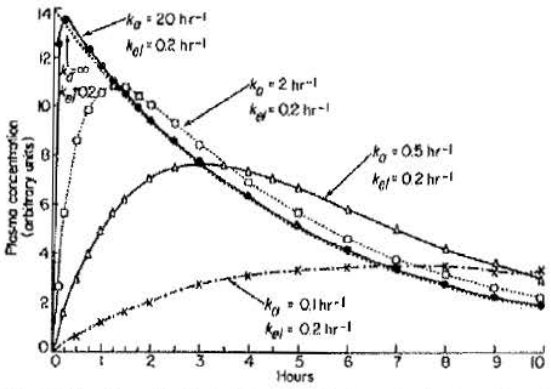

Fig 36-10. The effect of differences in the rate of absorption of drugs on the peak concentration, time of peak concentration and sojourn in the body. The rate of elimination is the same for all curves. The dotted line ($k_a = \infty$) is approximately what the concentration curve would be, had the drug been given intravenously. The data were calculated from a one-compartment model.

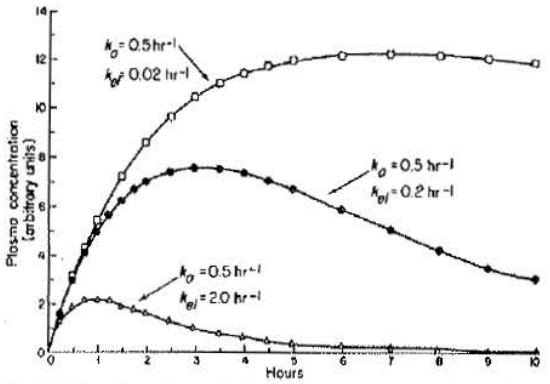

Fig 36-11. The effect of differences in the rate of elimination of drugs on the peak concentration, time of peak concentration and sojourn in the body. The rate of absorption is the same for all curves. The data were calculated from a one-compartment model.

treated as a single phenomenon if the ratio of k_a/k_{el} is considered rather than the separate rate constants (Fig 36-12).

The effects illustrated in Figs 36-10 to 36-12 have certain clinical implications:

1. *Differences in the rate of absorption are of more significance for slowly than for rapidly absorbed drugs.* In Fig 36-10, the peak blood levels are achieved when $k_a = 2$ hr^{-1} ($t_{1/2} = 0.35$ hr) is only 13% lower than when $k_a = 20$ hr^{-1} ($t_{1/2} = 0.035$ hr), but the difference in the level when $k_a = 0.1$ hr^{-1} ($t_{1/2} = 6.93$ hr) is 49% lower than that when $k_a = 0.5$ hr^{-1} ($t_{1/2} = 1.39$ hr), even though in the latter the rate difference was less than in the former comparison. It is thus apparent that differences in the release rates among different products of the same drug, or that differences in gastrointestinal motility, blood flow, etc, may be important, depending upon k_a/k_{el}. This point has a special relevance to sustained-release and depot formulations. With a number of drugs, especially among the anoroctic drugs, the dose with a sustained-release form often is approximately the same as that of a rapid-release form; thus, the former has a long duration in the body but yields low blood levels when used in a single dose. Except with the initial dose, the differences are of lesser importance in a multiple-dose regimen. Small differences in the rate of absorption of rapidly absorbed drugs are usually of minor significance.

2. *When the rate of absorption is rapid relative to that of elimination, differences in the rate of elimination do not greatly affect the peak concentration consequent to a single dose* (compare top two curves of Fig 36-12). Thus, in such instances, the peak concentration is relatively insensitive to normal variations in the rate of elimination. Consequently, with such a drug, the size of the initial dose in a multiple-dose regimen often may not need to be diminished in the presence of renal or hepatic impairment; however, subsequent doses require adjustment.

3. *A change in the time of peak concentration or of peak effect is usually an indication of a change in one of or both k_a and k_{el}.*

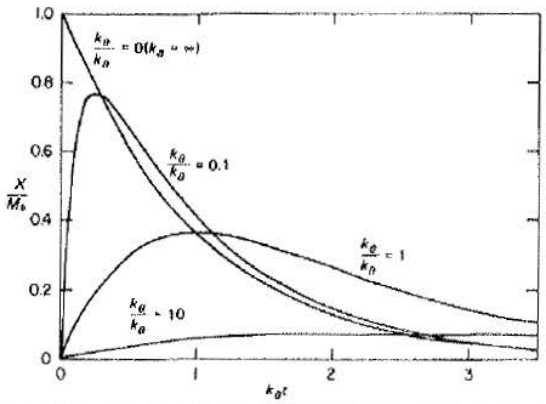

Fig 36-12. The effect of differences in the ratio, k_{el}/k_a (k_e/k_a in diagram), on the peak concentration, time of peak concentration and sojourn in the body. The ordinate, X/M_b, actually represent the fraction of a dose that is in the body, but they are directly proportional to concentration and thus serve to represent concentration. The abscissa can be converted to time by dividing by k_e, the elimination rate constant (courtesy, Goldstein, *et al* [6]).

Duration of Action—The duration of action of a drug is related to its pharmacokinetics in a rather complicated way. It is usually shorter than the sojourn of the drug in the body, because a threshold, or minimal effective, concentration must be reached before the effect occurs (see Fig 36-9), and the effect usually ceases when the plasma concentration falls below the threshold level. In a one-compartment system, duration of action tends to be proportional to log-dose. In a two-compartment system, it tends to be proportional to log-dose only when the site of action is in the central compartment and the effective concentrations (minimum to maximum) are entirely within the concentrations found during the elimination phase. In Fig 36-9, the duration of action is 3.25 hr with dose D, 4.6 hr with $1.5D$ and 5.4 hr with $2D$; were the threshold at 6 (dotted line), instead of 4 (dashed line), the respective durations would have been 1.5, 3.25 and 4.25 hr. Although the example in which the threshold is 6 provides that the duration of action would be disproportionately prolonged as the dose is increased, the contrary is seen when the threshold is 4. Consequently, *increasing the dosage is usually not a feasible way of increasing the duration of action* and toxic concentrations are often reached more predictably than duration is prolonged.

With a few drugs, there is no mathematically definable relationship between duration of action and persistence of the plasma concentration. With reserpine, for example, the effect outlasts the sojourn of the drug, because of the depletion of a slowly replaceable biological mediator.*

Multiple-Dose Administration—This refers to the administration of a succession of doses at intervals such that the drug does not leave the body completely in each interval between doses. The usual procedure in a multiple-dose regimen is to administer a drug repetitively with a constant dose interval, designated τ, with both dose and τ chosen so as to maintain the plasma concentration in the therapeutic

* Careful studies show that trace amounts of reserpine in the body outlast the effect and the duration of action may be related to these trace amounts. These residual amounts, however, are much smaller than are required to initiate the catecholamine-depleting action.

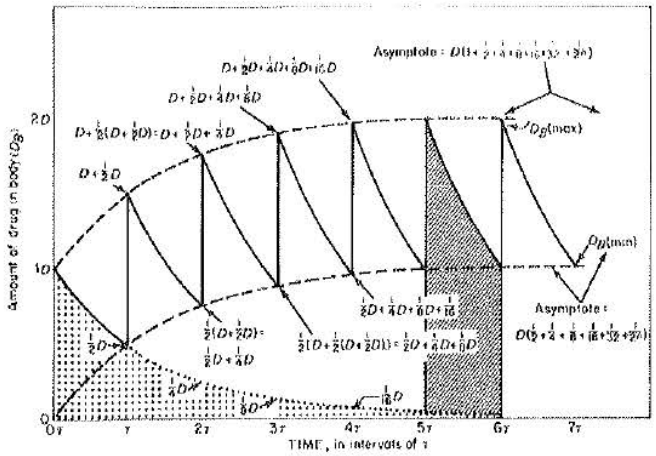

Fig 36-13. The accumulation of drug in the body during a regime of multiple dosing. Dose, D, is administered intravenously at intervals, τ, equal to the half-life, $t_{1/2}$. Thus, after each dose, the amount in the body, D_B, has decreased to half the previous peak amount at the time each dose is administered. When the cumulated amount in the body after injection reaches $2D$, the body content will fluctuate from $2D$ to $1D$ during each dose interval thereafter. Approximately 5 half-lives are required before this leveling off (plateau) of the body content occurs. The stippled area is the area under the elimination curve of a single injection, if no second dose had been given. The cross-hatched area is the area under the curve during a single-dose interval. The two areas are equal.

range. Some features of such repetitive dosing may be seen from the construction reproduced in Fig 36-13.

Accumulation and Plateau Principle—If the novice reader will make his own construction, it will aid greatly his understanding of the subject. In the construction, the amount of drug in the body, D_B, is plotted against time. Dose, D, is given repetitively, intravenously, at intervals such that $\tau = t_{1/2}$, in order to facilitate the construction. The first dose is given at $\tau = 0$; since it is given intravenously, the amount in the body rises to $D_B = 1$ essentially instantaneously. Immediately, D_B falls exponentially with the first-order kinetics of Eq 1, except that whole-body content, rather than C_p, is plotted. Since $\tau = t_{1/2}$, at τ, $D_B = {}^1/_2D$; when the next dose, D, is added, it brings the body content up to $D + {}^1/_2D$. During each dose interval, D_B falls exponentially to one-half the previous postinjection peak. As D_B rises after each administration, the rate (*not* the rate constant) of elimination rises proportionately, until eventually the amount eliminated during τ essentially equals the amount injected. The maximum and minimum values of D_B, $D_{B(max)}$ and $D_{B(min)}$, during τ, approach respective asymptotes, shown on the graph. As $t \to \infty$, $D_{B(max)} \to 2D$ and $D_{B(min)} \to D$. Thus, although D_B fluctuates between $D_{B(max)}$ and $D_{B(min)}$, once the asymptotes are approximated closely, D_B can be thought of as having reached a qualified *steady-state* condition, and the pharmacokinetics are sometimes called steady-state pharmacokinetics. Also, D_b is said to have reached a *plateau*. It is important to note that the rate at which the plateau is reached is at exactly the same rate at which drug is eliminated from the body after a single dose. Thus, the exponentially falling line for the elimination of D given at $\tau = 0$ (had no further doses been given) is the mirror image of the line connecting the sequential $D_{B(max)}$s. The principle that *when the rate of absorption is fast compared to the rate of elimination ($k_a > 5k_{el}$) the rate at which the multiple-dose steady state is approached is determined only by k_{el}*, and is known as the *plateau principle*. This is the fundamental feature of one-compartment multiple-dose kinetics. It obtains irrespective of the value of τ. However, the plateau concentrations do depend upon τ (see below).

In Fig 36-13, the drug was administered intravenously, so that no time-dependent absorption had to be considered. When absorption is involved, the $C_{p(max)}$ is not as high as with intravascular administration, but is blunted and occurs with a latency after administration that is determined by k_a/k_{el}, just as in single-dose administration. The appearance of the C_p-time curve with multiple-dose administration is shown in Fig 36-14. The value of C_p at any time during multiple-dose administration can be calculated according to Eq 30.

$$C_p = \frac{fk_a}{V_d(k_{el} - k_a)}\left[\left(D^*e^{-nk_a\tau} + D \cdot \frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a}}\right) - \left(D^*e^{-nk_a\tau} + D \cdot \frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)\right] \quad [\text{wt} \cdot \text{vol}^{-1}] \quad (30)$$

where n is the nth dose, τ is the dose-interval, t is the time since the last dose, D is the maintenance dose, D^* is the initial or loading dose (see below) and f is the fraction absorbed (bioavailability factor). With this equation, C_p, rather than D_B, is calculated; however, it will be recalled that

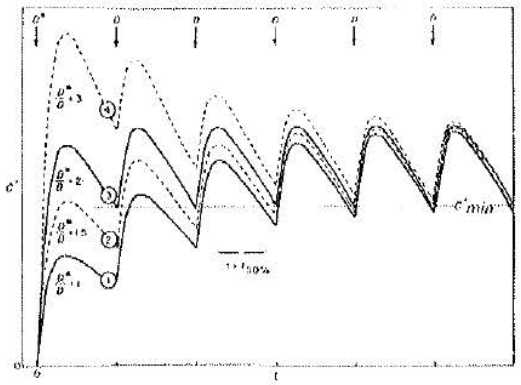

Fig 36-14. Time course of the plasma concentration of a drug administered according to a multiple-dose schedule. C' (ordinate): concentration; t (abscissa): time; D^*: initial dose; D: maintenance dose; τ: dose-interval (equal to $t_{1/2}$ in this illustration); C'_{min}: minimum concentration after each dose (same as $C_{p(min)}$ in text) (courtesy, Krüger-Thiemer[7]).

$C_p^0 = D/V_d$, and similarly, $C_p = D_B/V_d$, so that the equation easily is modified to calculate either C_p or D_B and the same principles apply in either form.

It is important to know how many half-lives must transpire before the plateau is approached closely enough to be considered complete for practical purposes. The value of $D_{B(min)}$ is approximately 93% complete at 4τ and 97% at 5τ; $D_{B(max)}$ is 97% at 4τ and 98.5% at 5τ. Thus, it may be stated that, for practical purposes, the plateau state is reached in approximately 5 half-lives, provided $k_a > 5k_{el}$. This is another form of the *plateau principle. The principle applies whenever the steady state conditions are perturbed;* that is, *5 half-times will be required to reach a new plateau,* whether the plasma concentration is rising or falling to a new plateau (see Fig 36-14).

Maximum and Minimum Concentrations—During multiple dosing, $C_{p(max)}$ and $C_{p(min)}$ are described by Eqs 31 and 32:

$$C_{p(max)n} = \frac{C_p^0\,(1 - e^{-nk_{el}t_a})}{1 - e^{-k_{el}\tau}} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (31)$$

$$C_{p(min)n} = \frac{C_p^0\,(1 - e^{-nk_{el}\tau})}{1 - e^{-k_{el}\tau}} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (32)$$

where n is the nth dose, C_p^0 is the concentration that would have occurred from instantaneous absorption and distribution (obtained by extrapolation of the elimination curve to zero time) and t_a is the absorption time. The term C_p^0 may be replaced by fD/V_d^{ss}. During the plateau state, $1 - e^{nk_{el}\tau}$ becomes $e^{-k_{el}\tau}$, and $C_{p(max)}$ and $C_{p(min)}$ are designated C_{max}^{ss} and C_{min}^{ss}, respectively. The equation is valid only when $k_a > 5k_{el}$. It can be seen that $C_{p(max)}$ is determined by both k_a and k_{el} (k_a shows itself only indirectly, in t_a) and $C_{p(min)}$ by k_{el}. The greatest difference between $C_{p(max)}$ and $C_{p(min)}$ occurs when the drug is given intravenously; when $\tau = t_{1/2}$, after intravenous injection, $C_{p(max)}/C_{p(min)}$ theoretically is equal to 2. With extravascular administration, the ratio is always less than that with intravenous administration, the ratio being determined by k_a/k_{el}. As k_a/k_{el} decreases, $C_{p(max)}/C_{p(min)}$ decreases.

Average Concentration and Body Content—The average concentration during the plateau state is described by Eq 33.

$$C_{p(ave)} = \frac{fD}{V_d k_{el}\tau} = \frac{1.44\,t_{1/2}fD}{V_d\tau} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (33)$$

The coefficient 1.44 is the reciprocal of 0.693 in Eq 3. The term $C_{p(ave)}$ is a time-averaged concentration and therefore is really a mean concentration. Since $C_p = D_B/V_d$, it follows that

$$D_{B(ave)} = \frac{fD}{k_{el}\tau} = \frac{1.44\,t_{1/2}fD}{\tau} \qquad [\text{wt}] \qquad (34)$$

It is self-evident that the plasma concentration, or amount of drug in the body, is directly proportional to the fraction of drug absorbed (f, bioavailability factor). The appearance of f in these equations and Eq 30, however, serves as a reminder that a change from one drug product to another with a different bioavailability, f', will be accompanied by changes in $C_{p(ave)}$ and $D_{B(ave)}$, as well as in the maxima and minima. The equations also reemphasize that a change in $t_{1/2}$ (or k_{el}) will affect $C_{p(ave)}$ and $D_{B(ave)}$, all other factors being held constant. Since k_{el} and f (and sometimes V_d in relation to weight) vary from patient to patient, the dosage of certain drugs always needs to be ascertained with laboratory assistance and acumen. The effects of changes in τ are discussed below.

Importance of Dose-Interval—The ratio $C_{p(max)}/C_{p(min)}$ depends on the dose-interval, τ. If the interval is increased and the dose is unchanged, $C_{p(max)}$, $C_{p(min)}$ and $C_{p(ave)}$ all decrease, but $C_{p(max)}/C_{p(min)}$ is increased. If τ is decreased, then $C_{p(max)}$, $C_{p(min)}$ and $C_{p(ave)}$ increase, but $C_{p(max)}/C_{p(min)}$ is decreased. This is shown in Fig 36-15. To avoid a change in $C_{p(ave)}$ consequent to a change in τ, the dose may be changed appropriately, in accordance with Eqs 32 and 33. Nevertheless, the wider fluctuations between $C_{p(max)}$ and $C_{p(min)}$, when τ is lengthened, cannot be avoided simply by adjusting the dose (see Fig 36-16, broken lines). If $C_{p(min)}$, rather than $C_{p(ave)}$, is held constant, the fluctuations become even larger (Fig 36-16, solid lines), and the hazard of the

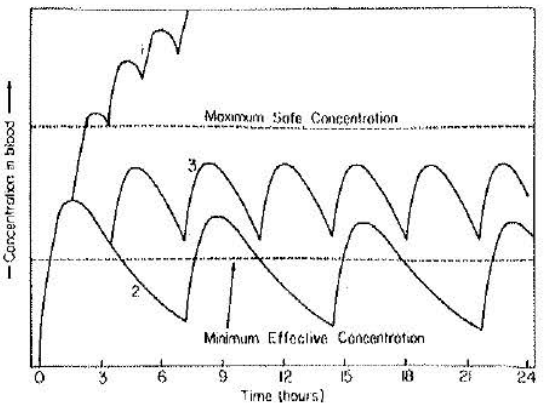

Fig 36-15. The effect of the dose interval on the time course of the plasma concentration of a drug administered in a multiple-dose regimen. $D^* = 4$, $D = 3$ and $k_a/k_{el} = 3$. The dose interval is 1.7 hr in Curve 1, 7.7 hr in Curve 2 and 3.8 hr in Curve 3 (courtesy, Notari[8]).

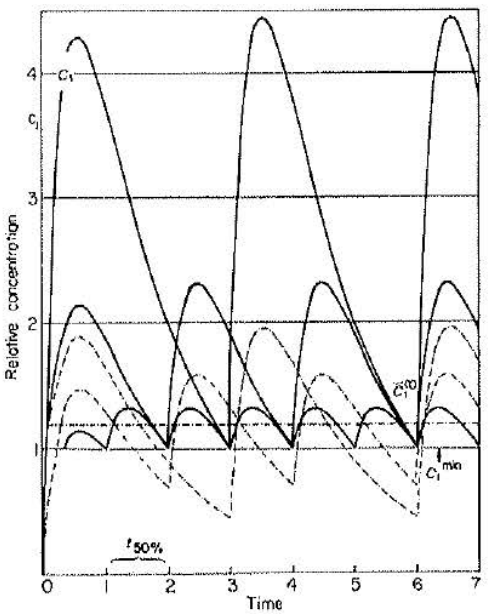

Fig 36-16. Fluctuations in the plasma concentration of a drug when the dose interval is changed but the dose is altered to maintain the same minimal (solid lines) or average (broken lines) concentration during maintenance. C_1^{min} is the minimal concentration (corresponding to $C_{p(min)}$ in the text) and $\overline{C}_1^{ss}$ is the average concentration during maintenance (corresponding to $C_{p(ave)}$ in the text). Time is in multiples of the half-life (courtesy, Kruger-Thiemer,[7] adapted).

concentration reaching the toxic range is increased. Conversely, *the greater the number of divided doses, the smaller the fluctuations in plasma concentration*. For drugs with a narrow therapeutic range, it is usually inadvisable to dose at intervals longer than $t_{1/2}$. With digitoxin, τ is much smaller than $t_{1/2}$, and the fluctuations in plasma concentration are consequently less than 10%. However, for drugs with a high therapeutic index and which do not require a steady plasma concentration for an adequate therapeutic action, dose intervals much larger than $t_{1/2}$ may be used conveniently. Penicillin G is such a drug; it is more convenient to give large doses at 4-hr intervals, or longer, than at 30- to 60-min intervals ($t_{1/2} \approx 30$ to 60 min).

