abstract ☐ A rigorously correct derivation is given for the time course of dissolution of powders that follow the log-normal probability distribution. The exact expression, based on reasonable assumptions, requires no integration but can be evaluated by use of a calculator and readily available mathematics tables. The approximations of earlier workers for the dissolution patterns of log-normal powders are tested against the exact equation.

Keyphrases ☐ Dissolution profiles—log-normally distributed powders, exact derivation ☐ Powders, dissolution—exact solution of log-normal distribution profile ☐ Particle dissolution—log-normally distributed powders, exact derivation

Recently, Carstensen and Musa (1) presented approximate dissolution patterns for powders obeying the log-normal distribution law. They, like earlier workers (2, 3), refrained from an exact treatment of this subject because the expressions involved tended to become "analytically unmanageable." Instead, Carstensen and Musa (1) used a computer to gain approximate numerical solutions of their complicated probability expressions.

In this paper, a rigorously correct expression is derived for the dissolution profiles of log-normally distributed powders. The exact expression for weight fraction undissolved with time can be evaluated by use of a calculator and a handbook of mathematics tables including the standardized normal probability distribution. The calculations are tedious but can be accomplished without the use of a computer.

THEORETICAL

Consider a powder containing spherical particles of diameters a_0 which are distributed, on a numbers basis, such that $\ln a_0$ is normal with population mean μ and population standard deviation σ[1]. The probability frequency f of log diameters is given by:

$$f = \frac{1}{\sigma\sqrt{2\pi}} e^{-(\ln a_0 - \mu)^2/2\sigma^2} \qquad \text{(Eq. 1)}$$

When particles are placed in a medium, the diameters diminish as dissolution proceeds. If it is assumed that the particles dissolve isotropically under sink conditions and that the solubility C_s is independent of particle size, then the diameter a_τ of a particle at some function τ of time is described (1) by:

$$a_\tau = a_0 - \frac{2kC_s}{p}t = a_0 - \tau \qquad \text{(Eq. 2)}$$

where a_0 is the initial (time $= 0$) diameter, k is a dissolution rate constant, t is time, and p is particle density. Here the function τ of time is $2kC_s t/p$, which is essentially the notation of Carstensen and

Musa (1). Obviously, the diameter is linear with time. The function τ has dimensions of length.

If the total number of particles in the powder is N, then the number dN of particles of initial diameter a_0 is given by:

$$dN = Nfd \ln a_0 \qquad \text{(Eq. 3)}$$

Initially, the contribution dw of particles of diameter a_0 to the total weight of the powder is the weight of one particle times the number in that cut or $\pi p a_0^3 dN/6$. As dissolution continues, the diameters of particles decrease; but as long as $a_\tau > 0$, the number of particles in that cut remains the same. Thus, the contribution to the total weight after some time such that $0 < \tau < a_0$ is:

$$dw = \frac{\pi p}{6}a_\tau^3 dN = \frac{\pi p}{6}(a_0 - \tau)^3 Nfd \ln a_0 \qquad \text{(Eq. 4)}$$

The weight of undissolved solid at τ is given by an integration of Eq. 4 for all remaining particles. The integration is in terms of initial diameters, since the numbers of particles were described on that basis. The lower limit of integration is rationalized by the fact that at any value of τ the smallest remaining particles ($a_0 - \tau \to 0$) were initially of size $a_0 = \tau$. Therefore, the weight w_τ is:

$$w_\tau = \int_{\ln a_0 = \ln \tau}^{\ln a_0 = \infty} \frac{\pi p}{6}(a_0 - \tau)^3 Nfd \ln a_0 \qquad \text{(Eq. 5)}$$

For purposes of integration, τ is a constant.