Cumulation Ratio and Persistence Factor—From the above, it is evident that the drug cumulated in the body during the repetitive administration approaches different amounts (asymptotes) in the plateau state according to the magnitude of τ in relation to $t_{1/2}$ (or k_{el}). The dose-interval must be a convenient interval that not only is easy for the patient or medical and paramedical personnel to keep track of but also one which does not subject the patient to an annoying or difficult number of doses per day. Furthermore, $t_{1/2}$ varies from patient to patient. Consequently, it is rare when $\tau = t_{1/2}$, although it is sometimes close enough that the difference is inconsequential. Therefore, it is important to be able to estimate the extent of cumulation with any dose interval in any patient. This can be done with information derived from a single dose, by means of the *accumulation factor*, r_a.

$$r_a = \frac{1}{1 - e^{-k_{el}\tau}} \qquad \text{[no units]} \tag{35}$$

The component factor, $e^{-k_{el}\tau}$, is the *persistence factor*, r, which is the fraction by which C_p or D_B falls during the dose interval. When the plateau, or steady state, is reached the cumulated plasma concentration or body content will be larger than that from the first dose by a factor known as the *cumulation ratio* (or *drug amount ratio*), R_c.

$$R_c = \frac{1}{k_{el}\tau} = \frac{1.44\, t_{1/2}}{\tau} = \frac{\bar{C}_\tau^{ss}}{\bar{C}_0^{\infty}} \left(\text{or} \frac{\bar{D}_{B\tau}^{ss}}{\bar{D}_{B0}^{\infty}} \right) \qquad \text{[no units]} \tag{36}$$

where $\bar{C}_\tau^{ss}$ is the mean concentration during one dosage interval during the steady state and $\bar{C}_0^{\infty}$ is the mean concentration from $t = 0$ to $t = \infty$ after a single dose; $\bar{D}_{B\tau}^{ss}$ and $\bar{D}_{B0}^{\infty}$ are the corresponding respective body contents. Since both $\bar{C}_0^{\infty}$ and $\bar{C}_\tau^{ss}$ can be estimated from the AUC, it is appropriate to discuss this further.

Area under Curve (AUC)—The area under the monoexponentially falling, single-dose plasma concentration-time curve is the integral of the differential form of Eq 1, from $t = 0$ to $t = \infty$:

$$AUC^{0\to\infty} = \bar{C}^{0\to\infty} = \int_0^\infty C dt$$

$$= \int_0^\infty C_p^0 e^{-k_{el}t} dt = \frac{C_p^0}{k_{el}} \qquad \text{[wt} \cdot \text{vol}^{-1} \cdot \text{time]} \tag{37}$$

Although the units are concentration times time, the value is equal to the time-averaged concentration and hence is called the *average concentration* $\bar{C}_0^{\infty}$, although it is more appropriately a *log-mean* concentration. If the amount of drug in the body is used, instead of plasma concentration, the AUC is equal to the *time-averaged body content*. The average body content could, of course, be calculated from $\bar{C}_0^{\infty}$ by multiplying by V_d.

Even when two or more exponential processes act additively on the plasma concentration (or body content), as in absorption plus elimination, the $AUC^{0\to\infty}$ equals $\bar{C}_p^{\infty}$ (or $\bar{D}_B^{\infty}$). The interested student may verify this by integrating any of Eqs 28–30. In the two-compartment system (see below), $AUC^{0\to\infty}$ for a plasma concentration-time curve correctly equals $\bar{C}_p^{\infty}$; however, $\bar{D}_B^{\infty}$ cannot be calculated from $\bar{C}_p^{\infty}$, because the plasma concentration differs from the average body concentration.

Since $AUC^{0\to\infty} = C_p^0/k_{el}$ in the one-compartment system, it is obvious that AUC does not provide any new information that otherwise cannot be obtained, as by back-extrapolation or regression analysis. Nevertheless, AUC frequently is used in lieu of C_p^0/k_{el}. For example, in the determination of the bioavailability factor, f, the $AUC^{0\to\infty}$, after *extra*vascular administration ($AUC_{ev}^{0\to\infty}$), divided by the AUC after *intra*vascular administration ($AUC_{iv}^{0\to\infty}$) is equal to f.

The term $AUC^{0\to\infty}$ is not the only AUC that may be used in pharmacokinetics. The AUC during different time intervals, under supposedly steady-state conditions, could be employed to detect time- or concentration-related changes in clearance (eg, see Eqs 11 and 27). During the plateau, or steady state, the AUC during one dose interval (AUC^{ss}) is of special interest. To evaluate $AUC^{0\to\infty}$ requires many samples taken over a long period of time, which is an inconvenience to the subject or patient. The value of AUC^{ss} can provide the same derived information with fewer samples and less time. This is because $AUC^{ss} = AUC^{0\to\infty}$. Thus, in Fig 36-13, the stippled area, which is $AUC^{0\to\infty}$, would be equal to the cross-hatched area, AUC^{ss}, except for the negligible stippled area that remains after 5τ. At $t = \infty$, the two areas would be essentially identical. In this comparison of AUCs, the identical areas do not mean that C_p^{∞} is identical to $\bar{C}_p^{ss}$, but it does enable AUC^{ss} to be used to calculate values of single-dose parameters and *vice versa*.

Constant Infusion and Sustained Release—A constant infusion or sustained release of a drug may be regarded as a series of minidoses given at infinitely short dose intervals. When infusion is intravascular, the plasma concentration will rise in logarithmic fashion with the same time course and cumulation factor as with multiple dosing, ie, with a rate constant of k_{el}. Thus, the plateau principle applies equally to constant infusion and multiple dosing. After discontinuation of infusion, the plasma concentration falls exponentially with a rate constant k_{el}, in accordance with Eq 1. These principles are illustrated in Fig 36-17.

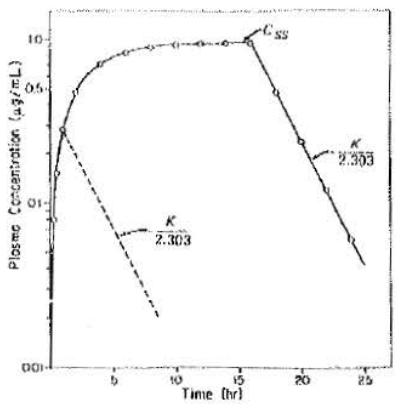

Fig 36-17. Semilogarithmic plot of plasma concentration during and after cessation of a constant intravenous infusion of a drug in a one-compartment system. Whether infusion is stopped prior to the attainment of a plateau or after, the plasma concentration will fall log-linearly with a slope of $-0.434k_{el}$. In the figure, K is k_{el} and $1/2.303 = 0.434$. C_{ss} is the steady-state concentration, C_p^{ss} (courtesy, Gibaldi and Perrier[9]).

The steady-state plasma concentration, C_p^{ss}, is equal to the infusion rate divided by the whole body clearance:

$$C_p^{ss} = \frac{R^0}{Cl_{tot}} = \frac{R^0}{V_d k_{el}} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (38)$$

where R^0 is the infusion rate. The term V_d must be expressed in the same volume units as R^0; Cl_{tot} and R^0 must be in the same time units as k_{el}.

With sustained-release dosage forms, in which the release is approximately constant for long periods of time, the pharmacokinetics are like those of constant infusion.

Loading and Maintenance—In Fig 36-13, $D_{B(max)} \rightarrow 2D$; consequently, had $2D$ been given for the first dose and D thereafter, the plateau condition would have been reached immediately. This illustrates the *principle of loading*. The same effect of loading is shown by curve 3 in Fig 36-14; in both these figures, $\tau = t_{1/2}$. The initial dose is called the *loading dose*, D^*, and each subsequent dose is called the *maintenance dose*, D. Since it takes about 5 half-lives to reach the plateau state, it is very important to use a loading dose with drugs that have long half-lives or in situations in which it is desirable that the optimal therapeutic concentration be reached rapidly.

The loading dose, D^*, should approximate the amount of drug in the body which will be contained during maintenance (ie, the plateau state). The most direct way to calculate D^* is with the equation

$$D^* = \frac{V_d \cdot C_{p(max)}^{ss}}{f} \qquad [\text{wt}] \qquad (39)$$

assuming that V_d^{ss} and $C_{p(max)}^{ss}$ are both known. A first dose so calculated achieves a $C_{p(max)}$ that is equal to that at the steady state only for *intra*vascular administration. After *extra*vascular administration $C_{p(max)}$ is less than that after *intra*vascular administration and hence the loading dose is proportionately smaller. With some intravascularly administered drugs, the loading dose is calculated deliberately to be less than that calculated by Eq 39. Among reasons for choosing a lower dose than that calculated by Eq 39 is that the effects of the first of a series of doses often elicits greater responses than do subsequent doses, because reflex, hormonal and other counter-regulatory effects have not had enough time to come into full play. This practice applies even to some *extra*vascularly administered drugs, such as prazosin. Consequently, C_p^{ss}, or even $C_{p(min)}^{ss}$, may be used *in lieu* of $C_{p(max)}^{ss}$. It must be remembered that with such underloading the steady state is not achieved fully with the loading dose. With drugs which have a very low and erratic therapeutic index and potentially fatal toxicity, the loading dose may be divided into smaller doses, to be given at various intervals before the first maintenance dose; this permits monitoring of both C_p and clinical effects during loading and allows an assessment of whether the intended maintenance dose is correct. Fractional loading also is used when a drug with a low therapeutic index has a significant distribution phase, such that toxic plasma concentrations occur before distribution equilibrium occurs. With some drugs, an appropriate V_d^{ss} is not known, thus making Eq 39 inapplicable. With such drugs, D^* can be calculated from traditional, empirical maintenance doses by means of the equation

$$D^* = \frac{D}{(1 - e^{-k_a \tau})(1 - e^{-k_{el} \tau})} \qquad [\text{wt}] \qquad (40)$$

The equation correctly applies only when $k_a > 3k_{el}$. Also, D^* can be calculated according to

$$D^* = fD/R_c = 1.44 f D t_{1/2}/\tau \qquad [\text{wt}] \qquad (41)$$

where R_c is the cumulation ratio (see Eq 36).

The time course of the plasma concentration after different loading doses is shown in Fig 36-14. When $D^* = 2D$, the plateau maintenance concentration is approximated closely when $\tau = t_{1/2}$ but is smaller than 2 when $\tau < t_{1/2}$ and greater when $\tau > t_{1/2}$.

In Fig 36-14, it should be noted that if the loading dose is not optimal, either too low or too high, the plateau state is approached with the same time course as when no loading dose is given.

When a constant intravenous infusion is used, the principle of loading also applies, because the plateau principle applies; loading may be accomplished with one or more rapid intravenous doses, called boluses or slugs, or by an initial period of rapid infusion to bring the plasma concentration to the maintenance level. The loading dose can be calculated from Eq 39 or the infusion rate and half-time, as

$$D_0^* = \frac{R_0 t_{1/2}}{0.434 \log 2} \qquad [\text{wt}] \qquad (42)$$

Open Two-Compartment Model

The one-compartment model adequately describes the pharmacokinetics of many drugs. However, with an even larger number of drugs, after intravenous administration, the decline in plasma concentration is not monoexponential but rather manifests two or more monoexponential components which are discernible in the semilogarithmic plot of C_p versus time. The most common is a decline which manifests two components; the open two-compartment model most adequately describes such pharmacokinetics. Other models having more compartments or other complexities will be mentioned later briefly.

Description of the Model—In the open two-compartment model, the body is considered to comprise two compartments in dynamic equilibrium, as depicted in Fig 36-18. The compartment into which the drug is directly absorbed and from which the drug is eliminated is called compartment 1, or the *central compartment*. The blood is a part of this compartment, is the transporting and distributing medium and is the medium actually sampled for chemical and pharmacokinetic analysis; consequently, compartment 1 is some-

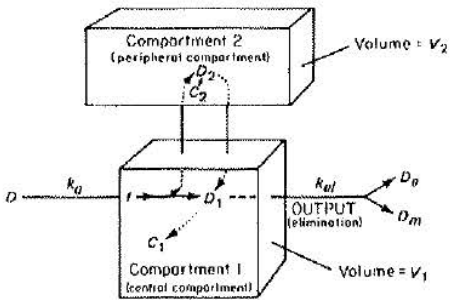

Fig 36-18. Diagram of open two-compartment pharmacokinetic model. An amount of drug, fD, is absorbed from the administered dose, D, with a first-order rate constant of k_a into compartment 1 of volume V_1. Some of the absorbed drug enters compartment 2 with a first-order rate constant of k_{12} and is returned into compartment 1 with a first-order rate constant of k_{21}. D_1 is the amount of drug in compartment 1 and D_2 in compartment 2; C_1 and C_2 are the respective concentrations in compartments 1 and 2 ($C_1 = C_p$). Drug is eliminated from compartment 1 with a first-order rate constant, k_{el}, which, however, is obscured by the lag in transfer of drug from compartment 2 to compartment 1. D_0 is the amount excreted into urine, feces, expired air, sweat, milk, etc; D_m is the amount of drug metabolized. The relative volumes of V_1 and V_2 may vary greatly, V_1 sometimes being the larger and other times the smaller.

times misleadingly called the blood or plasma compartment, even though the erythrocytes or plasma proteins may sometimes behave kinetically as though they were part of compartment 2. In the simple two-compartment model, compartment 2 is closed and communicates with the environment only through the central compartment, being, as it were, peripheral to the events of absorption and elimination; consequently, it is called the *peripheral compartment*. Sometimes, it also is called the tissue compartment, which is misleading, since usually some tissues, or certain cell types within otherwise peripheral tissues, may be kinetically in compartment 1. It is important to reiterate that the compartments are fictive and are defined by the kinetic behavior of the drug within the body and not necessarily by identifiable anatomical entities. To avoid confusion and to enable a simple numerical designation of model components and distribution rate constants by number, the terms compartment 1 and compartment 2 will be used hereafter.

The movement of drug between compartments is defined by characteristic first-order rate constants. The subscript indicates the direction of movement; thus k_{12} (subscript one-two, not twelve) indicates movement from compartment 1 to compartment 2 and k_{21} the reverse direction. The constants k_a and k_{el} are entirely analogous to the like-designated respective absorption and elimination rate constants of the one-compartment model. However, k_{el} is not observed directly from the decline in plasma concentrations, since both the characteristic overall rate of the elimination processes and the rates of diffusion into, and recruitment from, compartment 2 combine to control the rate of decline in plasma concentration (see below). Once an infinitesimal amount of drug is absorbed, all processes occur simultaneously, ie, in parallel. Nevertheless, since the various processes have different time constants, one process will run its course to a practical end earlier than another, and events may be thought of as occurring sequentially, with overlap, in the order; absorption, distribution and elimination. So long as $k_a > (k_{12} + k_{21})/k_{21} > k_{el}$, the terminal phase will be a steady decline in concentration (see Fig 36-19), during which the distribution ratio, C_1/C_2, will be constant.

Absorption—Absorption does not differ from that in the open one-compartment model and does not require further description. However, the determination of absorption characteristics from the log plasma concentration-time curves is complicated by the distribution phase, and the method of residuals (page 733) entails the resolution of three, rather than two, components (see below).

Distribution and Elimination—After the intravascular administration of a drug which obeys two-compartment kinetics, the plasma concentration falls in a complex two-process fashion, but in an arithmetic plot the two components may not always be evident to the eye. When concentration-time data are plotted semilogarithmically, however, the separate processes of distribution and elimination are identified easily by the method of residuals (back-feathering, page 733 and Fig 36-8), if the rate of distribution exceeds significantly that of elimination. In Fig 36-19, such a resolution has been made for the drug pralidoxime. In the figure, it may be seen that after 2 hr the curve assumes a log-linear character. The assumption is made that the distribution phase essentially is complete and a pseudoequilibrium has been reached between the two compartments. Therefore, the late log-linear segment of the line, with the slope -0.434β, represents the elimination phase. If this line is subtracted from the nonlog-linear portion of curve, the distribution phase is the residual line. In order to do this, the log-linear segment is back-extrapolated. From this extrapolated line are obtained the antilogs to be subtracted from the temporally corresponding antilogs on the unresolved, original curve. The respective differences, or residuals,

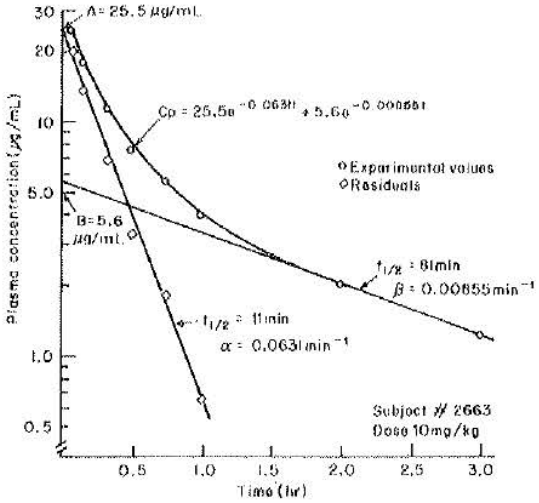

Fig 36-19. Resolution of the plasma concentration curve for pralidoxime into its distribution and elimination components after intravenous administration. Note that plasma concentration is plotted on a logarithmic scale. The time constant for the elimination phase is determined from the slope, -0.434β; it is a hybrid constant and β is not the same as k_{el} (see text). Likewise, the time constant for distribution, α, is obtained from the slope, -0.434α, of the distribution line; α is also a hybrid constant (courtesy, Gibaldi and Perrier[9]).

then are plotted semilogarithmically to reveal the log-linear line that represents distribution only. From the log-linear properties of the separate, but algebraically additive, lines representing the two processes of distribution and elimination, it may be inferred that the equation for the original compound curve was

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t} \qquad [\text{wt} \cdot \text{vol}^{-1}] \tag{43}$$

where C_1 is the concentration of drug in compartment 1 (the central compartment), α and β are first-order rate constants for the distribution and elimination phases, respectively and A and B are fictive plasma concentrations to be discussed on page 740. The constant β describes the late rate of disappearance of drug from compartment 1 but is not the same as k_{el} (see below). It is the rate constant from which the biological half-life is calculated in a two-compartment system ($t_{1/2} = 0.693/\beta$).

Hybrid and Prime Kinetic Parameters—In Fig 36-19, the slope of the late, slower elimination line is -0.434β, where β is a first-order time constant for elimination. However, β is determined not only by the rate capacities of the irreversible elimination processes but also by the rates at which drug is transferred out of and back into compartment 1. Therefore, β is a compound, or hybrid, rate constant. It is equal to the fraction of drug in the central compartment, sometimes designated as f^*, in the postdistributive (elimination) phase times the elimination constant, k_{el}, for the central compartment. Thus

$$\beta = f^* k_{el} \qquad [\text{time}^{-1}] \tag{44}$$

Alpha, α, is a hybrid constant that combines k_{21}, k_{el} and β:

$$\alpha = \frac{k_{21} k_{el}}{\beta} \qquad [\text{time}^{-1}] \tag{45}$$

Interestingly, the equation for α does not include k_{12}, although f^* does depend upon $(k_{12} + k_{21})/k_{21}$. The sum of α and β can be expressed entirely in terms of prime constants:

$$\alpha + \beta = k_{12} + k_{21} + k_{el} \qquad [\text{time}^{-1}] \tag{46}$$

However, these prime constants cannot be determined directly and must be derived from the hybrid constants that are obtainable from graphical or regression analysis. The formulae are

$$k_{el} = \frac{A + B}{\frac{A}{\alpha} + \frac{B}{\beta}} \qquad [\text{time}^{-1}] \tag{47}$$

$$k_{12} = \frac{AB\,(\beta - \alpha)^2}{(A + B)(A\beta + B\alpha)} \qquad [\text{time}^{-1}], \tag{48}$$

and

$$k_{21} = \frac{A\beta + B\alpha}{A + B} \qquad [\text{time}^{-1}] \tag{49}$$

where A and B are the zero-time intercepts of the residual distribution line and the postdistributive (elimination) line, respectively. Each represents a fictive concentration that describes a limit when the other variable is set to zero (ie, the other process is nonexistent).

The volume of compartment 1 (central compartment) can be obtained from C_p^0 (ie, $V_1 = fD/C_p^0$). From the fictive concentration, B, the apparent volume of distribution during the postdistributive phase can be calculated, since $A + B = C_p^0$. From $A - B$ may be obtained the value of compartment 2. (Volumes of distribution are discussed below.) C_p^0 can be determined more accurately by summing the two log-linear extrapolates than from extrapolation of the unresolved curve. The coefficients A and B are also hybrid, since the value of B depends upon all of k_{21}, k_{12} and k_{el}.

Volumes of Distribution—The volume of distribution, V_d, of a drug is a useful pharmacokinetic parameter that relates C_p to D_B (see page 727). Even though it is fictive, it provides not only some insight into distribution but also importantly relates to the rate of clearance of drug from plasma, and changes in pathological conditions reveal changes in the physiological-biochemical conditions. By means of the distribution coefficient, Δ', data from one patient may be applied to others of different body weights (see page 728).