By expanding the cubic term and letting $r = \pi p N/6$, Eq. 5 becomes:

$$w_\tau = r \int_{\ln \tau}^{\infty} a_0^3 fd \ln a_0 - 3r\tau \int_{\ln \tau}^{\infty} a_0^2 fd \ln a_0 +$$

$$3r\tau^2 \int_{\ln \tau}^{\infty} a_0 fd \ln a_0 - r\tau^3 \int_{\ln \tau}^{\infty} fd \ln a_0 \qquad \text{(Eq. 6)}$$

When considering any of the four integrals in Eq. 6, let there be a number β ($\beta = 0, 1, 2, 3$) such that:

$$I_\beta = \int_{\ln \tau}^{\infty} \frac{a_0^\beta}{\sigma\sqrt{2\pi}} e^{-(\ln a_0 - \mu)^2/2\sigma^2} d \ln a_0 \qquad \text{(Eq. 7)}$$

It is convenient to express a_0^β as $e^{\beta \ln a_0}$ and then to manipulate the resulting integral in much the same manner as is done when developing the moment generating function for the normal distribution (4). First, the powers of e in the integral are collected so that:

$$\beta \ln a_0 - \frac{(\ln a_0 - \mu)^2}{2\sigma^2} = -\frac{[\ln^2 a_0 - 2(\mu + \beta\sigma^2) \ln a_0] + \mu^2}{2\sigma^2} \qquad \text{(Eq. 8)}$$

By completing the square of the bracketed part of Eq. 8, that is, by adding and subtracting $(\mu + \beta\sigma^2)^2$, and collecting terms, the exponent of e becomes:

$$\beta\left(\mu + \frac{\beta}{2}\sigma^2\right) - \frac{[\ln a_0 - (\mu + \beta\sigma^2)]^2}{2\sigma^2}$$

and I_β becomes:

$$I_\beta = e^{\beta(\mu + \beta\sigma^2/2)} \int_{\ln \tau}^{\infty} \frac{e^{[\ln a_0 - (\mu + \beta\sigma^2)]^2/2\sigma^2}}{\sigma\sqrt{2\pi}} d \ln a_0 \qquad \text{(Eq. 9)}$$

The new integral in Eq. 9 is that of a random variable ($\ln a_0$) which is normally distributed with mean ($\mu + \beta\sigma^2$) and standard

Table I—Dissolution Patterns for Log-Normal Powders with a Geometric Mean of 40 µm. (μ = 3.68888) as Calculated from Eq. 13 for Exact and for Truncated (at μ + 3σ) Distributions

	τ	Exact	Truncated	Percent Relative Error[a]
		Calculated Weight Fraction Remaining		
σ = 0.03178	0	1.0000	1.0000	—
	5	0.6707	0.6707	—
	10	0.4231	0.4231	—
	15	0.2455	0.2455	—
	20	0.1263	0.1263	—
	25	0.0538	0.0538	—
	30	0.0164	0.0165	—
	36.36(τ_c)[b]	0.0010	0.0010	—
σ = 0.10000	0	1.0000	1.0000	—
	10	0.4337	0.4333	0.1
	20	0.1381	0.1376	0.4
	29.63(τ_c)	0.0255	0.0254	0.4
	30	0.0234	0.0233	0.4
	35	0.0063	0.0059	6.4
σ = 0.30000	0	1.0000	1.0000	—
	5	0.7320	0.7294	0.4
	10	0.5215	0.5173	0.8
	16.26(τ_c)	0.3273	0.3221	1.3
	25	0.1575	0.1521	3.4
	40	0.0372	0.0330	11.3
σ = 0.50000	0	1.0000	1.0000	—
	8.93(τ_c)	0.6929	0.6793	1.0
	10	0.6625	0.6476	2.3
	20	0.4326	0.4097	5.3
	40	0.1831	0.1567	14.4
	80	0.0361	0.0195	46.0
σ — 1.08304	0	1.0000	1.0000	—
	1.55(τ_c)	0.9938	0.9877	0.6
	40	0.8632	0.7380	14.5
	80	0.7594	0.5543	28.9
	120	0.6769	0.4201	38.0
	200	0.5529	0.2438	58.4
	280	0.4634	0.1404	69.8
	350	0.4034	0.0842	79.2

[a] Percent relative error = (exact — truncated)/exact $\times$ 100. [b] τ_c refers to the value of τ equivalent to a diameter given by ln a_0 = μ — 3σ.