In the open two-compartment system, the determination of V_d is complicated by the slow attainment of distribution "equilibrium" (ie, steady state) between two compartments, and the volume of distribution is changing continually during the distribution phase. It is especially important to know V_d during the postdistribution phase (in which case V_d only applies during postdistribution times) or to estimate V_d by methods that cancel the distributive factors.

Theoretically, the most accurate method for estimating V_d is known as the *steady-state* method, of which there are three variations. In this, the ideal procedure is to give a continuous intravenous infusion until the steady state (ie, plateau) is reached. During the steady state, the amount of drug in the peripheral compartment (compartment 2) is constant. Under these conditions

$$V_d^{ss} = \frac{k_{12} + k_{21}}{k_{21}} \cdot V_1 \qquad [\text{vol}] \tag{50}$$

Note that V_d^{ss} is independent of k_{el} and β. There are, however, several disadvantages to this approach, the principal ones being that for most drugs the steady state is reached only after prolonged infusion, since 5 or more half-lives often will require days of infusion, and that V_1, k_{12}, k_{21} and β need to be determined. This can be done by discontinuing infusion and resolving the curve of the declining plasma concentration into its component parts. Fortunately, the same information can be obtained from the mean plasma concentration during one dose-interval at steady state, C^{ss}. In this,

$$V_d^{ss} = \frac{fD(k_{12} + k_{21})}{C^{ss}k_{21}k_{el}\tau} \qquad [\text{vol}] \tag{51}$$

where k_{el} is the rate of elimination from the central compartment. Provided that elimination occurs only from the central compartment, Eqs 50 and 51 are valid for any n-compartment model. This method has the same disadvantage as the infusion method in that dosing must be continued to the steady state, which, however, with repetitive dosing is more comfortable and less expensive than continuous infusion. An advantage is that extravascular routes may be employed and that only one dose-interval need be sampled, thus making the determination of V_d^{ss} applicable to drugs with long half-lives.

The value of V_d^{ss} also can be determined from areas under the curve (AUC) during and after constant intravenous infusion

$$V_d^{ss} = \frac{D_\Sigma \cdot AUC_{t(ss)}}{C^{ss} \cdot AUC^{0\text{-}\infty}} \qquad [\text{vol}] \tag{52}$$

where $t(ss)$ is the time to reach steady state, D_Σ is the cumulated dose at $t(ss)$, $AUC_{t(ss)}$ is the area under the plasma concentration-time curve from $t = 0$ to $t = t(ss)$ and $AUC^{0\text{-}\infty}$ is the total area under the curve from $t = 0$ to $t = \infty$, providing that the infusion is stopped at the achievement of steady state or that the AUC, during any overrun into the plateau state, is eliminated from the determination of $AUC^{0\text{-}\infty}$. The method has the advantage that the determination of k_{12}, k_{21}, k_{el} or V_1 is not necessary.

A second method of determining V_d is that in which V_d is calculated from V_1, k_{el} and β:

$$V_{d(\beta)} = \frac{V_1 k_{el}}{\beta} \qquad [\text{vol}] \tag{53}$$

The designation $V_{d(\beta)}$ indicates the method of calculation. The rationale for the method is the valid assumption that plasma and tissue concentrations decline in parallel during the postdistributive phase, so that the distribution ratio, which will be equal to Δ', is constant after the distributive phase has come to completion. The method has been shown to yield the same values for V_d as one based on area:

$$V_{d(area)} = \frac{fD}{AUC^{0\text{-}\infty}} = \frac{fD}{(A/\alpha + B/\beta)\beta} = V_{d(\beta)} \qquad [\text{vol}] \tag{54}$$

The method is independent of the route of administration, so long as the fraction absorbed, f, is used.

On page 739, on which the parameters derived from curves such as that in Fig 36-19 were discussed, it was pointed out that the zero-time extrapolates A and B were fictive concentrations from which apparent volumes of distribution could be obtained. The extrapolate β gives a volume known as $V_{d(extrap)}$:

$$V_{d(extrap)} = \frac{D}{B} \qquad [\text{vol}] \tag{55}$$

The method does not take into account the effect of process k_{21} to limit the size of the peripheral compartment and hence tends to overestimate D_B, except at zero time. However, it has the advantage of rapid determination.

The value of $V_{d(area)}$ is the most correct approximation of V_d to apply to the postdistribution phase and $V_{d(ss)}$ is correct for constant infusion at steady state but otherwise underestimates D_B. By magnitude, these three volumes of distribution rank as follows: $V_d^{area} > V_d^{ss} > V_1$.

Clearance—The definition and concept of clearance can be found on page 729. The definition of clearance applies

whether the elimination occurs in a one- or multi-compartment system, hence clearance is model-independent. However, mathematical identities of clearance do depend on the model. In the open two-compartment model, β and $V_{d(area)}$ are applicable in the calculation of total body clearance:

$$Cl_{tot} = \beta V_{d(area)} \qquad [\text{usually mL} \cdot \text{min}^{-1}] \qquad (56)$$

Since it is customary to express clearance in units of mL/min, β must be expressed in min and $V_{d(area)}$ in mL. An analogous formula is based on the condition of the model that elimination occurs only from the central compartment, so that the applicable volume and elimination-rate constant are used:

$$Cl_{tot} = k_{el} V_1 \qquad [\text{mL} \cdot \text{min}^{-1}] \qquad (57)$$

Cl_{tot} also can be expressed in terms of α, A, β, B and D:

$$Cl_{tot} = \frac{D}{A/\alpha + B/\beta} \qquad [\text{mL} \cdot \text{min}^{-1}] \qquad (58)$$

Absorption Plus Distribution and Elimination—After extravascular administration in a two-compartment system, there are three first-order processes occurring simultaneously: absorption, distribution and elimination. These processes all add algebraically, as follows

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} - C_p^0 e^{-k_a t} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (59)$$

They can be resolved by various methods, of which the easiest is the method of residuals already illustrated in Figs 36-8 and 36-19. However, in a two-compartment system, the first residual line is a compound line (absorption + distribution) and must be resolved further into its two component lines. Figure 36-20 is an example of the method of residuals applied to two-compartment data. The first step is the subtraction of the late postdistribution (elimination) line (with slope -0.434β) from the curve, which leaves a two-component residual curve. This residual curve has a late, postabsorptive log-linear segment of slope -0.434α. If the absorption segment of the curve of residuals is subtracted from the extrapolated α-line, a log-linear second residual line with a slope of $-0.434k_a$ will be generated. The extrapolated intercepts A and B have the meanings previously discussed. The zero-time intercept of the absorption residual line is equal to C_p^0 and hence, theoretically equals $A + B$. Kinetic parameters other than α, A, β and B are calculated by means of Eqs 44 and 45. The absorption parameters for other routes of absorption can be determined similarly, except with certain sustained-release dosage forms, which release approximately at a steady rate over long periods of time.

In the example illustrated by Fig 36-20, only two or three points each could be used for establishing the log-linear segments of the residual distribution and absorption lines, which, therefore, may be in considerable error. This indicates the importance of taking frequent enough samples, especially during the absorption and distribution phases, to provide reliable kinetic data.

Multiple-Dose Administration—Equations 30–34, which describe various aspects of the fluctuating plasma concentrations in the one-compartment system, are complex. It may be appreciated that the additional complexities conferred by two compartments renders the analogous equations intricate and difficult to follow for the nonspecialist. However, one-compartment equations modified in minor ways apply to two-compartment systems with reasonable accuracy, when the distribution phase after one dose is approximately complete before the next dose is administered. Under these conditions, β may be substituted for k_{el} and $V_{d(area)}$ for V_d, to adapt one-compartment equations to two-compartment systems for rough approximations of the

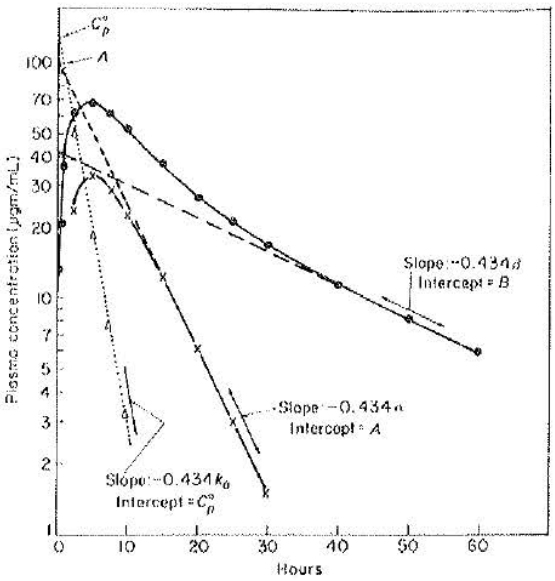

Fig 36-20. Resolution of absorption, distribution and elimination components of a concentration-time curve of a drug with two-compartment kinetics. The solid curve is a semilogarithmic plot of plasma concentrations. The method of residuals was used to resolve the component lines. The postdistribution, or elimination, line of slope -0.434β (— — —) was subtracted from the concentration-time curve. The difference, or residual line (X—X) retained the absorption and distribution components. The log-linear segment of this line represents the postabsorption ("distribution") line, of slope -0.434α. A second residual line representing the absorption phase was obtained by subtracting the absorptive segment (first four points) of the first residual curve (X—X) from the extrapolated α line of slope -0.434α (----) to give the residual absorption line of slope $-0.434k_a$ (· · · · ·). The zero-time intercepts of the extrapolated lines defined by k_a (· · · · ·), α (----) and β (— — —) are C_p^0, A and B, respectively (courtesy, data, Gibaldi and Perrier[9]).

two-compartment parameters and plasma concentrations. Thus,

$$C^{ss} = \frac{fD}{\beta V_{d(area)}\tau} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (60)$$

Adaptation of one-compartment equations for accumulation ratios and loading dose also usually gives values that satisfactorily approximate those calculated with more rigorous equations. The respective adapted equations are

$$R_r = \frac{1}{1 - e^{-\beta\tau}} \qquad [\text{no units}] \qquad (61)$$

and

$$D_0^* = R_r D \qquad [\text{wt}] \qquad (62)$$

where R_r, D_0^*, and D are the accumulation ratio, optimal loading dose and maintenance dose, respectively. In some instances, eg, when a rapid response to lidocaine is desired, a loading dose calculated with Eq 61 will be too low to provide adequate antidysrhythmic effects of the drug during the distribution phase. In this case, a loading dose can be approximated by use of the formula

$$D^* = V_1 C_p \qquad [\text{wt}] \qquad (63)$$

where D^* is the loading dose, V_1 is the volume of the central

compartment and C_p is the target (immediate central compartment) plasma concentration.

The rate at which the steady state is attained depends almost entirely on β. The plateau principle essentially applies, and approximately 5 half-lives, based on β, are required to reach the *steady state*. Essentially all precepts emanating from the one-compartment plateau principle are applicable if two-compartment β is used in place of one-compartment k_{el}.

Nonconformities and Miscellany

Fallibility of Assumptions—General pharmacokinetic concepts are applicable to many drugs without significant modification. Implicit in these concepts are certain assumptions which, however, do not apply to all drugs or drug recipients. Some of the basic assumptions are (1) the pharmacological effect is elicited by the drug administered (and which is being assayed in the blood), (2) the pharmacokinetic parameters remain constant with both time and dose and (3) the peak effect occurs when the concentration is at its peak at the site of action, binding and sequestration follow first-order kinetics and, in short, the models chosen for kinetic analysis are correct. When these assumptions are not valid, significant clinical consequences accrue, and theoretical and/or empirical modification of the models may be necessary. Therefore, it is worthwhile to examine some departures from the more common or commonly assumed behavior and some miscellaneous pharmacokinetic considerations not stressed elsewhere in this chapter.

Active Metabolites and Latentiation—Some drugs are biotransformed to a metabolite that has a pharmacological action like that of the parent drug. With these, the pharmacokinetics of each of parent drug and its metabolite may or may not be simple and easy to define, but the combined pharmacodynamic (and sometimes pharmacokinetic) action may rise and fall in a complex way because of the different time courses, distributions and routes of elimination of the two active molecules. For example, the anticonvulsant trimethadione (TMO) is un-ionized at body pH, is little excreted and has a V_d of about 600 mL/kg and a half-life of about 4 hr, whereas its anticonvulsant metabolite, dimethadione, is a weak acid, is excreted and excretion is affected by urine pH, has a V_d of 400 mL/kg and has a half-life of about 10 days. It is obvious that a study of the pharmacokinetics of TMO alone would be of little value in predicting a therapeutic regimen and precautions.

Two or more active metabolites may increase the complexity greatly. There are a few drugs in which it is only the metabolite, not the parent drug, that is active; with these, the relationship of pharmacokinetics to pharmacodynamics is simpler, provided that it is the metabolite that is followed. It is sometimes deliberately the practice to prepare a drug that is inactive with the intention that the drug be converted to an active metabolite once it is in the tissues. This practice is known as *latentiation*. Latentiation may be used when it is desired to slow down the rate of delivery of drug to the tissues, a kind of systemic sustained release, as it were, or when the active metabolite is locally toxic at the site of administration. Some drugs which generate active metabolites are shown in Table III. Not shown are drugs whose metabolites have no therapeutic activity but which have toxic or other pharmacodynamic activity.

The amount of a metabolite of a drug in the body at any one time depends upon both the rate of transformation of the drug to metabolite and the rate of disposition of the metabolite. The body content of metabolite will continue to rise so long as the content of precursor is high enough that the rate of biotransformation to metabolite exceeds the rate of elimination of the metabolite. When the concentration of drug or precursor falls to a level below which there is no longer a net gain in content of metabolite, the metabolite concentration will fall.

Table III—Some Drugs with Pharmacologically Active Metabolites

Parent Drug	Active Metabolite(s)
Acetohexamide	Hydroxyhexamide
Allopurinol	Alloxanthine
Aldophosphoramide	Phosphoramide mustard
Amitriptyline	Nortriptyline
Chloral Hydrate	Trichloroethanol
Chlordiazepoxide	Desmethylchlordiazepoxide, Demoxepam
Codeine	Morphine
Dacarbazine	5-Aminoamidazole-4-carboxamide
Diazepam	Desmethyldiazepam
Digitoxin	Digoxin
Flurazepam	Desalkylflurazepam
Fluorouracil	Fluorodeoxyuridine phosphate
Glutethimide	4-Hydroxyglutethimide
Imipramine	Desipramine
Lidocaine	Glycinexylidide
Meperidine	Normeperidine
Mephobarbital	Phenobarbital
Methyldopa	α-Methylepinephrine, α-methylnorepinephrine
Methamphetamine	Amphetamine
Phenacetin	Acetaminophen
Phenylbutazone	Oxyphenbutazone
Prednisone	Prednisolone
Primidone	Phenobarbital
Propoxyphene	Norpropoxyphene
Procainamide	*N*-Acetylprocainamide
Propranolol	4-Hydroxypropranolol
Spironolactone	Canrenone, Canrenoate
Sulfasalazine	Sulfapyridine
Tamoxiphen	4-Hydroxytamoxiphen
Trimethadione (TMO)	Dimethadione (DMO)

The kinetics of the fall in concentration depends upon which rate is faster, the elimination of drug precursor or the elimination of metabolite. If that of the drug is faster, the content of metabolite will rise above that of the drug, and the drug will soon disappear. This eventually leaves the content of cumulated metabolite to decline according to the kinetics of its own disposition.

In Fig 36-21, drug B illustrates the rate-limiting effect of the disposition of a metabolite. When the rate constant for the elimination of the drug or precursor is slower than that of the metabolite, as with drug A in Fig 36-21, the content of metabolite never reaches that of the drug and it eventually declines according to the kinetics of biotransformation of the drug. That is, the content of metabolite is mainly that which is being produced moment-to-moment. The figure is adapted from a plot of data from a computer analysis of a multivariable model.

The kinetics of the generation and elimination of a metabolite relative to those of its drug precursor are important when the metabolite is either toxic or therapeutically active. In the latter instance the kinetics are the kinetics of latentiation. Where the metabolite is toxic, a pattern such as in A would be less likely to generate toxic concentrations as in B.

When the disposition of the drug precursor involves more than one process, or when there is more than one metabolite, the kinetics necessarily are more complex than in the illustrations presented above.

Other Pharmacokinetic Models—Apparent kinetic nonconformities may result when the system does not obey the simple open one- or two-compartment models. In the two-compartment model discussed in this chapter, elimination took place from the central compartment; however,

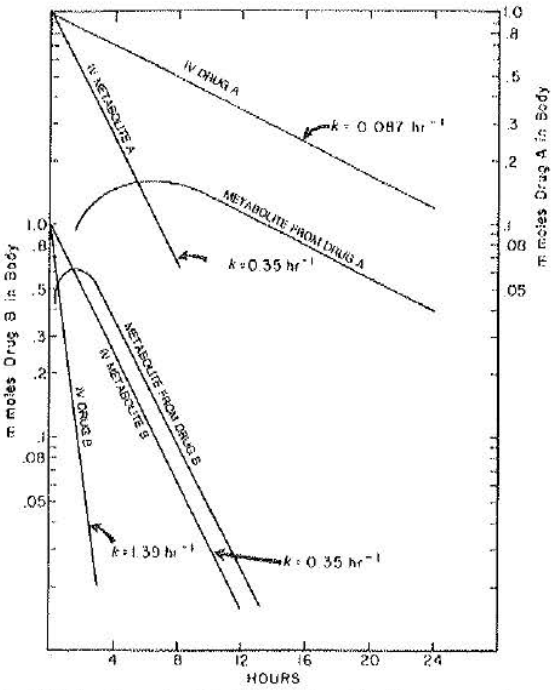

Fig 36-21. Computer plot of the relationship of the amount of drug metabolite in the body to the amount of drug in the body at different relative rates of disposition of drug and metabolite. With Drug A, the metabolite is eliminated at a much faster rate than the parent drug. Curve "IV Metabolite A": the blood concentration when the metabolite is given intravenously; curve "Metabolite from Drug A": the concentration of metabolite actually biotransformed from Drug A. With Drug B the metabolite is eliminated at a much slower rate than the parent drug (courtesy, combined replot of two figures, Martin[19]).

other two-compartment models in which elimination takes place partly or entirely in the peripheral compartment are more appropriate with some drugs. Even absorption into a peripheral compartment appears to occur with some drugs. In addition to alternate two-compartment models, three- or multi-compartment models are required occasionally to account for the pharmacokinetic behavior of certain drugs. In the common *three-compartment* model, the central compartment communicates with two peripheral compartments (which are not interconnected), one called the *shallow compartment* and the other the *deep compartment*. Distribution into the shallow compartment is faster than into the deep compartment.

Many drugs that are described as having one- or two-compartment kinetics actually have more complicated kinetics. There is no drug that displays true one-compartment kinetics, since distribution is never instantaneous. With any drug, sampling within the first minute to one-half hour will show one or more distribution phases.

Nonlinearities—Nonlinearity is a term applied to all nonconformities in which a semilogarithmic plot of plasma concentration-time data cannot be resolved completely into log-linear components, ie, into first-order processes. There may be various causes, such as capacity-limited elimination (ie, saturation of elimination system), capacity-limited absorption or transport, changes in protein binding, changes in pH at the site of absorption, changes in blood flow to the site of absorption and/or elimination, low or erratic dissolution or release rates from dosage forms, low solubility of the drug, drug-induced or other change in body temperature, etc. Some apparent nonlinearities are the result of fitting straight lines to nonlinear data under the assumption that deviations are experimental error.

Protein Binding—The binding of a drug to protein or other macromolecules can affect the pharmacokinetics of a drug, the magnitude of the effect depending on the fraction of the drug that is bound, the fraction of the binding sites that are occupied by the drug and the rates of association and dissociation. If only a small fraction of drug is bound, the kinetic consequences may be minor or negligible, even if binding is very tight. The effect of the binding of a large fraction of drug depends somewhat on whether the drug is bound tightly or loosely; if the rate of dissociation is quite rapid in comparison to the rate of delivery to sites of distribution and elimination or in comparison to the intrinsic rate of elimination, the kinetic consequences also may be minor. The greatest consequences accrue to binding with high capacity and slow dissociation.

It cannot be overemphasized that in the analysis of plasma, the total concentration of drug (ie, both free and bound drug) usually is determined. However, it is only the free drug that can move across cell membranes, and equilibrium or steady-state conditions are established only through the movement of free drug. Therefore, total drug concentrations are defective indicators of a true kinetic situation unless a correction is made for the extent of protein binding. Without such corrections, errors can be serious. Binding to plasma protein has a profound effect not only on V_d but also on apparent renal filtration fraction and clearance, as may be seen in Eqs 13 and 15. If the plasma concentration was not corrected for binding, Cl_{ren} would be in error by a factor of $1/(1 - p)$, where p is the fraction bound; however, when excretion occurs mainly by active tubular transport, protein binding often has a negligible effect on renal clearance. Similarly, when intrinsic hepatic clearance is low, protein binding greatly affects the clearance, the effect being to decrease clearance.

The binding of a drug to plasma proteins retards the rate of distribution and delays the attainment of equilibrium or steady-state conditions. It is as though the transport of some molecules of the drug across a membrane has to wait until these molecules dissociate and are free to diffuse.

When the amount of a drug bound to plasma proteins does not approach saturation, ie, the binding capacity of the proteins, the fraction of drug bound approximately is constant over a therapeutic dose range. However, when the amount exceeds about 50% of the saturation value, the percent of drug bound may vary considerably with dose, which will give rise to dose-dependent kinetics (see below). Under the condition of near-saturation, changes in the protein content of the blood also will make large differences in the percent bound and hence in the various pharmacokinetic parameters. Certain pathological conditions, such as uremia, some congestive heart failure, starvation, etc, may be accompanied by hypoproteinemia and albumin with altered binding properties and hence abnormal pharmacokinetics.

Time-Dependent Kinetics—A drug with low to intermediate intrinsic clearance, and which induces an increase in the activity of its own biotransforming enzyme system, will decrease $t_{1/2}$ and increase clearance and, if its kinetics show two-compartment kinetics, its V_d. Since such an induction requires time, usually several dose-intervals of repetitive dosing, the kinetics vary with time and are called time-dependent. Allosteric (or feedback) inhibition by accumulated metabolites of a drug, or an effect of a drug to impair its route or elimination, also will cause time-dependent (and dose-dependent) changes in the kinetics. Drugs that cause the depletion of some slowly repleteable intermediary factor, such as the depletion of norepinephrine by reserpine or the irreversible inhibition of acetylcholinesterase by isoflur-

ophate, will manifest time-dependent effects on body function which do not correlate with the drug pharmacokinetics. With some drugs, especially central nervous system depressants, the drug effect recruits time-dependent homeostatic counteradjustments that tend to terminate the effect prematurely and to increase the dose requirement for effect (ie, causes tolerance), so that the pharmacokinetics lose their predictability with time. Similarly, drug-induced changes in the receptor properties of the response system will tend to produce a time-dependent dissociation of the pharmacokinetics from the pharmacodynamics.

Dose-Dependent Kinetics—With some drugs, the pharmacokinetics differ more with high, than with low doses. Such changes may be due to: saturation of a biotransforming enzyme or excretory transport system, toxic impairment of the organ of excretion at high doses, differences in intercompartment permeability and V_d at high and low doses, drug-induced changes in blood flow and hence in distribution and clearance, saturation of protein binding sites or the recruitment of new binding sites at high doses, etc. In those instances in which the elimination route is saturated (also called capacity-limited), it is evident that the half-life will increase, as can be seen in Fig 36-22. The cause of the dose-dependent increase in $t_{1/2}$ at the higher doses is the saturation of the enzyme systems that form salicyluric acid and carboxybenzoxyglucuronide. It is usual to speak of the kinetics during the saturation phase as being zero-order, but they are not truly zero-order. The saturated system manifests zero-order kinetics, but alternative routes of elimination, such as through salicyl glucuronide and glomerular filtration and renal tubular secretion, still manifest first-order kinetics, so that elimination is a mixture of zero- and first-order processes. In any event, since elimination is no longer completely a first-order process in the saturation phase, there is no overall elimination rate constant and hence no constant half-life. During repetitive dosing with the large doses, the new $\bar{C}^{ss}$ will be determined by both the zero-order and first-order elimination processes, as well as the dose, but the time required to reach the new plateau will be determined only by the remaining first-order processes; since the first-order overall elimination constant, K, has been diminished, the time-to-plateau will be increased accordingly. Kinetic behavior of this type is mathematically analogous to the familiar Michaelis-Menten expression for enzyme kinetics, and dose-dependent kinetics are sometimes called *Michaelis-Menten* kinetics. They also are called *saturation*, or *capacity-limited*, kinetics.

Examples of important drugs which show dose-dependent kinetics are aspirin, phenylbutazone, probenecid, levodopa, phenytoin and dicumarol. Ethanol obeys essentially zero-order elimination kinetics at blood concentrations above 0.02–0.04%, which is a fact of considerable importance in court cases involving ethanol. The clinical significance of dose-dependent kinetics will be discussed further in Chapter 37.

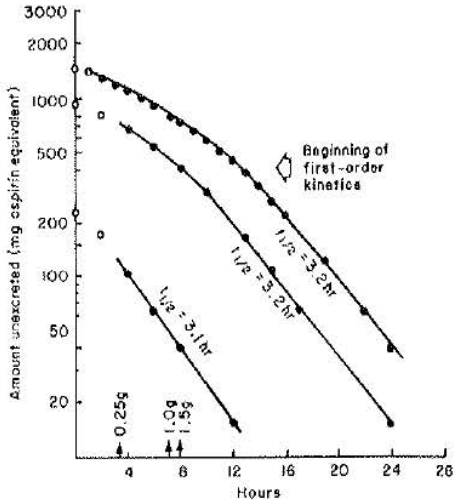

Fig 36-22. Dose-dependent elimination of salicylate in a normal 22-year-old male. Doses taken were 0.25, 1.0 and 1.5 g aspirin, respectively. Vertical arrows on the time axis indicate the time necessary to eliminate 50% of the dose. Stated half-times ($t_{1/2}$) are for straight-line portion of curves where elimination rate is first-order. However, during the early hours after the larger doses, the slope at any time (tangent to the curve) is flatter, hence $t_{1/2}$ is longer, than during the first-order phase (courtesy, Gibaldi and Perrier,[9] modified from Levy[11]).

Chirality—Chiral drugs often are given as racemic mixtures, and the pharmacokinetics and pharmacodynamics of the drugs are studied as if the drug were one entity. It is now becoming clear that this approach may be in error because evidence is accumulating which shows that the pharmacokinetics (as well as pharmacodynamics) of individual enantiomers are not the same and that failure to differentiate among them will give misleading kinetic data for the active form of the molecule. Details of the importance of chirality in pharmacokinetics have been summarized.[12]

Kinetics in the Evaluation of Drugs and Drug Products

The utility of pharmacokinetics in devising appropriate dosage regimens is obvious. Kinetic studies also are important to the study of the influence of inhibitors of elimination, eg, probenecid on the excretion of penicillin, and the effect of one drug on the disposition of another.

Plasma or tissue concentrations and their kinetics are not only valid but essential in comparing the bioavailability of drug products in which the excipients, adjuvants, etc, may vary but the active ingredients are the same. Such data are critical to a proper appraisal of the practice of prescribing drugs by proprietary names.

Kinetics also are employed to compare different drugs, but the meaning of such comparisons is often obscure, and claims of therapeutic superiority based on kinetics must be accepted cautiously. The kinetics of disposition are important to a comparison of drugs in a class in which toxic effects are frequent; it is often desirable to use a drug with a short biological half-life, so that a toxic episode may be terminated quickly upon discontinuation of medication. Furthermore, it is valid to compare the fluctuations in plasma concentration among drugs consequent to multiple-dose administration, provided, of course, that for the class of drugs in question, the extent of fluctuation has an important bearing on efficacy or toxicity.

A comparison of peak or mean blood levels achieved by equal doses of different drugs is not entirely meaningless. It is true that the dose of a drug may be adjusted to compensate for a difference in potency from some reference drug, but it is often difficult for the physician to alter the dose except in multiples of the unit dose provided by the manufacturer. Partly because of the inertia of precedence and habit and partly because it is easier for the physician to memorize

doses as a group, closely related drugs whose potencies differ only moderately may all be available in the same dose. Thus, tetracyclines are available as "250's" or "500's," even though they are not equipotent, sulfonamides as 1 g, etc. It is therefore valid for the physician to choose the drug whose unit dose yields a blood level closest to the optimum. Unfortunately, many physicians do not have the prerequisite knowledge for such a choice and hence may be susceptible to misleading promotional arguments about the superiority of one product over another. Some of these points will be elaborated in the following chapter on *Clinical Pharmacokinetics*.

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Supplementary Reading

Note: Refs 6–9 are textbooks or monographs on general pharmacokinetics. Ref 5 is a monograph on hepatic clearance.

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CHAPTER 37

Clinical Pharmacokinetics

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In Chapter 36 the basic principles of pharmacokinetics were presented. Clinical pharmacokinetics is the discipline in which basic pharmacokinetic principles are applied to the development of rational dosage regimens. In this chapter the concepts of pharmacokinetics are placed into perspective with the development of individualized drug dosage regimens. The clinical significance of the processes of drug absorption, distribution, elimination and influence of disease states on these processes are emphasized. Examples will be given of the ways pharmacokinetic principles can be applied in the calculation and adjustment of dosage regimens designed to fit the pharmacokinetic and pharmacodynamic properties of drugs and specific disease states that alter drug disposition. The principles of therapeutic drug monitoring and the rational use of this clinical science in the management of patients also are discussed.

An individualized dosage regimen for a patient involves a decision about the dose or amount of drug to be administered, interval between doses, route of administration and patient factors that may change during the course of drug administration. The latter implies that there is a plan for monitoring the therapeutic and adverse effects of the drug. Decisions about drug dose, dosage intervals and route of administration are based on the clinical knowledge of the disease being treated, efficacy of the drug in treating the disease and absorption, distribution and elimination of the drug.

Absorption

Drugs are administered by a variety of routes including intravenous, intramuscular, inhalation, oral, rectal, vaginal and topical application to the skin. The choice of the route depends on the many patient- and drug-related factors discussed in Chapter 35. In practical terms, the important considerations in this choice include the systemic availability of a particular dosage form, rate and extent of drug absorption and patient convenience.

Oral Route—This route is chosen most frequently because of ease of administration and patient acceptance. However, the number of variables involved in the absorption of drugs from the stomach and small intestine make the oral route of administration quite complex.

Plasma concentration-time curves will reflect some of these complexities. One of these is the relative rates of absorption of different preparations of the same drug (Fig 37-1[1]), in which preparation *A* represents a simple, rapidly absorbed preparation of a drug; *B* is a more slowly absorbed derivative of the same base. The bioavailabilities of *A* and *B* are identical and *C* is the same compound as *B*, but in a dosage form that is only 50% as bioavailable as *B*. *A* is absorbed rapidly (ie, k_a for *A* is greater than for *B* or *C*) and the peak level is in the therapeutic plasma concentration range.

The advantage of such a preparation is that a pharmacodynamic response can be expected to occur quickly, provided the response is related to plasma concentration. To appreciate the clinical relevance of the situation, consider *A* to be quinidine sulfate, an antiarrhythmic drug. For quinidine sulfate, the absorption rate constant, k_a, is large in relation to the elimination rate constant, k_{el}, and the peak concentration usually occurs in 1 to 2 hr. The rapid absorption is important in clinical situations in which some degree of urgency exists.

It may be desirable, in the initiation of therapy of ominous ventricular premature contractions, to use a preparation with the characteristics of quinidine sulfate. The half-life of quinidine is 4 to 6 hr, so that frequent doses (every 4 hr) are necessary to maintain effective blood concentrations of the drug. The short half-life can be an advantage, since steady-state concentrations of quinidine are achieved within 24 hr (plateau principle). Therefore, one can decide within a day whether quinidine will be useful in suppressing the ventricular premature contractions. However, the fact that a dose must be administered every 4 to 6 hr to maintain therapeutic plasma concentrations is somewhat of a disadvantage in that it is inconvenient and may result in noncompliance.

B, with its slower rate of absorption, reaches a lower peak concentration at a considerably later time even though given in the same dose. There are clinical consequences of this. For example, if *B* was the sustained-release form of quinidine gluconate, it would be less desirable than quinidine sulfate for the initiation of drug therapy, where a rapid therapeutic response is needed. Because of its prolonged

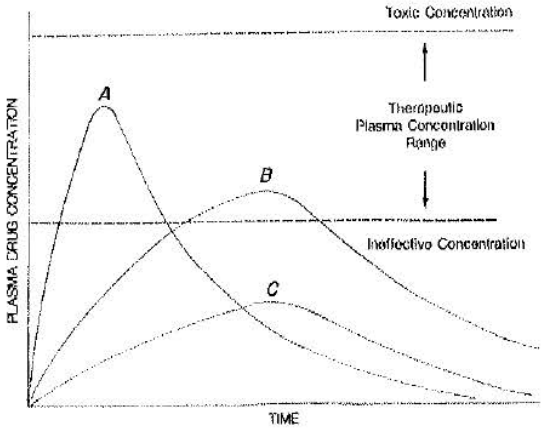

Fig 37-1. Plasma drug concentration-time curves of three preparations of the same drug. *A* is rapidly and completely absorbed. *B* is not absorbed as rapidly as *A* but is 100% available. *C* has the same time-to-peak concentration as *B* but is only 50% as available (Courtesy, adaptation, Benet[1]).

absorption, this preparation commonly is administered every 8 to 12 hr. This is so because the slower rate of absorption enables the dose to be increased commensurate with a longer dose-interval without peak concentrations that rise into the toxic range.

When treating a patient in which a rapid (but not immediate) effect is required (as with asymptomatic ventricular premature contractions), it is advisable to use a dosage form to initiate therapy that is rapidly and completely absorbed. Once the drug is shown to be effective in a particular patient, the dosage form can be changed to one with characteristics similar to *B*, so that less-frequent dosing is required and patient compliance is improved.

The preparation represented by *C in the same dose* as *A* or *B* is probably not an acceptable way to administer this drug. The total amount of drug *C* that is absorbed is only half of that of *B* (area-under-the-plasma concentrations-time curve, AUC, for *C* is half of the AUC for *B*). Thus, it would require twice the dose to attain blood levels equivalent to *A* or *B*.

The treatment of asthma with theophylline is an example in which a rapidly absorbed dosage form is used to initiate therapy and a prolonged-release dosage form is used for maintenance therapy. When a patient has an acute asthma attack or worsening bronchitis that requires bronchodilator therapy, it is advisable to use the theophylline-ethylenediamine complex (aminophylline). This dosage form can be administered either intravenously or orally; the former should be used to initiate treatment in the acute asthmatic patient who requires prompt therapy, so that neither a delay in achieving therapeutic plasma concentrations nor bioavailability are factors in the initial therapeutic response.

Following the administration of a loading dose (see under *Distribution*, page 749), the drug should be given by continuous intravenous infusion until the acute symptoms have subsided, which may take 24 to 72 hr. In the patient with less-severe symptoms, aminophylline can be administered orally four times a day. Once the patient's condition has improved and an effective dose of theophylline has been established, then it may be possible to switch the patient to a prolonged-release formulation for maintenance therapy.

The absorption and bioavailability of Theodur and Sustaire, two sustained-release theophylline preparations, permit 12-hr dosing intervals; Slo-Phyllin Gyrocaps should be given every 8 hr. The total daily dose of theophylline that was required during intravenous aminophylline administration is divided into smaller oral doses given at intervals appropriate for the characteristic of the preparation or dosage form used.

It is important to keep in mind that the absorption and plasma-time curve characteristics for these preparations usually have been established in healthy volunteers or asthmatic patients without other illnesses. Patients who eliminate theophylline rapidly (ie, smokers) may have increased dosage requirements, and the dosage interval may have to be shortened to avoid recurrent asthmatic symptoms between doses.

Prolonged-release dosage forms have the additional advantage that fluctuations in blood levels of the drug will be less than with rapidly absorbed dosage forms. There is evidence for some drugs that the reduction in rapidly changing blood levels may improve efficacy and decrease adverse effects. For example, the dose of fentanyl or ketamine required to maintain anesthesia was reduced by nearly 50% when the drugs were given by continuous infusion rather than by intermittent bolus.[2]

This reduced dose also resulted in more rapid recovery with less-prolonged sedation. These findings suggest that a reduction of fluctuation in the plasma concentrations will reduce total dosage requirement. If such a reduction in plasma concentration fluctuation also applies to oral prolonged-release dosage forms, it would provide a distinct advantage for their use.

The bioavailability of a particular drug product, by any route of administration, can be determined by comparison of the AUC of a drug given by the route of interest with that of the same dose given intravenously (see Chapter 35). In the case of an orally administered drug, it is the ratio of the AUC after an oral dose to the AUC after an intravenous dose. The decreased bioavailability of an oral dose may be due to poor gastrointestinal absorption of the drug because it does not go completely into solution, as it may be degraded in the gastrointestinal lumen, or it does not pass across the intestinal mucosa. Furthermore, in order to reach the general circulation, drugs taken orally must pass through the wall of the gastrointestinal tract and then to the liver via the portal vein. Thus, drug metabolism may occur in the gut wall or in the liver and severely limit the delivery of parent drug to the general circulation.

If the extraction of the drug by the liver is efficient, oral administration results in low bioavailability and sometimes limited pharmacological effect. This is commonly referred to as *first-pass metabolism*. Table I lists some of the drugs known to exhibit first-pass metabolism. Because their extraction is high and their rate of metabolism great, the rate-limiting step in the clearance of drugs in Table I is liver blood flow. The metabolism of these drugs can be referred to as *flow-limited*. The clinical significance of changes in liver blood flow on drug bioavailability will be discussed under *Drug Therapy in Hepatic Disease*.

Different dosage forms of the same drug may have different systemic bioavailabilities. The ratio of the AUC for one dosage form to that of another dosage form is termed the *relative bioavailability*. A drug usually has the highest bioavailability if administered orally as an aqueous solution; finely comminuted drugs in suspension follow closely. However, as a drug is packed into hard gelatin capsules or compacted into tablets, its bioavailability decreases. Furthermore, a drug in one dosage form made by one manufacturer may have a different bioavailability from that of another manufacturer.

With drugs for which bioavailability varies significantly from product to product, if one product initially has been efficacious, it is advisable to continue with that product. If for economical or other reasons the product must be changed to that manufactured by a different company, it is wise to observe the patient carefully for a possible change in clinical response indicative of a change in bioavailability. Products designed for prolonged-release sometimes have a low bioavailability. However, this may not be a problem during maintenance therapy so long as therapeutic serum concentrations are achieved consistently.

The presence of food in the stomach or intestine can have a profound influence on the rate and extent (bioavailability) of drug absorption. Initial absorption studies for a new drug, performed in healthy volunteers, commonly include fasting and nonfasting conditions. Therefore, in general, and for controlled diets, the effect that food may have on

Table I—Drugs that Exhibit First-Pass Metabolism

Acetylsalicylic acid	Metoprolol
Alprenolol	Morphine
Amitriptyline	Nitroglycerin
Desipramine	Nortriptyline
Dopamine	Pentazocine
Imipramine	Prazosin
Isoproterenol	Propoxyphene
Lidocaine	Propranolol
Meperidine	Salicylamide

drug absorption may be known when a drug is introduced into the market. Unfortunately, food-drug interactions are not consistent, and the presence of food may enhance or diminish the absorption of drugs. The most common type of interaction occurs when a food constituent binds the drug and the food-drug complex cannot pass through the gut wall. For example, complexation of tetracycline antibiotics may occur when these drugs are administered with dairy products or with antacids containing aluminum, calcium or magnesium.

The presence of a large meal in the stomach will delay gastric emptying. If a drug that is absorbed in the intestine is ingested with a large meal, the delay in gastric emptying may result in a delay in absorption of the drug. However, the presence of food in the stomach also has been shown to *increase* absorption of some drugs. For example, the bioavailabilities of the β-adrenergic blocking drugs, propranolol and metoprolol, are enhanced by the presence of food.[3] Therefore, because of the difficulty in predicting the absorption pattern of a drug in the presence of food, it is usually advisable to administer drugs when the stomach is empty or 30 min prior to meals; an exception is with drugs which cause gastrointestinal irritation and nausea. These drugs must be given with food to prevent these side effects. It is recommended that such drugs *always* be taken with food to compensate for the differences in absorption that might occur if they were given one time with food and another time without food.

Water taken concomitantly with certain drugs may increase bioavailability. The administration of aspirin, erythromycin stearate, amoxicillin or theophylline with 250 mL of water results in greater bioavailability than if the same drugs are ingested with only 25 mL of water.[4] It is probable that the increased amount of water enhances the amount of drug absorbed by improving drug dissolution as well as by hastening gastric emptying.