deviation σ. If x = [ln a_0 — (μ + $\beta\sigma^2$)]/σ and dx = d ln a_0/σ, then Eq. 9 can be changed to:

$$I_\beta = e^{\beta(\mu+\beta\sigma^2/2)} \int_{x=[\ln \tau - (\mu+\beta\sigma^2)]/\sigma}^{\infty} \frac{e^{-x^2/2}}{\sqrt{2\pi}} dx \quad \text{(Eq. 10)}$$

which can be evaluated by use of tables of the standard normal distribution. If:

$$F(x) = \int_{-\infty}^{x} \frac{e^{-x^2/2}}{\sqrt{2\pi}} dx \quad \text{(Eq. 11)}$$

then it follows that I_β is to be evaluated by:

$$I_\beta = e^{\beta(\mu+\beta\sigma^2/2)} \left(1 - F\left[\frac{\ln \tau - (\mu + \beta\sigma^2)}{\sigma}\right]\right) \quad \text{(Eq. 12)}$$

where $F\{[\ln \tau - (\mu + \beta\sigma^2)]/\sigma\}$ is a tabled value.

The exact and rigorously correct expression for the weight undissolved, Eq. 6, becomes:

$$w_\tau = re^{3(\mu+3\sigma^2/2)} \left(1 - F\left[\frac{\ln \tau - (\mu + 3\sigma^2)}{\sigma}\right]\right) -$$

$$3r\tau e^{2(\mu+\sigma^2)} \left(1 - F\left[\frac{\ln \tau - (\mu + 2\sigma^2)}{\sigma}\right]\right) +$$

$$3r\tau^2 e^{(\mu+\sigma^2/2)} \left(1 - F\left[\frac{\ln \tau - (\mu + \sigma^2)}{\sigma}\right]\right) -$$

$$r\tau^3 \left(1 - F\left[\frac{\ln \tau - \mu}{\sigma}\right]\right) \quad \text{(Eq. 13)}$$
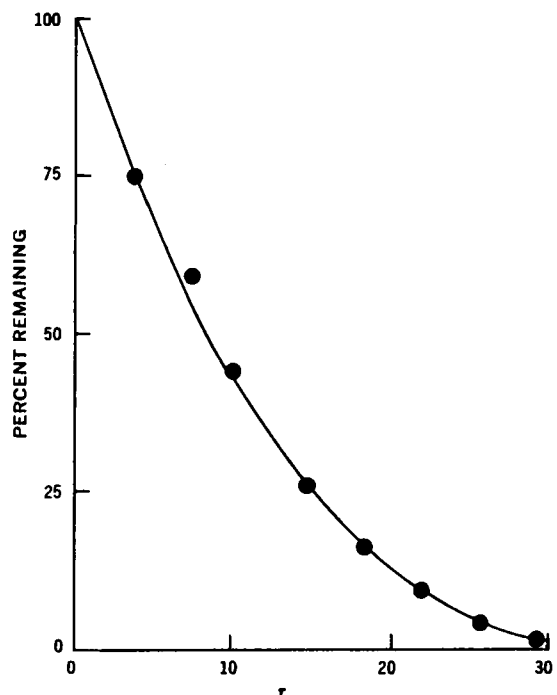
Figure 1—_Dissolution pattern for a log-normal powder with a geometric mean diameter of 40 µm. The population parameters were μ = 3.68888 and σ = 0.03178. The solid line was calculated from Eq. 13. The circles are the Carstensen and Musa (1) estimates for this distribution as reported in their Table II._

It is clear that an expression of weight fraction undissolved, w_τ/w_0, is a function only of τ, μ, and σ.

RESULTS AND DISCUSSION

The dissolution profiles for five log-normally distributed "powders" were treated for this paper using an electronic programmable calculator[2]. In each case the powder was assigned a geometric mean diameter of 40 µm. (μ = 3.68888). Standard deviations were chosen so that the distributions ranged from rather narrow to very broad. A dissolution pattern, as calculated from Eq. 13, for a powder with σ = 0.03178 is shown in Fig. 1. Such a powder would have 99.74% of its particles in the range 36.36–44.00 µm. This is perhaps a narrower distribution than could be expected for most pharmaceutical powders.

The distribution treated in Fig. 1 is the same one treated by Carstensen and Musa (1) by computer techniques and reported in their Table II. The circles in Fig. 1 are the values of Carstensen and Musa. The excellence of their approximations is obvious.

Carstensen and Musa assumed a powder containing no particles outside of a range within 3 standard deviations from the mean. In practical situations it is probable that many (or even most) actual powders follow truncated distributions. If this be the case, then it is possible that using an ideal (as opposed to truncated) log-normal distribution for actual powders could lead to errors in the calculated dissolution profile. Conversely, when dealing with a powder that is "ideally" log-normal, arbitrary truncation for the convenience of computer fitting could lead to errors. Whether or not significant errors occur because of these considerations depends upon the parameters (μ and σ) of the distribution. More specifically, the larger the value of the standard deviation σ, the more chance that application of the exact equation (Eq. 13) to a truncated distribution will lead to errors. The converse is also true.

Let it be assumed that there is a powder that follows a truncated log-normal numbers distribution, with the smallest particle given by ln a_0 = ln τ_c = μ — $c\sigma$ and the largest particle given by μ + $c\sigma$, where c is a constant. Use of the ideal log-normal distribution

[2] Monroe 1665.

Table II—Dissolution Patterns as Calculated Exactly by Eq. 13, as Calculated by the Carstensen and Musa (1) Approximation with a Knowledge of Weight Fraction at τ^*, and as Calculated by the Carstensen and Musa (1) Approximation by Assuming the Weight Fraction to be Zero at τ_o

	τ	Exact Equation	Weight Fraction Remaining Calculated by——Carstensen and Musa —Approximation— Using Known Weight Fraction at τ^*	Assume Weight Fraction 0 at τ_c
$\sigma = 0.03178$	0	1.0000	1.0000	1.0000
$\mu = 3.68888$	5	0.6707	0.6728	0.6416
	10	0.4231	0.4261	0.3810
	15	0.2455	0.2485	0.2027
	20	0.1263	0.1288	0.0911
	25	0.0538	0.0554	0.0350
	30	0.0164	0.0171	0.0054
	36.36 τ_c,τ^*	0.0010	0.0010	0
$\sigma = 0.10000$	0	1.0000	1.0000	1.0000
$\mu = 3.68888$	10	0.4337	0.4424	0.2909
	20	0.1381	0.1438	0.0344
	29.63 τ_c,τ^*	0.0255	0.0256	0
$\sigma = 0.30000$	0	1.0000	1.0000	1.0000
$\mu = 3.68888$	5	0.7320	0.7398	0.3321
	10	0.5215	0.5295	0.0571
	16.26 τ_c,τ^*	0.3273	0.3274	0
	25	0.1575	0.1424	—
	40	0.0372	0.0130	—
$\sigma = 1.08304$	0	1.0000	1.0000	—
$\mu = 3.68888$	40	0.8632	0.8962	—
	80	0.7594	0.8000	—
	120	0.6769	0.7108	—
	200 τ^*	0.5529	0.5529	—
	280	0.4634	0.4203	—
	350	0.4034	0.3232	—

for this case has the effect of erroneously adding a few larger particles and a few smaller particles than actually exist. If $c = 3$, the number of particles added to each end represents only 0.13% of the total number of particles in the powder. However, it is not the small *number* of particles wrongly added that should cause worry—it is the *weight* that they represent.

If there is a log-normal distribution on a *numbers basis* with mean μ and standard deviation σ, then, by the Hatch and Choate equations (5), the distribution of particles on a *weight basis* is log-normal with mean $(\mu + 3\sigma^2)$ and standard deviation σ. Let z be the standard normal variable for the weight distribution. Thus:

$$z = \frac{\ln a_0 - (\mu + 3\sigma^2)}{\sigma} \qquad (\text{Eq. 14})$$

If the lower limit of particle sizes is $\ln a_0 = \ln \tau_c = \mu - c\sigma$ for the numbers distribution, then for the weight distribution the limiting z is:

$$z = \frac{\mu - c\sigma - (\mu + 3\sigma^2)}{\sigma} = -(c + 3\sigma) \qquad (\text{Eq. 15})$$

Thus the weight wrongly added to the small end by using the ideal log-normal where the truncated distribution should have been used can be calculated. If $c = 3$, the error corresponds to no more than about 0.13% of the actual weight. Even if $c = 2$, the error is still less than about 2.27% of the actual weight. Thus it can be assumed that truncating (or not truncating) at the small end of the distribution will rarely lead to significant errors in calculated profiles.