Diseases that affect the structure and function of the gastrointestinal tract also are capable of altering the absorption of drugs after oral administration. However, no consistent pattern develops; rather, there appears to be a complex relationship between the effect of the disease on stomach and intestinal functions and the absorption of the drug in question. For example, diseases, such as diabetes mellitus or chronic renal failure, which delay gastric emptying, will markedly delay the absorption and onset of effect of drugs that must reach the small intestine before they are absorbed. This has been a problem with the use of phenytoin in patients with chronic renal failure. Celiac disease and Crohn's disease, which alter the intestinal epithelium, have been studied in detail.[5] In these diseases, absorption of some drugs is affected greatly, but there is no consistent pattern of altered drug absorption.

When a drug is to be administered orally to a patient with altered gastrointestinal motility, diseases of the stomach and small or large intestine, previous stomach or intestinal surgery or gastrointestinal infection, there is a considerable probability that drug-absorption characteristics in these patients will differ from those in healthy volunteers. This may result in a change in the time of peak blood level or the extent of absorption. It is advisable to observe such patients closely for clinical effect during initial drug administration and during chronic dosing in order to assess the influence of alterations in absorption and correct dosing regimens accordingly. Monitoring drug blood concentrations may be beneficial in adjusting dose.

Nonoral Routes—Drugs are administered by a variety of nonoral routes including subcutaneous, intramuscular, intravenous, inhalation, percutaneous, buccal, sublingual, rectal, vaginal, intra-arterial and intrathecal. In the cases of inhalation, topical application to the skin or mucous membranes, rectal, vaginal, intra-arterial or intrathecal administration, the route often is chosen to ensure that drugs reach a specific site with a minimum of systemic absorption. The rationale is that the maximum concentration of drug will be at the site of action so that side effects will be lessened. Nevertheless, if large doses are administered by these routes, enough drug may reach the general circulation to produce side effects. Therefore, the dose and preparation should be such that limited quantities of drug reach the systemic circulation.

The beta-adrenergic agonists, metaproterenol and albuterol, when administered by inhalation, produce bronchodilatation at doses that avoid serious systemic side effects. Similarly, the corticosteroid, beclomethasone, also can be administered by this route for the management of chronic asthma. Low doses of beclomethasone by inhalation are without the serious systemic side effects of oral steroids. However, as the dose is increased beyond two inhalations 4 times a day, for an average daily dose of 400 μg, there is a greater incidence of side effects, including adrenal suppression.

The *topical* administration of drugs rapidly is becoming an important route of drug administration of systemic drugs. Previously used only for the application of drugs for local effects in diseases of the skin, it now is being explored as a means of administering drugs for their systemic effects.

Nitroglycerin commonly is applied to the skin in the form of an ointment or transdermal patches; it is absorbed rapidly and provides sustained blood levels. Sublingual nitroglycerin also is employed to produce therapeutic blood levels; it produces a maximal effect on anginal pain within 3 to 5 min but lasts only 20 to 60 min. In contrast, nitroglycerin ointment provides peak blood concentrations in about 1 hr and the effect on anginal pain may last for several hours. The sublingual tablets should be used to suppress acute angina attacks, whereas nitroglycerin ointment or transdermal patches may be useful to prevent recurrence of episodes of angina for prolonged periods, such as during the night. Whether or not the continuous administration of nitrates by this route will result in the development of tolerance is not clear at this time. Transdermal patches containing clonidine or estrogen are available for the treatment of hypertension or estrogen-replacement therapy, respectively.

Close *intra-arterial* administration of drugs is used to get drugs directly to a target site or organ in high concentration. After it has passed through the target region it is distributed in the entire blood volume, which reduces the systemic levels of the drug and the consequent side effects. One example is the use of cytotoxic drugs for the treatment of primary or metastatic tumors of the liver. The infusion of drugs into the hepatic artery exposes the tumor to higher drug concentrations than can be tolerated with intravenous administration. If the drug is extracted efficiently by the liver, the exposure of sensitive tissues such as bone marrow and gastrointestinal epithelium to the drug will be decreased. For example, after hepatic artery infusion of floxuridine (FUDR), hepatic vein concentrations are 2 to 6 times higher than comparable drug concentrations following intravenous infusion, yet systemic blood concentrations are 75% less.[6] Thus, the therapeutic index of FUDR in the treatment of liver cancer is increased considerably by hepatic arterial infusion. This type of selective drug administration may be beneficial with other drugs that have low therapeutic indices.

Intrathecal injection is used to deliver drugs to the spinal cord or brain in sufficient concentration to produce an effect but at the same time to reduce the incidence or severity of systemic side effects. The intrathecal administration of the cancer chemotherapeutic agent, methotrexate, frequently is employed in the management of leukemic involvement of

the central nervous system. The epidural administration of morphine, which produces long-lasting (6 to 30 hr) analgesia with minimal side effects, is proving to be of benefit in the management of chronic pain.

Distribution

Once a drug is absorbed into the general circulation, it distributes into various tissues and body fluids. The nature and extent of this distribution depends on several factors such as the extent of drug binding to plasma or tissue proteins, blood flow to selected areas of the body, lipid-solubility of the drug and, consequently, its ability to permeate membranes. In clinical practice, concern about drug distribution often arises regarding the penetration of an antibiotic into the central nervous system, into abscesses at any location, into bone for the treatment of osteomyelitis and into specific body fluids such as synovial fluid.

In most cases, the distribution of a drug within the body is determined by the nature of the drug. However, distribution occasionally is altered by the disease process for which it is being used. For example, in healthy individuals, the concentration of penicillin in the nervous system is much less than in serum. However, in patients with inflamed meninges, as in bacterial meningitis, large daily parenteral doses of penicillin can result in bactericidal concentrations in the cerebrospinal fluid. Thus, pneumococcal and meningococcal meningitis can be treated effectively with intravenous penicillin. Increased penetration into the brain in these diseases occurs because the inflamed meninges are more permeable to the penicillin. Also, active transport of penicillin out of the cerebrospinal fluid back into plasma may be impaired in meningitis, thus causing an increase in penicillin concentration in the brain.

In Chapter 36 the term *volume of distribution* (V_d) was introduced. Despite the fact that the V_d of a drug is a very important pharmacokinetic term, it is important to recall that knowing the V_d of a drug does not indicate necessarily how or where a drug is distributed within the body. The abstract nature of the V_d is illustrated with a drug such as the tricyclic antidepressant, amitriptyline. The V_d for amitriptyline is 20 L/kg, which represents a total V_d of 1400 L in a 70-kg man. This large V_d indicates that the amount of drug in the plasma is small in relation to the amount in extravascular compartments and implies that tissue concentrations of the drug probably are very large. Since the volume of total body water in a 70-kg man is less than 70 L, a V_d of 1400 L also illustrates that V_d does not represent a real volume. Drugs with a large V_d usually are distributed extensively to tissues where they commonly are bound to tissue constituents such as DNA or other macromolecules, or dissolved in lipids, whereas drugs that are bound extensively to *plasma* proteins will have smaller V_ds.

One situation in which knowledge of the size of the V_d is useful clinically is in the management of the patient with a severe drug overdose. If a drug such as amitriptyline has a large V_d, it is likely that after an overdose neither hemodialysis nor hemoperfusion will be an effective way of lowering the total body concentration of the drug. Dialysis may lower the plasma drug concentration temporarily, but there will be redistribution from tissues into plasma soon after the dialysis is stopped.

Knowledge of the V_d also is important in determining the loading dose of a drug. This is the dose of a drug administered initially to bring the plasma concentration to a level anticipated during maintenance. An example will illustrate how the V_d is used to determine the loading dose of theophylline. The V_d of theophylline is approximately 0.5 L/kg, and a commonly desired plasma concentration is 10 μg/mL (10 mg/L). Equation 7 (page 728) shows that

$$V_d = \frac{fD}{C_p}$$

where f is the bioavailability factor or the fraction of drug administered that reaches the systemic circulation, D is the dose of drug administered and C is the plasma concentration desired. Since the f for theophylline is 0.96 it can be considered to be 1. Thus

$$0.5 \text{ L/kg} = \frac{1 \cdot D}{10 \text{ mg/L}}$$

and

$$D = 5 \text{ mg/kg} = 350 \text{ mg/70 kg}$$

This dose, administered as a 30-min intravenous infusion, an oral solution or as an uncoated, rapidly dissolving tablet, will result in a peak plasma theophylline concentration of approximately 10 mg/L in patients who have not received theophylline recently.

The V_d usually is considered to be a constant parameter of a drug, so that the loading dose is independent of subsequent changes in drug elimination produced by disease. For example, the loading dose of gentamicin in a patient with severe renal failure usually will not be different from that in a patient with normal renal function. Therefore, therapy can be started with the conventional loading dose without knowing the actual status of renal function.

The severity of renal failure as measured by creatinine clearance (see below) nevertheless will have to be determined prior to calculation of the maintenance dose. There are some clinical situations, however, in which the V_ds of various drugs may be altered so that the loading dose may have to be altered appropriately. The V_d of a drug may be affected by a variety of factors such as protein binding, disease states, body habitus and age. As a rule, the effect of changes in protein binding on the V_d are important only for drugs which are bound 90% or greater to plasma proteins.

Propranolol provides an example in which in patients with chronic liver disease the V_d is increased significantly because plasma protein binding is decreased. This occurs because a greater fraction of unbound drug has access to tissue. The V_d of digoxin in patients with severe congestive heart failure usually is decreased from that in patients with normal cardiac output. Consequently, the loading dose of digoxin is reduced in these patients. Severe dehydration and sepsis result in contraction of the extracellular space and a consequent decrease in the V_d of drugs that largely are confined to this physiological space.

The degree of obesity also may affect the V_d of some drugs. The relative V_d (Δ'; V_d/kg) of water-soluble, lipid-insoluble drugs varies inversely with percent body fat; the Δ' of lipid-soluble, water-insoluble drugs varies directly with body fat. Even in extremely obese patients the increase in body weight may not be accompanied by an increase in the V_d for water-soluble drugs, such as aminoglycoside antibiotics, which will not distribute into fat tissue.

Calculation of the loading dose of these antibiotics in obese patients illustrates this problem. If actual body weight, rather than the ideal body weight or lean body mass, is used to calculate a loading dose of an aminoglycoside antibiotic, elevated peak concentrations may occur in obese patients. Nevertheless, an excessive loading dose is preferable to the risk of possible subtherapeutic concentrations from a miscalculated adjusted dose in a seriously ill patient.

Calculation of maintenance dosing should be made using ideal body weight to avoid consistently elevated peak plasma concentrations. In the first year of life, infants are known to have a larger extracellular space per unit of body weight than adults so that the Δ' of some drugs is also greater. This has been shown to be true for ampicillin, ticarcillin and amika-

cin. Changes in the V_d occur frequently in elderly patients as the result of changes in lean body mass. A linear increase in the Δ' with increasing age has been demonstrated to occur with diazepam.[7]

It should be kept in mind that the V_d for a particular drug in an individual patient may change during therapy. An example might occur when a severely dehydrated patient is treated with intravenous fluids. Unfortunately, there are no accurate means by which the V_d of a particular drug can be determined in an individual patient without first administering the drug in question. Therefore, in situations where one suspects that the V_d may be altered, it is important to monitor blood concentrations of drug, or clinical response, to ensure that therapeutic, and neither toxic nor inadequate, plasma concentrations are being achieved. This particularly is true during initial cumulative drug administration or when a loading dose is being given.

Protein Binding—Pharmacological effect is related closely to the free concentration of drug at its site of action. However, all drugs are bound to some extent to plasma and/or tissue proteins, and the free-drug concentration often may represent only a fraction of the amount of drug in the body. For most drugs the total-drug concentration is measured in plasma and related to an observed therapeutic effect. Thus, recommended therapeutic concentrations commonly are expressed as the total drug concentration in plasma, simply because total-drug concentration is much easier to assay than free-drug concentration. If something occurs that perturbs the protein binding of drug, then either more or less may be free in plasma (and thus free at the site of action) and "standard" therapeutic drug concentration guidelines no longer apply. This situation is made more complex because changes in protein binding may alter elimination as well as distribution. There is definitely a need to understand the therapeutic consequences of alterations in drug-protein binding in order to individualize drug therapy.

The major factors that affect drug-protein binding include the types of proteins available for binding, the binding affinities and capacities and the presence of competing substances, such as endogenous substances and other drugs. Albumin is the major protein in serum, and drug binding to albumin, consequently, has been studied in detail. Drug binding to alpha$_1$-acid glycoprotein and lipoprotein also has been shown to be of clinical significance for certain drugs. There are little data on the ability of other plasma proteins to bind most drugs.

For the purpose of discussing protein binding, drugs can be classified as either acidic or basic (Table II). Acidic drugs commonly bind to plasma albumin, and concomitantly administered acidic drugs may displace one another from their binding sites. Basic drugs may bind to either albumin or alpha$_1$-acid glycoprotein. If a drug is displaced from its binding protein by another drug or by a disease process, the concentration of free drug in plasma (and at the receptor site) will increase temporarily, an effect which then may increase temporarily the pharmacologic response.

Table II—Drugs More Than 90% Bound To Plasma Proteins

Basic drugs	Acidic drugs
Alfentanil	Acetylsalicylic acid
Amitriptyline	Cloxacillin
Chlorpromazine	Naproxyn
Desipramine	Penicillin
Diazepam	Phenylbutazone
Flurazepam	Phenytoin
Imipramine	Probenecid
Lidocaine	Sulfinpyrazone
Lorazepam	Tolbutamide
Nifedipine	Warfarin
Nortriptyline	
Propranolol	
Quinidine	
Verapamil	

The clinical impact of displacement depends on the total amount of drug in the body that is bound, the extent of displacement, whether the drug is also tissue-bound, the V_d and whether the drug is a high-clearance or low-clearance drug. High-clearance drugs are those with an extraction ratio (see below) of close to 1, so that the extraction usually is insensitive to the extent of protein binding. A low-clearance drug, on the other hand, has a lower extraction ratio, and the clearance of the drug may be very sensitive to protein binding.

Warfarin is an example of a low-clearance drug for which the clearance has been shown to vary with the fraction of unbound drug. Thus, after warfarin has been displaced from protein binding sites, $C_{p(free)}$ increases and clearance increases. The increased metabolism will result in the elimination of excess $C_{p(free)}$ and restore the original free-drug levels. Nevertheless, the initial release of bound drug may cause a temporary depletion of clotting factors and consequent bleeding.

The effects of protein displacement are usually of clinical significance only when binding exceeds 85 to 90%. Consider a drug which is 98% bound to plasma proteins. A displacement of 2% potentially will increase free-drug concentration by 100%. However, this does not mean necessarily that free-drug concentration in plasma actually will increase by 100%, because free drug usually distributes quickly into tissues. After redistribution, the actual increase in free-drug concentration in plasma depends on the V_d. If the V_d is large, the increase in plasma concentration may be minimal; if the V_d is small, the concentration at the receptor site may rise significantly and elicit an increase in intensity of drug action. To make matters more complex, a decrease in protein binding also can increase directly the V_d by decreasing the total concentration in plasma, from which the V_d is calculated.

Diseases can alter drug-protein binding by decreasing the amount of protein available for binding and by inhibiting drug binding. Table III lists some conditions that increase or decrease plasma proteins.

Hypoalbuminemia and elevated alpha$_1$-acid glycoprotein have been shown to have the most dramatic effect on drug-protein binding. A normal concentration of serum albumin is 4 g/dL, and a concentration of 2 g/dL would be considered

Table III—Conditions Capable of Altering Plasma Proteins

	Albumin	Alpha$_1$-Acid Glycoprotein
Decreased plasma protein	Burns	Nephrotic syndrome
	Chronic liver disease	
	Cystic fibrosis	
	Protein-losing enteropathy	
	Nephrotic syndrome	
	Pregnancy	
	Chronic renal failure	
	Trauma	
Increased plasma protein	Hypothyroidism	Celiac disease
		Crohn's disease
		Myocardial infarction
		Renal failure
		Rheumatoid arthritis
		Trauma

severe hypoalbuminemia. The effect of hypoalbuminemia on drug-protein binding has the greatest impact if 90% or greater of the drug is bound, if the number of binding sites on albumin are limited or if the drug has a low V_d. It has been shown that a change in plasma albumin concentration from 3.5 down to 2.3 g/dL causes the protein binding of phenytoin to change from 90% to 80.8%.[8] The reduced binding results in an inversely proportional increase in total plasma clearance, so that in steady-state the unbound-drug concentration remains unchanged. Thus, it is probably unnecessary to alter the total daily dose. However, the decrease in total plasma drug concentration poses a potential problem for the interpretation of routine plasma concentrations. This problem is discussed in further detail under *Drug Therapy in Renal Disease*.

Diseases also can affect the affinity of drugs for albumin. The best-known example occurs in chronic renal failure, in which accumulated endogenous compounds, which are not significantly removed by dialysis, displace acidic drugs from albumin binding sites. In disorders or situations in which free fatty acid levels are increased, acidic drugs are displaced from albumin binding sites. Quantitatively, when the free fatty acid/albumin ratio exceeds 3.5, the binding of acidic drugs usually is reduced significantly.[9]

Elimination

The elimination of drugs from the body usually occurs either by excretion into the urine or by biotransformation to metabolites that are eliminated in the urine or feces. The mechanisms whereby the kidneys and liver eliminate drugs and the pharmacokinetic principles behind these processes were presented in Chapters 35 and 36, respectively. In this section, emphasis will be placed on the practical application of these principles toward the development of individualized dosage regimens.

When drugs are approved by the FDA, their elimination has been studied in detail, usually only in healthy volunteers. Nevertheless, there is often enough information available to make rational decisions about the individualization of drug doses in patients who might have impaired elimination. The most important information is whether the drug is eliminated unchanged in the urine or biotransformed in the liver. With a drug for which the major route of elimination is renal, it is necessary to know if excretion is by tubular secretion, glomerular filtration or by a combination of secretion and filtration. With a drug of which the elimination is principally by the liver it is necessary to know if the biotransformation is primarily by a Phase I (oxidation) reaction or a Phase II (conjugation) reaction, if the metabolite(s) is/are pharmacologically active and if the drug exhibits first-pass metabolism. With the knowledge of these facts about each drug, one can determine if it is necessary to adjust the dosage regimen in a patient with kidney or liver impairment.

As indicated in Chapter 36, drug clearance is a more direct expression of elimination than is half-life. This is mentioned here only to remind the reader to be cautious about equating impaired renal or hepatic function with a change in drug half-life. If a decrease in the renal elimination of a drug is accompanied by an increase in half-life, it is necessary to know this to adjust the dosage regimen. However, the elimination half-life of a drug is a complex function of elimination and the V_d, and it is possible to have a change in the V_d in patients with renal or hepatic impairment such that there is no alteration in half-life. Furthermore, it is possible to have a drug with a high total body clearance yet a long half-life. This seeming contradiction occurs when drugs with a very high clearance also have a large V_d.

One class of drugs that displays this contradiction is the tricyclic antidepressants; the members have rapid clearances of about 1500 mL/min as the result of hepatic metabolism, but their plasma elimination half-life may be as long as 20 hr. Because of their large V_d (1000 to 2000 L) and rapid redistribution between tissues and plasma, drug cleared from the plasma almost completely is replaced by drug from the peripheral compartment. As already mentioned, this is important to remember when deciding about the use of extracorporeal (hemodialysis or hemoperfusion) systems to remove drugs from the body of an overdosed patient.

For a drug with a half-life of 20 hr it might appear that an extracorporeal system would enhance drug elimination. However, clearance of the tricyclic antidepressants by dialysis is small compared to normal hepatic clearance. If the drug also has a large V_d, redistribution likely would keep the plasma levels elevated and hemodialysis or hemoperfusion would have to be continued for an unusually long time to enhance significantly the removal of drug from the body.

Renal Excretion—Unchanged drug or drug metabolites can be eliminated from the body by way of the kidneys, as mentioned above. Drug excretion by this route takes place either as a result of filtration through the glomerulus, by tubular secretion or both. A knowledge of how a drug is excreted can be useful in predicting the effect that renal disease will have on its elimination. Drugs that are excreted by tubular secretion generally can be divided into organic acids, such as penicillin and probenecid, and organic bases such as cimetidine.

As indicated in Chapter 35, the organic acids and bases are secreted by separate transport systems. Among the organic acids there is competition in transport such that the coadministration of two such drugs can result in decreased elimination and elevated blood concentrations of each.

Sometimes this competition can be used to advantage, as in the administration of probenecid in combination with penicillin in the treatment of gonorrhea. The result is that the clearance of penicillin is reduced and the plasma penicillin concentrations remain high for a prolonged period of time; the combination is more effective than penicillin alone. Since the therapeutic index of penicillin is high, such interactions are useful. However, if probenecid is administered with the cytotoxic drug, methotrexate, the secretion of the latter drug is impaired and significant toxicity may occur. When tubular secretion is high, plasma protein binding usually does not affect active secretion by the proximal tubule.

Most drugs are excreted by the kidney via filtration across the glomerular membrane. Glomerular filtration is a passive, nonsaturable process. Because of the small size of the pores of the glomerular membrane, only free drug in plasma can be filtered; consequently, drugs that are bound to plasma proteins are filtered poorly. Displacement from proteins actually can increase the amount of drug filtered in the glomerulus and hence eliminated in the urine.

The glomerular clearance of drugs is directly proportional to the glomerular filtration rate (GFR). It follows that a decrease in GFR will result in a proportional decrease in the rate of glomerular elimination of a drug. Thus, measurement of the GFR can be very helpful in the individualization of dosage regimens in patients with impaired renal function. The GFR generally is estimated by measuring the clearance of either inulin or creatinine. Inulin must be infused intravenously, whereas creatinine, a product of muscle metabolism, is released *in vivo* at a relatively constant rate, thus obviating the need for constant intravenous infusion. Urinary creatinine excretion usually exceeds the amount filtered by about 10% because of a small amount of renal tubular secretion of creatinine. However, because determination of GFR by creatinine clearance is inexpensive and easy to do and, because the difference between inulin and

creatinine clearance is not significant *clinically*, creatinine clearance commonly is used to estimate GFR. It is very important to realize that the creatinine clearance is an accurate estimate of GFR only if renal function is stable. If renal function is decreasing, serum creatinine concentrations will be increasing, and it may take several days to reach a new steady-state. Until a new steady state is reached, the GFR cannot be estimated accurately from serum creatinine concentrations, and serum creatinine should not be used to calculate an individualized dose of a drug. Although creatinine clearance only measures the GFR, it frequently is used in the determination of the dosage regimens of drugs that are eliminated both by filtration and by tubular secretion. Unfortunately, there is no simple test to measure tubular secretion. Therefore, dosage adjustment based on creatinine clearance may not be appropriate for patients receiving drugs that are secreted actively by the renal tubules.[10]

The effect of changes in urine pH and urine flow on drug excretion already have been discussed in Chapter 35. In routine drug therapy, these parameters are not considered to be of great importance. However, the alkalinization of urine to pH 8 by the administration of sodium bicarbonate is used routinely to treat overdoses of phenobarbital and salicylates, since ionization of these weak acids reduces their reabsorption and increases their elimination.

Drug Therapy In Renal Disease—Drug administration to patients with impaired renal function is complicated by their associated medical problems, by the number of drugs they receive and by the alterations in drug disposition and elimination that occur. In renal disease, the protein binding of acidic or neutral, but not basic, drugs in plasma usually is altered. Some of the reasons to explain changes in protein binding include:

1. Hypoalbuminemia that occurs as a result of protein loss in the urine.
2. Competition for protein binding sites with small acidic molecules that accumulate in uremia.
3. Changes in the conformation of albumin that results in decreased affinity for binding sites.
4. Accumulation of drug metabolites that might displace parent drug from proteins.

Whichever the cause for changes in binding, the clinical importance of changes in plasma binding and/or protein concentration is that care must be used to interpret plasma drug concentrations.

Measured plasma drug concentrations usually are reported as total drug, ie, bound plus free drug. For example, therapeutic plasma concentrations of phenytoin in persons with normal plasma protein content are 10 to 20 mg/L, of which only 1 to 2 mg/L represents free drug. In patients with renal failure, the *free* phenytoin concentration is unchanged, whereas the *total* drug concentration falls to 5 to 10 mg/L, because of changes in protein concentration. The clinician might, therefore, be mislead into thinking that an increase in dose was necessary to increase the plasma concentration. In fact, because the free phenytoin levels are unchanged in patients with renal disease a dosage adjustment is not warranted. The renal elimination of metabolites can also be affected by impaired renal function.

The uremic state has been shown to have an effect on the biotransformation of many drugs. However, the effects of uremia on drug metabolism often are inconsistent and not predictable, and the clinical significance of such effects usually are not known. The clinical importance of the reduced elimination of drug metabolites is better understood. Table III in Chapter 36 lists active drug *metabolites*, many which are eliminated by the kidneys.

Procainamide is acetylated in the liver to *N*-acetylprocainamide, which has cardiac effects similar to those of the parent drug. This metabolite is eliminated by the kidneys, and its plasma concentration is increased in patients with impaired renal function. Patients with renal failure who are treated with procainamide should be observed closely for signs of clinical procainamide toxicity, and plasma concentrations of both procainamide and *N*-acetylprocainamide should be monitored.

Dosage adjustment of drugs in patients with renal impairment should be based on a knowledge of the pharmacokinetic parameters of the drug and, when indicated, on monitoring of plasma drug concentration. The aim of individualizing dosing regimens in patients with impaired elimination (renal or hepatic) is to maintain an average plasma concentration ($C_{p(ave)}$) similar to that of patients with normal elimination and, thus, to avoid unnecessary toxicity or loss of efficacy.

In Eq 32 in Chapter 36 it can be seen that $C_{p(ave)}$ is a direct function of dose (D) and bioavailability (f) and an inverse function of the dosing interval (τ) and clearance ($V_d \cdot k_{el}$). In the patient with impaired elimination or decreased clearance, $C_{p(ave)}$ will increase until a new plateau is reached (plateau principle). If clearance is impaired markedly or if the therapeutic index of the drug is small, toxicity may occur.

It is apparent from the same equation that either an appropriate decrease in dose or increase in the dosing interval will offset a decrease in elimination, and a $C_{p(ave)}$ can be attained that is similar to that in a nonimpaired patient.

In the patient with renal impairment, individualization of drug therapy requires knowledge of the degree of impairment and its effect on drug elimination in order to choose a proper dose or dosing interval to achieve a desired $C_{p(ave)}$. As discussed above, the endogenous creatinine clearance is usually the most practical index of GFR and it is used widely (with the limitations indicated) to determine the degree of renal impairment in a patient with renal disease.

The translation of the degree of impairment into a dosage regimen is not simple. In the literature there are a variety of nomograms and equations available to aid in calculating dosage regimens in patients with renal impairment. Each has its proponents and opponents and each is based on a set of assumptions that provide limitations to its use. None take into account all of the complexities discussed above. Therefore, a nomogram or an equation used to determine a dose of a drug to be given to a patient with renal impairment must be used only as a guideline and, when possible, should be used along with monitoring of plasma drug concentration, when indicated, and careful clinical observation to ensure optimal therapy.

Drug clearance in patients with renal insufficiency (Cl_{ri}) can be estimated from the relationship of the creatinine clearance in the renal-impaired patient, the creatinine clearance of normal persons and the clearance of drug by renal and nonrenal clearance mechanisms according to the equation

$$Cl_{ri} = Cl_{renal} \times \frac{Cl_{creat\ impaired}}{Cl_{creat\ normal}} + Cl_{nonrenal} \qquad (1)$$

where Cl_{renal} is the normal renal clearance, $Cl_{creat\ impaired}$ is the creatinine clearance in the patient, $Cl_{creat\ normal}$ is the creatinine clearance in normal persons and $Cl_{nonrenal}$ is the nonrenal clearance. The renal and nonrenal clearances may not be available; therefore, to determine a proper dosage regimen, one must rely on the pharmacokinetic information that is available in the literature; the elimination rate constants, k_{el}, in normal patients and in patients with complete anuria frequently are available. The values for these constants for many drugs have been listed in Table IV. Dettli[11] has derived a nomogram in which these elimination rate constants and the creatinine clearance can be used to determine an individualized dosage regimen for patients with

Table IV—Drug Elimination Rate Constants in Normal and Anephric Patients

Drug	Normal k_{el} (hr^{-1})	Anephric k_{el} (hr^{-1})
Alpha-methyldopa	0.17	0.03
Amikacin	0.40	0.04
Amoxicillin	0.70	0.10
Amphotericin B	0.04	0.02
Ampicillin	0.70	0.10
Carbenicillin	0.60	0.05
Cefazolin	0.40	0.04
Cephacetrile	0.70	0.03
Cephalexin	1.00	0.03
Cephalothin	1.40	0.04
Cephaloridine	0.50	0.03
Chloramphenicol	0.30	0.20
Chlorpropamide	0.02	0.008
Chlortetracycline	0.10	0.10
Clindamycin	0.47	0.10
Cloxacillin	1.40	0.35
Colistimethate	0.20	0.04
Digitoxin	0.004	0.003
Digoxin	0.017	0.006
Doxycycline	0.03	0.03
Erythromycin	0.50	0.14
Ethambutol	0.58	0.09
Fluorocytosine	0.24	0.01
Gentamicin	0.30	0.01
Isoniazid		
(fast acetylators)	0.60	0.20
(slow acetylators)	0.20	0.08
Kanamycin	0.40	0.01
Lidocaine	0.40	0.36
Lincomycin	0.15	0.06
Methicillin	1.40	0.17
Minocycline	0.05	0.03
Nafcillin	1.20	0.48
Oxacillin	1.40	0.35
Oxytetracycline	0.08	0.02
Penicillin G	1.40	0.05
Polymyxin B	0.16	0.02
Procainamide	0.22	0.01
Propranolol	0.20	0.16
Quinidine	0.07	0.06
Rifampin	0.25	0.25
Streptomycin	0.27	0.01
Sulfadiazine	0.08	0.03
Sulfamethoxazole	0.70	0.70
Tetracycline	0.06	0.01
Ticarcillin	0.60	0.06
Tobramycin	0.36	0.01
Trimethoprim	0.60	0.02
Vancomycin	0.12	0.003

decreased renal function. This nomogram is reproduced in Fig 37-2.

An example of how this nomogram can be applied is as follows. The ratio $k_{el(anephric)}/k_{el(normal)}$ is the fraction of the usual dose of a drug to be administered when there is anuria. When this ratio is entered on the left ordinate of the nomogram in Fig 37-2 and connected by a line to the upper-right-hand corner, the dose fraction is described for a range of creatinine clearances from 0 to 100 mL/min (100 mL/min is that of a normal 70-kg person). A line then is drawn vertically from the patient's creatinine clearance on the abscissa to the dose fraction line. From this point of intersection, a second line is drawn horizontally to the left ordinate of the nomogram. The point of intersection on the left ordinate is the dose fraction for that particular drug corresponding to the compromised creatinine clearance.

Insofar as the maintenance dose is concerned, the dosage regimen in the patient in renal failure can be modified by

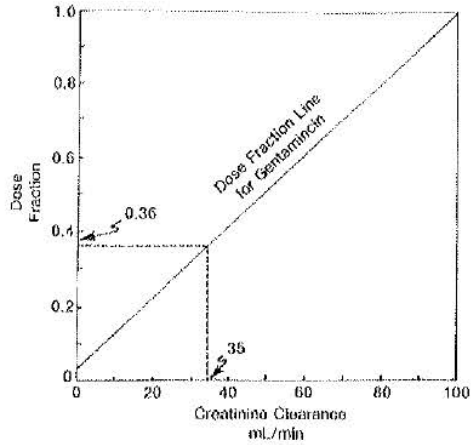

Fig 37-2. Nomogram used to determine the fraction of a dose that should be administered to a patient with a particular creatinine clearance. An example is given for a patient with a creatinine clearance of 35 mL/min and a ratio of $k_{el(anephric)}/k_{el(normal)}$ of 0.03. The dose fraction in this case is determined to be 0.36. This dose fraction then is used to adjust the dose or dosage interval for a patient with that degree of renal impairment (courtesy, adaptation, Dettli[11]).

adjusting either the dose or the dosage interval according to the calculated dose fraction. The maintenance dose can be adjusted by multiplying the normal dose by the dose fraction

$$D_{ri} = D\text{-Dose Fraction} \quad (2)$$

where D_{ri} is the dose in renal insufficiency, D is the usual dose in normal persons and dose fraction is the value determined from the nomogram as described above. The dosage interval, τ, can be adjusted by dividing by the dose fraction

$$\tau_{ri} = \tau/\text{Dose Fraction} \quad (3)$$

where τ_{ri} is the dosage interval in renal insufficiency. An example of an adjustment in a gentamicin dosage regimen for a patient with an impaired creatinine clearance of 35 mL/min is as follows: the usual gentamicin dosage regimen in a patient with normal renal function is a loading dose of 80 mg followed by 80 mg every 8 hr. From Table IV it can be seen that

$$k_{el(anephric)}/k_{el(normal)} = 0.01/0.30 = 0.03$$

When 0.03 is entered on the left ordinate of the nomogram and a line is extended to the upper-right-hand corner, the dose-fraction line for gentamicin is described. From a creatinine clearance of 35 mL/min on the abscissa a line is drawn vertically to the gentamicin dose-fraction line. From this point of intersection a corresponding point on the left ordinate of the nomogram is a dose fraction of 0.36. The dosage interval then can be adjusted as

$$\tau_{ri} = \tau/\text{Dose Fraction}$$
$$= 8\text{ hr}/0.36$$
$$= 22.2\text{ hr}$$

Thus, in a patient with such an impaired renal function, a once-a-day dose of 80 mg is likely to maintain therapeutic plasma concentrations. The maintenance dose for gentamicin in this patient also could be adjusted using Eq 2 as follows

$$D_n = D\text{-Dose Fraction}$$
$$= 80\ \text{mg} \cdot 0.36$$
$$= 28.8\ \text{mg}$$

Thus, 29 mg administered every 8 hr would provide therapeutic plasma concentrations in this patient. The decision to adjust the dose or the dosage interval also should be individualized. Fluctuations in plasma concentration of gentamicin will be less if the dosage interval is lengthened to 24 hr. However, there may be a therapeutic reason to have peak plasma concentrations occur 3 times a day rather than only once. As mentioned above this, or any other nomogram or calculation for dosage adjustment, is only an approximation. Once the dosage adjustment has been made, careful clinical observation and, when indicated, monitoring of plasma concentrations is warranted. Since the loading dose depends primarily on the V_d, a change only in k_{el} does not necessitate a change in the loading dose.

Drug Therapy in Hepatic Disease—The biotransformation of drugs is discussed extensively in Chapter 35. Although many organs are involved in drug biotransformation, the liver is the most important. One might therefore assume that all patients with liver disease would demonstrate a predictable decline in drug elimination by the liver. This is not the case. There are several factors that complicate the management of drug therapy in patients with liver disease.

There are no routinely performed laboratory tests that predict the effect of liver disease on drug metabolism. Unlike the correlation between creatinine clearance and renal clearance of drugs, there is not a good correlation between the commonly available tests of liver function and drug clearance by the liver. In fact, the elimination rates of many biotransformed drugs are unaffected by liver disease.

Drug elimination by the liver may be affected by several factors including liver blood flow, protein binding and volume of distribution, in addition to drug-metabolizing capacity.

Liver disease is not a single well-defined entity but comprises a number of various structural and functional alterations. These include inflammation and necrosis, which generally alter only liver cell function and hence drug-metabolizing activity; cirrhosis, which may impair both liver cell function and liver blood flow; cholestasis, which may impair both biotransformation and biliary elimination and neoplasia, which may both impair cell function and decrease blood flow.

The discussion of biotransformation in Chapter 35 indicates that the process of hepatic elimination of drugs is complex, involving many different types of chemical reactions. While this is true, for practical purposes it is most important to know whether a drug is metabolized by an oxidation (Phase I) or conjugation (Phase II) reaction. The specific type of chemical reaction is of less clinical importance. Many drugs are biotransformed first by an oxidation reaction and the resulting metabolite then is conjugated to facilitate urinary excretion. In these cases it is the oxidation reaction that probably is most important.

The clinical significance of knowing the general reactions involved in the metabolism of drugs is related to administration of such drugs in the patient with hepatic impairment. It generally is accepted that liver disorders which affect hepatocyte cell function will impair drug oxidation long before drug conjugation is altered. A specific example occurs within the benzodiazepine class of drugs. On the one hand, chlordiazepoxide and diazepam are metabolized initially by oxidation reactions that have been demonstrated to be impaired in patients with alcoholic cirrhosis.[7,12]

Accordingly, the elimination of these drugs is decreased, and elevated blood levels may result during chronic therapy. On the other hand, oxazepam and lorazepam undergo only conjugation with glucuronic acid prior to being eliminated in the urine. Glucuronidation does not appear to be affected in clinically stable alcoholic cirrhosis, and the elimination of these drugs is no different than in healthy volunteers.[13,14] From a pharmacokinetic point of view, oxazepam and lorazepam are more rational choices than diazepam or chlordiazepoxide for use in patients with alcoholic cirrhosis.

Most studies of drug elimination in patients with liver disease have been performed in patients with either acute viral hepatitis or alcoholic liver disease. One should be careful about extrapolating these data to patients with other types of liver disease, such as chronic forms of hepatitis, neoplasias of the liver or cholestasis. Furthermore, one must not extrapolate studies of the metabolism of one drug in patients with liver disease to another drug, even though the metabolic reactions appear to be similar. There is a multiplicity of subpopulations of cytochrome P-450 enzymes. One drug may be metabolized by one of these subpopulations, while another drug is metabolized by another enzyme. For this reason, there is often poor correlation between the oxidations of two drugs.

Hepatic disease also can produce changes in serum proteins and in liver blood flow which can influence the elimination of drugs. Because the liver is the site of synthesis of serum proteins, patients with severe chronic liver disease frequently have decreased protein binding of drugs. In addition, there may be decreased protein binding as a result of qualitative changes in serum proteins. Liver blood flow is dominated by the portal venous system that drains the mesenteric veins. Thus, all drugs absorbed from the oral route pass through the liver via the portal vein. In certain types of liver disease, most commonly alcoholic cirrhosis, there is shunting of the portal circulation away from functioning hepatocytes. This leads to increased pressures within the portal system and shunting of drugs away from the drug-metabolizing enzymes.

One method of classifying drugs by the characteristics of hepatic elimination is to divide them into those with a high hepatic extraction ratio and those with a low hepatic extraction ratio. As described in the explanation of Eq 23 of Chapter 36, the hepatic extraction ratio is defined as

$$E = \frac{C_{ap} - C_v}{C_{ap}}$$

where C_{ap} is the hypothetical mean of mixed hepatic arterial and portal venous drug concentrations, and C_v is the hepatic venous drug concentration. The hepatic clearance, Cl_H, of a drug is determined by its extraction ratio as

$$Cl_H = HBF \cdot E$$

where HBF is total hepatic blood flow. The classification of drugs according to their hepatic extraction ratios is shown in Table V. Hepatic blood flow is usually the rate-limiting factor in the hepatic clearance of drugs with high extraction

Table V—Classification of Drugs According to Their Hepatic Extraction Ratios

Drugs with an Extraction Radio Greater than 0.5	
Lidocaine	Nortriptyline
Propranolol	Morphine
Pethedine	Labetalol
Pentazocine	Verapamil
Propoxyphene	Metoprolol

Drugs with an Extraction Ratio Less than 0.5	
Binding-Sensitive	*Binding-Insensitive*
Phenytoin	Theophylline
Diazepam	Acetaminophen
Tolbutamide	Hexobarbital
Warfarin	Chloramphenicol
Chlorpromazine	
Digitoxin	
Quinidine	

ratios, and the metabolism of such drugs are considered to be *flow-limited* metabolism. These drugs demonstrate first-pass metabolism in that after oral administration a major portion of the drug does not reach the systemic circulation. Their bioavailability is low and their metabolism is sensitive to anything that alters hepatic blood flow. Thus, for example, the elimination of lidocaine can be decreased substantially in patients with congestive heart failure, which usually causes a reduction in hepatic blood flow. In patients with cirrhosis and portal hypertension, the shunting of blood away from functioning hepatocytes has the greatest impact on drugs with a high hepatic extraction ratio. In patients with portal hypertension, the bioavailability of drugs with a high extraction ratio may be increased significantly, so that toxic blood levels may result. At the present time there is no routine laboratory test that will predict this effect in an individual patient. Rather, it is advisable to start with a low dose of drug and increase the dose slowly to achieve the desired response.

The rate of metabolism for drugs with a low extraction ratio is dependent on the concentration of drug at the hepatic enzyme site, which is proportional to the free concentration of drug in plasma. Consequently, drugs in this class can be divided further into those in which hepatic elimination is either sensitive or insensitive to protein binding. Drugs with a hepatic elimination distinctly sensitive to protein binding are generally 80 to 99+% bound, whereas drugs with a hepatic elimination clearly insensitive to protein binding are less than 30% bound. Conditions that affect plasma protein binding can have a significant effect on the hepatic clearance of a binding-sensitive drug but usually not a binding-insensitive drug.

Although much is known about the hepatic metabolism of drugs and the factors that can affect their hepatic elimination, the use of drugs in patients with potential altered hepatic clearance is still empirical in that there are no specific guidelines relating the severity of hepatic disease and drug elimination. To a great extent this is due to the multiplicity of drug-metabolizing enzymes, and it is unlikely that a single or simple battery of laboratory tests will suffice to predict the hepatic elimination of all drugs. Applying the known facts about liver disease along with the knowledge of drug elimination by the liver usually will permit a rational use of drugs in patients with disorders of the liver.