At the large end, if the largest particle is given by $\ln a_0 = \mu + c\sigma$, then:

$$z = \frac{\mu + c\sigma - (\mu + 3\sigma^2)}{\sigma} = c - 3\sigma \qquad (\text{Eq. 16})$$

If σ were vanishingly small, the errors involved would be relatively small for $c = 2, 3, \ldots$. But if $c = 3$ and (say) $\sigma = 1$, then the standard
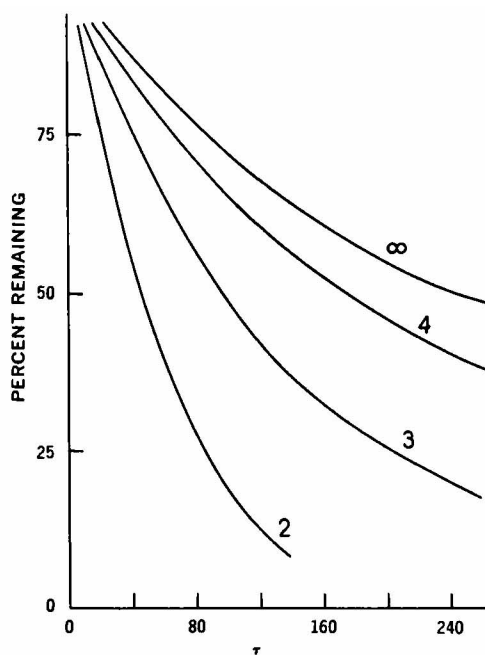

Figure 2—*Plot showing the effect of truncating the log-normal distribution at $\mu + c\sigma$ on the calculated dissolution patterns where c = 2, 3, 4, or ∞. The distribution parameters are $\mu = 3.68888$ and $\sigma = 1.08304$.*

normal variable z would be zero. The effect would be the erroneous addition of a weight of particles *equal to* the actual weight of the powder. The resulting errors in the calculated profile would be great.

The exact equation (Eq. 13) that was developed for an ideally log-normally distributed powder can be altered to take into account a truncation at the upper end of the distribution at $\mu + c\sigma$. This simply involves changing the integral terms I_β so that:

$$I_\beta = e^{\beta(\mu+\beta\sigma^2/2)} \left[F(c - \beta\sigma) - F\left(\frac{\ln \tau - (\mu + \beta\sigma^2)}{\sigma}\right) \right]$$

(Eq. 17)

It is now clear that the dissolution profile calculated exactly and shown in Fig. 1 excellently reflects the results of the Carstensen and Musa (1) approximation, because the standard deviation was vanishingly small.

The effect of arbitrarily truncating at $\mu + 3\sigma$ when dealing with a number of exact distributions that vary only as to standard deviation is shown in Table I. The effect of truncating an ideal log-normal distribution at various upper limits is shown in Fig. 2.

The standard deviations of the particle distributions treated by Carstensen and Musa (1) are all small, and any truncating effects would be negligible. Actually, the dissolution of powders of the distributions treated by those authors was essentially complete before the smallest particles in those distributions began to disappear. Their smallest particles were assigned by $\ln \tau_c = \mu - 3\sigma$, where τ_c was the diameter of the smallest particle considered. The calculations in Table I show that for $\sigma = 0.03178$, 99.9% of the weight had disappeared before τ_c was reached. For $\sigma = 0.1, 97.45\%$ of the weight had dissolved before τ_c was reached. If such were always the case, i.e., if σ were vanishingly small when compared with the mean, Eq. 13 could be changed to:

$$W_\tau \, (\sigma \rightarrow 0) = re3(\mu + 3\sigma^2/2) - r\tau e2(\mu + \sigma^2) +$$

$$r\tau^2 e(\mu + \sigma^2/2) - r\tau^3 \qquad (\text{Eq. 18})$$

because the $(1 - F)$ terms are essentially unity through most of the dissolution profile. However, it seems likely that powders like that of Table I, with $\mu = 3.68888$ and $\sigma = 0.3000$, will often be encountered in pharmacy so that calculations by Eq. 13 will be required for precision.