Therapeutic Drug Monitoring

Rational drug therapy requires individualization of the dosage regimen for a particular patient. In many instances this can be done by *monitoring the clinical response* to drug therapy. For example, if a patient with hypertension is not responding to therapy and there is no reason to suspect poor compliance, it may be appropriate to increase the dose until the patient's blood pressure is under control. Whenever a drug is administered, well-defined therapeutic end-points should be a preferred part of the management plan.

Observation of the clinical response or monitoring a reliable laboratory test may be easy with certain classes of drugs such as antihypertensives, oral hypoglycemics, oral anticoagulants, analgesics or drugs used to lower serum uric acid or serum lipids. For other drugs, the definition of a therapeutic end-point may not be clear or the onset of toxicity may occur at dosages only slightly above therapeutic concentrations. For some of these drugs one should monitor the serum drug concentration and thus determine if the dose administered to an individual patient is achieving therapeutic concentrations.

The following are several criteria and typical examples that should be considered before measured drug serum concentrations are of clinical value.

The drug must have a reversible action. An example of drugs with irreversible action would be the alkylating agents which exert a lasting effect after a single dose. At the present time there seems to be little need for routinely monitoring the plasma concentration of these drugs.

The development of tolerance at the receptor site should not occur. A therapeutic concentration range for morphine is not rational, since the dose requirements may increase with use.

The pharmacokinetic properties of the drug are taken into account in the blood sampling schedule. If sampling is performed in a maintenance regimen, steady state should have been achieved prior to sampling. Steady state may occur 4 to 5 half-lives after the initiation of therapy if a loading dose is not administered. Changes in drug half-life produced by disease must be taken into account. Qualitative differences in the metabolism or excretion of drugs also are known to occur in patients with hepatic and/or renal disease. For example, patients with impaired renal function may experience prolonged respiratory depression when treated with morphine, due, in part, to the accumulation of an active metabolite, morphine-6-glucuronide. For drugs with a short half-life, peak (1 or 2 hr after oral dosing) and trough (predosing) determinations are advisable. The distribution phase should be complete before drug concentrations are measured. Slow-release formulations of drugs have different absorption characteristics and different plasma concentration versus time profiles that must be taken into account when interpreting a single plasma concentration. The chronic administration of some drugs (ie barbiturates) results in the induction of hepatic drug-metabolizing enzymes. A decrease in the steady-state plasma concentration of that drug, or others metabolized by the induced hepatic enzymes, may occur unless the dose of that drug is increased.

The presence of active metabolites should be taken into consideration. The serum concentrations of the *N*-acetylprocainamide metabolite of procainamide should be considered when assessing antiarrhythmic activity after administering procainamide. This is particularly true in patients with renal failure who may eliminate the metabolite slowly. Active metabolites also are responsible for toxicity (ie acetaminophen). Most assays for the measurement of plasma drug concentrations do not account for active toxic metabolites that are present at very low plasma concentrations.

The analytical method must be sensitive enough to measure accurately the expected serum concentrations and selective enough to be certain that interfering substances will not influence the results. Most clinical drug assays do not distinguish between enantiomers if a racemic mixture of drug is administered. It is important to consider this when interpreting the plasma concentration of a drug if one enantiomer is more active or there is stereoselective disposition. The (*S*)-warfarin enantiomer is about five times more potent in man than the (*R*)-enantiomer; the *S*-(+)-enantiomer of disopyramide is bound more avidly to plasma proteins than its corresponding *R*-(−)-enantiomer. Some drugs (ie phenytoin) may be adsorbed by plastics in intravenous tubing, syringes and blood-collection tubes. When analytical results do not fit the clinical situation, consideration should be given to adsorption as a potential problem.

The data must be evaluated in the context of sound clinical judgment. Treat the patient, not the serum drug concentration. An example is the patient who is taking digoxin and develops a low plasma potassium. Hypokalemia makes the myocardium more sensitive to the rhythm disorders produced by digoxin. Thus, the patient with a normal serum digoxin concentration may experience drug-induced cardiotoxicity if hypokalemia also is present.

Table VI—Therapeutic Ranges for Drugs

Amikacin	Trough	4–8	mg/L
	Peak	20–30	mg/L
Carbamazepine		4–8	mg/L
Digoxin		0.8–2	ng/L
Disopyramide		2–5	mg/L
Ethosuximide		40–100	mg/L
Gentamicin	Trough	0.5–2	mg/L
	Peak	5–10	mg/L
Lidocaine		1.2–5	mg/L
Phenobarbital		15–40	mg/L
Phenytoin		10–20	mg/L
Primidone (see phenobarbital)		5–12	mg/L
Procainamide		4–10	mg/L
N-Acetylprocainamide		10–30	mg/L[a]
Quinidine		1.5–4.5	mg/L
Theophylline		10–20	mg/L
Tobramycin	Trough	0.5–2	mg/L
	Peak	4–10	mg/L
Valproic Acid		50–100	mg/L

[a] Total of procainamide and *N*-acetylprocainamide.

Table VII—Pharmacokinetic Parameters of Commonly Monitored Drugs

Drug	Volume of distribution (L/kg)	Protein binding (%)	Oral availability (%)	Route of elimination	Half-Life		Dose adjustment required	
					Normal	Anephric	Renal failure	Liver failure
Amikacin	0.25	<5	Parenteral only	Renal	3 hr	2–4 days	Yes	No
Carbamazepine	0.8–1.4	75	70	Hepatic—epoxide metabolite is active	10–26 hr	—	No	No
Digoxin	5.1–7.4	20–40	50–93	Renal	33–51 hr	3.6 days	Yes	No
Disopyramide	0.5	50–80	80–85	Renal and Hepatic	6–10	45	Yes	No
Ethosuximide	0.62	Negligible	100	Hepatic	60 hr adults 30 hr children	—	No	No
Gentamicin	0.25	<5	Parenteral only	Renal	2 hr	2–3 days	Yes	No
Lidocaine	1.6	60	Parenteral only	Hepatic—metabolites are active	1.5 hr	—	No	Yes
Phenobarbital	1.0	46	80–100	Hepatic primarily	3–4 days	—	No	Yes
Phenytoin	0.6	90	90	Hepatic	10–30 hr concentration dependent	—	No	Only in severe cases
Primidone	0.6	14	100	Hepatic—phenobarbital and phenylethylmalonylamide (PEMA) are active metabolites	3–12 hr 29–36 hr metabolites	—	No	No
Procainamide	2.2	15	75–95	Renal and Hepatic *N*-acetylprocainamide is active	2.5–4.5 hr	10–15 hr	Yes	No
Quinidine	0.5	60–80	70–95	Hepatic—metabolite active	6 hr	—	No	No
Theophylline	0.3–0.6	55	Complete	Hepatic	3–9 hr	—	No	Yes
Tobramycin	0.25	<5	Parenteral only	Renal	2 hr	2–4 days	Yes	No
Valproic acid	0.2	90	70–100	Hepatic	10–15 hr	—	No	Yes, use with caution

Therapeutic drug monitoring requires as much clinical skill as does titration of an oral anticoagulant dose by monitoring the prothrombin time. A basic assumption in this principle is that free drug at the *active site* is in equilibrium with total drug in plasma or serum. This has been shown probably to be true for many drugs. Furthermore, for these drugs, optimum therapeutic effects and minimal toxicity is observed when the serum drug concentration lies within an empirically determined therapeutic plasma concentration range. However, there is overlap between the therapeutic and subtherapeutic serum drug concentrations. Therefore, therapeutic drug monitoring should be considered as an aid to, not a substitute for, careful clinical observation in the management of drug therapy.

The purpose of this section is to provide some guidelines to follow for therapeutic drug monitoring and some of the salient features of the drugs being monitored. Table VI contains a list of drugs commonly monitored and the serum concentrations thought to represent the therapeutic range.

Interpretation of plasma drug concentrations clearly requires a broad knowledge of clinical pharmacokinetics. Recently, several sources of pharmacokinetic data have become available.

An appendix of pharmacokinetic data, developed by Benet and Sheiner,[15] is available. Included are excellent compilations of availability, urinary excretion, protein binding, clearance, volume of distribution, half-life and therapeutic and toxic concentrations for most of the currently used drugs. Data are accompanied by references so that the original work can be documented.

The newsletter, *Perspectives in Clinical Pharmacy*,[16] provides timely discussions of popular topics in clinical pharmacokinetics.

Another useful reference is by Gerson.[17] Included are chapters on the major drug classes with detailed discussions of the commonly used drugs.

The pharmacokinetics of abused substances are covered by Barnett and Chiang.[18]

Table VII provides important pharmacokinetic information for commonly monitored drugs. A sound knowledge of the clinical pharmacokinetics of each drug, a critical use of plasma drug concentrations as described above and a thorough clinical evaluation of the patient will provide the data required for the development of rational drug therapy.

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CHAPTER 38

Topical Drugs

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A large number of chemical agents may be applied to the skin and mucous membranes for their local effects. Many of these, such as antibiotics, antiseptics, corticosteroids, antineoplastics and local anesthetics, belong to distinct pharmacologic classes treated elsewhere in this text, and will not be discussed in this chapter. The remainder comprise a heterogeneous group of agents which, by exclusion, are mostly nonselective in action.

Those locally acting agents that have limited chemical and pharmacologic activity generally have a *physical* basis of action. Included in this group are protectives, adsorbents, demulcents, emollients and cleansing agents. The relative inertness of many of these substances renders them of value as vehicles and excipients. Consequently, many in this group are also pharmaceutical necessities and may be treated in Chapter 66.

Those locally acting agents that have general *chemical* reactivity include most astringents, irritants, rubefacients, vesicants, sclerosing agents, caustics, escharotics, many keratolytic (desquamating) agents and a miscellaneous group of dermatologics including hypopigmenting and antipruritic agents.

Although the skin and mucous membranes differ considerably in structure and function, they are similar in penetrability (to chemical agents) and in their response to certain physical and pharmacologic stimuli. Thus, many of the agents found in this chapter may be applied to both types of surfaces. Nevertheless, it is obvious that many agents, for which there is either contraindication or no rationale for their application to the mucous membranes, may be applied only to the skin.

In its broadest pharmacologic sense a protective is any agent that isolates the exposed surface (skin or mucous membrane) from harmful or annoying stimuli. In common practice only those substances that protect by mechanical or other physical means are considered to be protectives, although the surface action of adsorbents and demulcents cannot be divorced from their chemical properties. Protectives such as demulcents and emollients customarily are placed in separate categories; that practice is followed here.

The abridged category of protectives mainly comprises the dusting powders, adsorbents, mechanical protective agents and plasters.

Protectives and Adsorbents

Dusting Powders

Certain relatively indifferent (inert and insoluble) substances are used to cover and protect epithelial surfaces, ulcers and wounds. Usually these substances are subdivided very finely. They generally absorb moisture and, therefore, also act as cutaneous desiccants. The absorption of skin moisture decreases friction and also discourages certain bacterial growth.

The water-absorbent powders should not be administered to wet, raw surfaces because of the formation of cakes and adherent crusts. Starch and other carbohydrate powders not only may become doughy but they also may ferment. Consequently, such powders often contain an antiseptic. Most impalpable powders are absorptive, to some extent. Whether absorption of substances, other than water, contributes to the protection of the skin is uncertain; however, absorption of fatty acids and other constituents of perspiration, along with cutaneous drying, contributes to a deodorant action of the powders. It generally is held that the adsorptive capacity is important to the gastrointestinal protective action of chemically inert powders taken internally.

The chemically inert dusting powders are not entirely biologically inert, despite the name. When entrained in pores or wounds or left upon parietal surfaces, certain of the dusting powders, eg, talc, may cause irritation, granulomas, fibrosis or adhesions. Even without direct irritation or obstruction of the perspiration, dust can be troublesome.

Several of the dusting powders are incorporated into ointments, creams and lotions.

Bentonite—page 1305.
Boric Acid—page 1318.
Calcium Carbonate, Precipitated—page 776.
Talc—page 1327.
Titanium Dioxide—page 772.
Zinc Oxide—page 762.

Zinc Stearate

Octadecanoic acid, zinc salt

Zinc stearate [557-05-1]. A compound of zinc with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of zinc stearate and zinc palmitate. It contains the equivalent of 12.5–14.0% of ZnO(81.38).

Preparation—An aqueous solution of zinc sulfate is added to a sodium stearate solution, and the precipitate is washed with water until free of sulfate and dried.

Description—Fine, white, bulky powder, free from grittiness with a faint characteristic odor; neutral to moistened litmus paper.

Solubility—Insoluble in water, alcohol or ether but is soluble in benzene.

Uses—In *water-repellent* ointments and as a *dusting powder* in dermatologic practice for its desiccating, astringent and *protective* effects. It has been removed from baby dusting powders, owing to accidental, fatal inhalations.

Mechanical and Chemical Protectives

Several materials may be administered to the skin to form an adherent, continuous coat which either may be flexible or semirigid, depending upon the substances and the manner in which they are applied. Such materials may serve three purposes: (1) to provide occlusive protection from the external environment, (2) to provide mechanical support and (3) to serve as vehicles for various medicaments.

The two principal classes of mechanical protectives are the collodions and plasters. Neither is used to much extent today. This is because there is increasing recognition of the beneficial effects of air in maintaining a normally balanced cutaneous bacterial flora of low pathogenicity. Also, the mechanical protectives may of themselves be somewhat irritating because of interference with normal water transport through the skin caused by certain oleaginous and resinous ingredients, especially in plasters. It also is recognized that rubber in adhesive plaster may induce eczema. The cerates may be employed similarly to the plasters. Bandages, dressings and casts also afford mechanical protection and support (see Chapter 105 for additional information). A brief discussion of plasters is included in Chapter 87.

A number of insoluble and relatively inert powders remain essentially unchanged chemically in the gastrointestinal tract. If the particles possess surface properties that favor their clinging to the gastrointestinal mucosa, and especially if they split up into tabular shapes, they offer mechanical protection against abrasion and may even offer slight protection against toxins and chemical irritants. Many such protectives also are adsorbents (charcoal, bismuth compounds, kaolin) or astringents (zinc and bismuth compounds). They are discussed under those categories.

Aluminum Hydroxide Gel—page 775.

Collodion

Contains not less than 5.0%, by weight, of pyroxylin.

Pyroxylin	40 g
Ether	750 mL
Alcohol	250 mL
To make about	1000 mL

Add the alcohol and the ether to the pyroxylin contained in a suitable container, and stopper the container well. Shake the mixture occasionally until the pyroxylin is dissolved.

Description—Clear, or slightly opalescent, viscous liquid; colorless, or slightly yellowish and has the odor of ether; specific gravity between 0.765 and 0.775.

Alcohol Content—22 to 26% of C_2H_5OH.

Uses—Chiefly to seal small wounds, for the preparation of medicated collodions and to protect nonaffected areas of the skin from topically applied irritants, corrosives, etc.

Caution—Collodion is highly flammable.

Flexible Collodion [Collodium Flexile]—See *RPS 16*, page 717. See also *Salicylic Acid Collodion* (page 768).

Absorbable Gelatin Film

Gelfilm (*Upjohn*)

A sterile, nonantigenic, water-insoluble, gelatin film obtained from a specially prepared gelatin-formaldehyde solution by drying on plates at constant temperature and humidity with subsequent sterilization by dry heat at 146° to 149°C for 12 hr.

Description—Light amber, transparent, pliable film that becomes rubbery when moistened.

Solubility—Insoluble in water; it assumes a rubbery consistency after being in water for a few minutes.

Uses—Both as a *mechanical protective* and as a *temporary supportive structure* and *replacement matrix* in *surgical repair of defects in membranes*, such as the dura mater and the pleura. When emplaced between damaged or operated structures, it prevents adhesions. When moistened, the film becomes pliable and plastic, so that it can be fitted to the appropriate surface. Absorption requires 1 to 6 months. It is also a component of stomadhesive, to be placed around an ostomy.

Dose—Applied in the form of sheets, previously soaked in isotonic sodium chloride solution and cut to the desired shape.

Dosage Forms—Film: 100 × 125 mm; Ophthalmic Film: 25 × 50 mm.

Zinc Gelatin

Zinc Gelatin Boot; Unna's Boot; Unna's Paste

Zinc Oxide	100 g
Gelatin	150 g
Glycerin	400 g
Purified Water	350 g
To make about	1000 g

Gradually add the gelatin to the cold purified water, with constant stirring, allow the mixture to stand for 10 min, and then heat on a steam bath until the gelatin dissolves. Add the zinc oxide, which previously has been rubbed to a smooth paste with the glycerin, and stir carefully until a smooth jelly result.

Uses—Melted and applied in the molten state between layers of bandage to act as a *protective* and to support varicosities and similar lesions of the lower limbs. After a period of about 2 weeks the dressing is removed by soaking with warm water.

Dose—*External*, as an occlusive boot.

Dosage Forms—Impregnated Gauze, in 10-yd lengths in following widths: 2¼, 2½, 3 and 4 in; impregnated with white or pink paste (the latter colored with a small amount of ferric oxide).

Kaolin—page 796.

Lanolin—page 1312.

Lanolin, Anhydrous—page 1311.

Mineral Oil—page 788.

Mineral Oil Emulsion—page 788.

Mineral Oil, Light—page 788.

Olive Oil—page 1309.

Peanut Oil—page 1303.

Petrolatum—page 788.

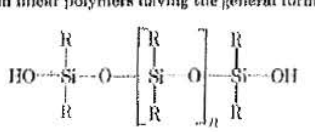
Other Mechanical and Chemical Protectives

Petrolatum Gauze [Petrolated Gauze]—Absorbent gauze saturated with white petrolatum. The weight of the petrolatum is 70–80% of the weight of the Gauze. It is sterile. Prepared by adding, under aseptic conditions, molten, sterile, white petrolatum to dry, sterile, absorbent gauze, previously cut to size, in the ratio of 60 g of petrolatum to each 20 g of gauze. *Uses:* A *protective* dressing; also as packing material for postoperative plugs, packs, rolls and tampons, and as a wick, drain or wrap-around for tubing. It is claimed that there is no danger of tissue maceration and that no growth of granulation tissue through it occurs.

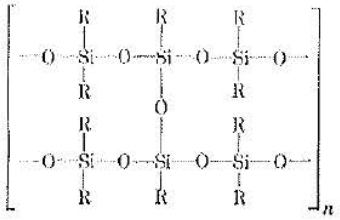
Dimethicone [Poly(dimethylsiloxane; poly[oxy(dimethylsilylene)] [9006-65-9] $(C_2H_6OSi)_n$]—A water-repellent silicone oil consisting essentially of dimethyl siloxane polymers of the 200 series of fluids (see *Silicones*, below). It is a water-white, viscous, oil-like liquid; immiscible with water or alcohol; miscible with chloroform or ether. *Uses:* Has skin-adherent and water-repellent properties. It is both a protective and an emollient, for which its FDA classification is Category I. Applied to the skin, it forms a *protective* film that provides a barrier to ordinary soap and water and water-soluble irritants. The film may last several hours if the skin is exposed mainly to aqueous media. The film provides a less-effective barrier to synthetic detergents and lipid-soluble materials, such as organic solvents. It should not be applied except in contact dermatoses and dermatoses aggravated by substances that can be repelled by the silicone. It is useful in preventing irritation from ammonia produced by the urine of infants, but it may exacerbate preexisting irritation. The occlusive protection by the silicone is detrimental to inflamed, traumatized, abraded or excoriated skin and to lesions requiring free drainage. However, applied adjacent to such lesions, it offers protection against irritating discharges and maceration. It practically is harmless, and does not sensitize skin but it does cause temporary irritation to the eyes. It may be incorporated into ointments, creams and gels. *Dose:* Apply uniformly with rubbing 3 or 4 times for the first day or two, then twice daily. *Dosage Forms:* Aerosol, Cream and Ointment: 20 and 30%. All concentrations from 1 to 30% are approved.

Silicones (*Polyorganosiloxanes*)—These are organosilicon polymers containing chains of alternating oxygen and silicon atoms with substituent organic groups, frequently methyl or phenyl, attached to each silicon atom.