Carstensen and Musa (1) developed equations to approximate the dissolution patterns. Their Eq. 8 was offered to approximate the dissolution time course before $\tau = \tau_c$. That equation in terms

of the notation used in this report was:

$$w_0^{1/3} - w_\tau^{1/3} = \frac{50\tau}{(\sigma/2.303)^{1.05} M} = \alpha\tau \qquad \text{(Eq. 19)}$$

where M is the geometric mean diameter of the distribution and the sense of α is obvious. This equation, rearranged to give:

$$w_\tau/w_0 = [1 - (\alpha/w_0^{1/3})\tau]^3 \qquad \text{(Eq. 20)}$$

was tested for its fidelity. This was done by calculating α and then finding a value for $w_0^{1/3}$ by plugging in a point τ^*, w_τ^*/w_0 from the exactly calculated profile. Then the entire dissolution pattern was calculated from Eq. 20 and compared with the exactly calculated values. These comparisons are shown in Table II for several different powder distributions. The point τ^*, w_τ^*/w_0 is indicated in Table II. For standard deviations that are small or of moderate size, the approximation of Carstensen and Musa as rearranged in Eq. 20 gives excellent values when compared with the precise dissolution curve even for values $\tau > \tau_c$. For large σ, the approximation is not quite as good. In those distributions where dissolution is essentially complete before $\tau = \tau_c$, Eq. 20 can be employed without a knowledge of the exact profile. The initial condition can be set by $(w_\tau/w_0) = 0$ at $\tau = \tau_c$. This works well for the distribution where only 0.1% of the initial weight remains at τ. It does not work well for the distribution where 2.56% of the weight remains at τ_c (Table II).

The growing importance of dissolution rate technology in pharmacy, coupled with the fact that many powders follow the log-normal distribution law, should lend importance to the exact equation derived here. In practical terms, however, the use of the exact equation for the dissolution of log-normal powders requires a knowledge of population parameters, solubility, and dissolution rate constant, none of which may be readily available. The popula-

tion parameters found may depend on the method of measurement. The solubility of the smallest particles should be greater than that of the largest particles. Few powders are composed of spherical particles that dissolve isotropically. And, finally, it would undoubtedly be difficult to design a dissolution rate experiment in which the agitation and, therefore, the diffusion barrier were the same for the entire surface of each particle and for every particle.

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Chronic Isoproterenol Treatment of Mice: Effects on Catecholamines and Rectal Temperature

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Abstract ☐ The chronic administration of isoproterenol (5 mg./kg. twice a day) to male and female mice resulted in increased wet weights and tissue weight–body weight ratios of the submaxillary and parotid glands. For the heart the ratio was elevated in male but not in female mice. The first dose of isoproterenol produced a decrease in the rectal temperature. Continuation of the treatment led to hyperthermia, which became maximum after treatment for longer than 10 days (20 doses). In these animals the predose rectal temperatures were lower than the pretreatment control values and the temperatures of control animals. A smaller, single dose (2.5 mg./kg.) did not alter the rectal temperature. The norepinephrine concentrations of the parotid and submaxillary glands were reduced in male and female mice, but the total norepinephrine content of these glands was decreased only in male mice. The cardiac norepinephrine levels were not affected. Chronically treated animals were less active than controls for about 90 min. after dosing and showed rarification of fur and hair loss. Isoproterenol treatment of dams before, during, and after pregnancy did not alter the body weight, gross appearance, and wet weight of organs and tissues of pups examined on the 3rd postnatal day.

Keyphrases ☐ Isoproterenol—effect on catecholamines and rectal temperature after chronic administration, mice ☐ Catecholamine concentration—effect of chronic isoproterenol administration, mice

A number of investigators have reported physiological and pathological changes in various species

following acute and chronic isoproterenol treatment (1–14). Depending on the species and duration of treatment, the reported effects have included hypertrophy and hyperplasia of the submaxillary and parotid glands, infarct-like lesions and fatty degeneration of the heart, growth stunting, premature opening of the eyes, sparse hair growth, prostration, lethargy, and changes in rectal temperature, norepinephrine levels, and wet weights of several peripheral tissues.

To gain a better understanding of the mode of action of isoproterenol, we investigated several effects of chronic treatment in mice, a species in which this drug has not been studied in detail. The factors studied included the wet weights and norepinephrine levels of several tissues and organs and the effects of acute and chronic administration on the rectal temperature.

METHODS

Animals—In one study, 16 adult male Swiss Webster mice were injected subcutaneously twice a day, except Sundays, with 5 mg./kg. isoproterenol hydrochloride and another 16 mice were injected with 0.85% sodium chloride solution for 15, 23, and 31 days. The animals were sacrificed by exsanguination under sodium pentobarbital anesthesia. Whole brain (minus the cerebellum) or brain-