Preparation: These polymers may be prepared synthetically by condensing alkylated or arylated *silanols*. Disubstituted *silanediols* $[R_2Si(OH)_2]$ form linear polymers having the general formula:



Cross-linked polymers result from condensation of mixtures of substituted silanediols and monosubstituted *silanetriols* [$RSi(OH)_3$], represented by the following partial formula where R is a hydrocarbon radical:



One method of preparation involves interaction of silicon tetrachloride with appropriate Grignard reagents to yield alkylated or arylated dichlorosilanes. After hydrolysis to the corresponding substituted silanols, dehydration procedures are used to effect condensation polymerization. The overall reaction, as it involves a disubstituted silanediol, may be represented as:

$$SiCl_4 \xrightarrow{RMgX} R_2SiCl_2 \xrightarrow{HOH} R_2Si(OH)_2 \xrightarrow{-HOH} HO[Si(R)_2O]_nH$$

Silicon tetrachloride	Disubstituted dichlorosilane	Disubstituted silanediol	Silicone linear polymer

Properties: Silicones with a wide range of properties may be produced by varying the substituent R and the degree of cross-linking. Physically, silicones vary from mobile liquids through viscous liquids and semisolids to solids. Viscosities range from 0.65 to 1,000,000 centistokes. In general, they display high- and low-temperature stability. They are odorless, tasteless, relatively inert chemically and physiologically, water-repellent and possess antifoam characteristics. Unmodified silicones are generally insoluble in water; because of this the liquids often are termed *silicone oils;* however, a water-soluble sodium salt of a simple silicone, chemically *sodium methyl siliconate* [$CH_3Si(OH)_2ONa$], has been marketed.

Uses: Preparations containing silicones have various dermatological uses (see *Dimethicone*) and are used as ingredients of bases for ointments and liniments. In the form of inhalation sprays, silicone preparations have been employed in the treatment of pulmonary edema involving frothing of fluid in the upper respiratory tract. They also are used orally as antiflatulent or gastric defoaming agents (see *Simethicone*, page 790). A silicone *bouncing putty* has found acceptance for use as a physical agent in treating conditions requiring finger exercise. The water-repellent properties of the silicones have found considerable use in a great variety of applications where complete drainage of aqueous fluids from surfaces is desirable.

Silicones virtually are nonirritating; consequently, silicone rubbers are used in various indwelling catheters, tubes, etc, and in some types of prostheses. Liquid silicones are used also to fill in hypoplastic body areas for cosmetic purposes, although they tend to relocate because of flow under gravity and motion.

In addition to uses involving antifoaming, water-repellent and nonirritating characteristics, silicones also are employed to prevent sticking of one object to another and then are referred to commonly as release agents. Examples of such employment include release of rubber and plastics from molds, food from metal, ice from the wings of aircraft and capsules and tablets from molds and dyes in which they are fabricated.

Silicone rubbers are used to encapsulate steroid hormones and other drugs intended for chronic use, in order to retard absorption and effect a repository action lasting in some instances for as long as 1 yr. Continuing developments in this field offer interesting possibilities.

Zinc Carbonate [CO_3Zn(125.38)]—White rhombohedroids. Soluble 10 ppm in water at 15°; soluble in dilute acids, alkalies or solutions of ammonium salts. *Uses:* Both for its lubricity and as a drying agent. As a skin protectant it falls into FDA Category I. It is included in commercial topical burn and sunburn products and extemporary protectants. *Dose:* 0.2 to 2%.

Demulcents

Demulcents are protective agents that are employed primarily to alleviate irritation (*demulcere*—to smooth down), particularly of mucous membranes or abraded tissues. They also often are applied to the skin. They generally are applied to the surface in viscid sticky preparations that cover the area readily. The local action of chemical, mechanical or bacterial irritants, thereby, is diminished, and pain, reflexes, spasm or catarrh are attenuated. They also prevent drying of the affected surface. The demulcents may be applied to the skin in the form of lotions, cataplasms or wet dressing, to the gastrointestinal tract in the form of demulcent liquors or enemas and to the throat in the form of pastilles, lozenges or gargles. Demulcents also are included in artificial tears and in wetting agents for contact lenses. When demulcents are applied as solid material (as in lozenges or powders), the liquid is provided by secreted or exuded fluids. Demulcents frequently are medicated. In such instances the demulcent may be an adjuvant, a corrective or a pharmaceutical necessity. Many of the demulcents are also laxatives (page 783) and are used as such, or they are used with laxatives or antacids for their demulcent and lubricating action.

A variety of chemical substances possess demulcent properties. Among these are the alginates, mucilages, gums, dextrins, starches, certain sugars and polymeric polyhydric glycols. Mucus, in itself, is a natural demulcent. Certain silicates that form silicic acid on exposure to air or gastric juice and glycerin, although it is of low molecular weight and has relatively low binding power, frequently are placed among the demulcents. Also the colloidal hydrous oxides, hydroxides and basic salts of several metals are claimed to be demulcent, but acceptable clinical proof of the claim has not been provided.

The hydrophilic colloidal properties of most of the demulcents make them valuable emulsifiers and suspending agents in water-soluble ointments and suspensions. They also retard the absorption of many injections and, thus, may be employed in sundry depot preparations. Many of the demulcents mask the flavor of medicaments by means of at least three physical phenomena: (1) they apparently coat the taste receptors and render them less sensitive, (2) they incorporate many organic solutes into micelles and, thereby, diminish the free concentration of such solutes and (3) they coat the surfaces of many particles in suspension. Because of the adhesiveness of the demulcents, they are employed widely as binding agents in tablets, lozenges and similar dosage forms. Consequently, certain demulcents will be discussed in Chapter 66.

Acacia—page 1304.

Benzoin

Gum Benjamin; Benzoe

The balsamic resin obtained from *Styrax benzoin* Dryander or *Styrax parallelonevrus* Perkins, known in commerce as Sumatra Benzoin, or from *Styrax tonkinensis* (Pierre) Craib ex Hartwich, or other species of the Section *Anthostyrax* of the genus *Styrax*, known in commerce as Siam Benzoin (Fam *Styracaceae*).

Sumatra benzoin yields not less than 75.0% of alcohol-soluble extractive, and Siam benzoin yields not less than 90.0% of alcohol-soluble extractive.

Constituents—Siam benzoin contains about 68% of crystalline *coniferyl benzoate* [$C_{17}H_{16}O_4$]; up to 10% of an amorphous form of this compound is also present. Some *coniferyl alcohol* (*m-methoxy-p-hydroxycinnamyl alcohol*, mp 73–74°) occurs in the free state as well. Other compounds that have been isolated are *benzoic acid* 11.7%, *d-siaresinolic acid* 6%, *cinnamyl benzoate* 2.3% and *vanillin* 0.3%.

Sumatra benzoin has been reported to contain benzoic and cinnamic acid esters of the alcohol *benzoresinol* and probably also of coniferyl alcohol, free *benzoic* and *cinnamic acids*, *styrene*, 2 to 3% of *cinnamyl cinnamate* (also called *styracin*), 1% of *phenylpropyl cinnamate*, 1% of *vanillin*, a trace of *benzaldehyde*, a little *benzyl cinnamate* and the alcohol *d-sumaresinol* [$C_{30}H_{48}O_4$].

Description—*Sumatra Benzoin:* Blocks or lumps of varying size made up of compacted tears, with a reddish brown, reddish gray or greyish brown resinous mass. *Siam Benzoin:* Compressed pebble-like tears of varying size and shape. Both varieties are yellowish to rusty

brown externally and milky white on fracture; hard and brittle at ordinary temperatures but softened by heat; aromatic and balsamic odor; aromatic and slightly acrid taste.

Uses—A *protective* application for irritations of the skin. When mixed with glycerin and water, the tincture may be applied locally for *cutaneous ulcers, bedsores, cracked nipples* and *fissures* of the lips and anus. For throat and bronchial inflammation, the tincture may be administered on sugar. The tincture and compound tincture sometimes are used in boiling water as steam inhalants for their *expectorant* and *soothing action* in acute laryngitis and croup. In combination with zinc oxide, it is used in baby ointments.

Dose—*Topical*, as a 10% tincture or compound tincture (below).

Compound Benzoin Tincture [Balsamum Equitis Sancti Victoris, Balsamum Commendatoris, Balsamum Catholicum, Balsamum Traumaticum, Balsamum Vulnerarium, Balsamum Persicum, Balsamum Suecium, Balsamum Friari, Balsamum Vervaini, Guttae Nador, Guttae Jesuitarium, Tinctura Balsamica, Balsam of the Holy Victorious Knight, Commander's Balsam, Friar's Balsam, Turlington's Drops, Persian Balsam, Swedish Balsam, Vervain Balsam, Turlington's Balsam of Life, Balsam de Maitha, Ward's Balsam, Jerusalem Balsam, Saint Victor's Balsam, Wade's Drops, Wound Elixir and Balsamic Tincture]—*Preparation:* With benzoin (in moderately coarse powder, 100 g), aloe (in moderately coarse powder, 20 g), storax (80 g) and tolu balsam (40 g), prepare a tincture (1000 mL) by Process M (page 1543), using alcohol as the menstruum. *Alcohol Content:* 74 to 80% of C_2H_5OH. *Uses:* Especially valuable in acute *laryngitis*, also in croup, when added to hot water and the vapor inhaled. By adding a teaspoonful of the tincture to boiling water in an inhaler, and inhaling the vapor, very effective results may be obtained. See Chapter 104. Also administered, on sugar, for throat and bronchial inflammation and as a local application, when mixed with glycerin and water, for *ulcers, bedsores, cracked nipples* and *fissures* of the lips and anus. *Dose: Topical*, as required; *inhalation*, 1% in very hot water.

Carbomer Methylcellulose—page 1306.

Gelatin—page 1306.

Glycerin—page 931.

Glycerin Suppositories—page 785.

Glycyrrhiza—page 1295.

Hydroxypropyl Cellulose—page 1306.

Hydroxypropyl Methylcellulose—page 1306.

Hydroxyethyl Cellulose—page 1306.

Hydroxypropyl Methylcellulose Ophthalmic Solution

A sterile solution of hydroxypropyl methylcellulose, of a grade containing 19.0–30.0% methoxy and 4.0–12.0% hydroxypropoxy groups; may contain antimicrobial, buffering and stabilizing agents.

Uses—A wetting solution for contact lenses. Its demulcent action decreases the irritant effect of the lens on the cornea. It also imparts viscous properties to the wetting solution, which assists the lens in staying in place. The demulcent effect also finds application in ophthalmic decongestants. "Artificial tear" formulations containing this drug may be used when lacrimation is inadequate. A 2.5% solution is used in gonioscopes.

Dose—*Topical, to the conjunctiva*, 1 **drop** of 0.3 to 1% solution 3 or 4 times a day.

Dosage Forms—0.3, 0.5 and 1% solutions.

Methylcellulose—page 1306.

Methylcellulose Ophthalmic Solution

A sterile solution of methylcellulose; may contain antimicrobial, buffering and stabilizing agents.

Uses—For the same purposes, and in the same manner, as *Hydroxypropyl Methylcellulose Ophthalmic Solution*, above.

Dosage Forms—0.25, 0.5 and 1%.

Pectin—page 796.

Polyvinyl Alcohol—page 1307.

Polyvinyl Alcohol Ophthalmic Solution

VasoClear A (*Cooper Vision*)

A sterile solution of polyvinyl alcohol, which may contain antimicrobial, buffering and stabilizing agents and other demulcent substances.

[9002-89-5] (Polyvinyl alcohol).

Preparation—By partial hydrolysis (*ca* 90%) of polyvinyl acetate.

Description—A white powder which is a linear polymer, $-(CH_2-CHOH)_n-$, where the value of n is between 500 and 5000; pH (1 in 25 aqueous solution) between 5.0 and 8.0.

Solubility—Soluble in water; insoluble in organic solvents.

Uses—A wetting solution for contact lenses. The polyvinyl alcohol has a demulcent action that helps protect the eye from irritation by the contact lens. It is also used in "artificial tears" employed when there is insufficient lacrimation. It is applied to the conjunctiva, 1 or 2 drops, 3 or 4 times a day or as needed.

Dosage Forms—1, 1.4, 2, 3, and 4% solutions.

Emollients

Emollients are bland, fatty or oleaginous substances which may be applied locally, particularly to the skin, and also to mucous membranes or abraded tissues. Water-soluble irritants, air and airborne bacteria are excluded by an emollient layer. The skin also is rendered softer (*emollier*—to soften) and more pliable through penetration of the emollient into the surface layers, through the slight congestion induced by rubbing and massage upon application and especially through mechanical interference with both sensible and insensible water loss.

Emollients have certain disadvantages. It now is recognized that retention of perspiration below the emollient and exclusion of air render conditions favorable to the growth of anaerobic bacteria. Furthermore, the rubbing during application aids in the spreading of cutaneous bacteria. Consequently, the use of emollients to cover burns and abrasions is diminishing. The liquid emollients may be used for mild catharsis (page 783) and for protection against gastrointestinal corrosives; however, castor oil is hydrolyzed in the gut to the irritating ricinoleic acid and, hence, is employed as an emollient only externally. Orally administered liquid emollients may be aspirated into the trachea and lungs, especially in infants and in the debilitated, and, thus, induce "oil aspiration pneumonia." This condition also may be induced by emollient nose drops.

The chief use of emollient substances is to provide vehicles for lipid-soluble drugs (as in ointments and liniments), hence, many of them are described among the pharmaceutical necessities (Chapter 66). It is widely, but incorrectly, held that such vehicles facilitate the transport through the skin of their active ingredients. On the contrary, when the oil:water partition coefficient is greater than 1.0, the penetration is retarded and the emollient vehicle prolongs the action of the active ingredient. Emollient substances also are employed commonly in both cleansing and antiphlogistic creams and lotions. Compound ointment bases, creams and other medicated applications are treated elsewhere in this book (Chapter 86). Only the simple emollients and important compounded ointments that are used frequently for their emollient actions are listed below.

Castor Oil—page 785.

Castor Oil, Sulfated—page 1311.

Cocoa Butter—page 1611.

Coconut Oil—page 1317.

Cold Cream—page 1312.

Corn Oil—page 1303.

Cottonseed Oil—page 1303.
Ointment, Hydrophilic—page 1312.
Rose Water Ointment—page 1315.
Sesame Oil—page 1303.
Theobroma Oil—page 1320.
White Ointment—page 1309.
Yellow Ointment—page 1309.

Other Emollients

Myristyl Alcohol [Tetradecyl Alcohol [112-72-1] $CH_3(CH_2)_{12}CH_2OH$ (214.38)]—White crystalline alcohol; specific gravity 0.824; melts at 38°. Insoluble in water; soluble in ether; slightly soluble in alcohol. Obtained by reduction of fatty acid esters. *Use:* Emollient in cold creams.

Shark Liver Oil—The oil extracted from the livers of the *soupfin shark, Galeorhinus zyopterus* or *Hypoprion brevirostris*, both of which are rich in vitamins A and D. *Uses:* An emollient and protectant, the FDA classification of which is Category I. It is used in burn and sunburn ointments. *Dose:* Usually 3%.

Astringents and Antiperspirants

Astringents are locally applied protein precipitants which have such a low cell penetrability that the action essentially is limited to the cell surface and the interstitial spaces. The permeability of the cell membrane is reduced, but the cells remain viable. The astringent action is accompanied by contraction and wrinkling of the tissue and by blanching. The cement substance of the capillary endothelium and the basement membrane is hardened, so that pathological transcapillary movement of plasma protein is inhibited and local edema, inflammation and exudation, thereby, are reduced. Mucus or other secretions also may be reduced, so that the affected area becomes drier.

Astringents are used therapeutically to arrest hemorrhage by congulating the blood (*styptic* action, page 816) and to check diarrhea, reduce inflammation of mucous membranes, promote healing, toughen the skin or decrease sweating. The *antiperspirant* effect is the result both of the closure of the sweat ducts by protein precipitation to form a plug and peritubular irritation that promotes an increase in inward pressure on the tubule. Astringents also possess some *deodorant* properties by virtue of interaction with odorous fatty acids liberated or produced by action of bacteria on lipids in sweat, and by an action suppressing bacterial growth, partly because of a decrease in pH.

Many astringents are irritants or caustics in moderate to high concentrations. Consequently, strict attention must be paid to the appropriate concentration. Most astringents are also antiseptics, hence, many of them are discussed in Chapter 62.

The principal astringents are (1) the salts of the cations aluminum, zinc, manganese, iron or bismuth, (2) certain other salts that contain these metals (such as permanganates) and (3) tannins, or related polyphenolic compounds. Acids, alcohols, phenols and other substances that precipitate proteins may be astringent in the appropriate amount or concentration; however, such substances generally are not employed for their astringent effects, because they readily penetrate cells and promote tissue damage. Strongly hypertonic solutions dry the affected tissues and, thus often, but wrongly, are called astringents, unless protein precipitation also occurs.

Alcohol—page 1314.

Alum

Sulfuric acid, aluminum potassium salt (2:1:1), dodecahydrate; Sulfuric acid, aluminum ammonium salt (2:1:1), dodecahydrate; Alumen; Alumen Purificatum; Purified Alum

Aluminum ammonium sulfate (1:1:2) dodecahydrate [7784-26-1]; anhydrous [7784-25-0] (237.14); or aluminum potassium sulfate (1:1:2) dodecahydrate [7784-24-9]; anhydrous [10043-67-1] (258.19).

The label of the container must indicate whether the salt is ammonium alum [$AlNH_4(SO_4)_2.12H_2O$ = 453.32] or potassium alum [$AlK(SO_4)_2.12H_2O$ = 474.38].

Preparation—Prepared from the mineral *bauxite* (a hydrated aluminum oxide) and sulfuric acid, with the addition of ammonium or potassium sulfate for the respective alums. Ammonium alum is prevalent on the market because of its lower cost.

Description—Large, colorless crystals, crystalline fragments or a white powder; odorless and has a sweetish, strongly astringent taste; solutions are acid to litmus.

Solubility—1 g ammonium alum is soluble in 7 mL water, and 1 g potassium alum is soluble in 7.5 mL water; both are soluble in about 0.3 mL boiling water, but they are insoluble in alcohol; alum is freely but slowly soluble in glycerin.

Incompatibilities—When alum is dispensed in powders with *phenol, salicylates* or *tannic acid*, gray or green colors may be developed due to traces of iron in the alum. A partial liberation of its water of crystallization permits it to act as an acid toward *sodium bicarbonate*, thus liberating carbon dioxide. Ammonia is liberated simultaneously from ammonium alum. *Alkali hydroxides and carbonates, borax* or *lime water* precipitate aluminum hydroxide from solutions of alum. The alums possess the incompatibilities of the water-soluble sulfates.

Uses—A powerful *astringent* in acidic solutions. It is slightly antiseptic, probably due to bacteriostasis through liberation of acid on hydrolysis. It sometimes is used as a local *styptic*, and frequently is employed in making astringent lotions and douches. It is used especially by athletes to toughen the skin. As an astringent it is used in concentrations of 0.5 to 5%. Some vulvovaginal cleansing and deodorant preparations contain alum.

Styptic pencils are made by fusing potassium alum, usually with the addition of some potassium nitrate, and pouring into suitable molds.

Caution—Do not confuse *styptic* pencils with *caustic* pencils (page 767); the latter contain *silver nitrate*.

Dose—*Topical*, as a 0.5 to 5% solution.

Aluminum Acetate Topical Solution

Acetic acid, aluminum salt; Liquor Burowii; Burow's Solution

$AlO(OCOCH_3)$

Yields, from each 100 mL, 1.20–1.45 g of aluminum oxide [Al_2O_3 = 101.96], and 4.24 to 5.12 g of acetic acid [$C_2H_4O_2$ = 60.05], corresponding to 4.8 to 5.8 g of aluminum acetate [139-12-8] $C_6H_9AlO_6$ (204.12). It may be stabilized by the addition of not more than 0.6% of boric acid.

Caution—This solution should not be confused with Aluminum Subacetate Topical Solution which is a stronger preparation.

Note—Dispense only clear Aluminum Acetate Solution.

Description—Clear, colorless liquid having a faint acetous odor, and a sweetish, astringent taste; specific gravity about 1.022; pH 3.6 to 4.4.

Uses—As an astringent dressing or as an astringent mouth wash and gargle. Aluminum acetate is included in preparations to treat athlete's foot, dermatidides, diaper rash, dry skin, poison ivy poisoning and inflammation of the external ear.

Dose—*Topical*, to the skin, as a wet dressing containing a 1:10 to 1:40 dilution of the solution.

Aluminum Chloride

[7784-13-6] $AlCl_3.6H_2O$ (241.43); *anhydrous* [7446-70-0] (133.34).

Preparation—By heating aluminum in chlorine gas, then dissolving the product in water and crystallizing, or by dissolving freshly precipitated aluminum hydroxide in hydrochloric acid and concentrating to permit crystallization.

Description—White or yellowish white, crystalline powder; deliquescent; sweet, astringent taste; solutions are acid to litmus.

Solubility—1 g in about 0.9 mL water or 4 mL alcohol; soluble in glycerin.

Uses—Extensively employed on the skin as an astringent and anhidrotic, it is included in some proprietary preparations formu-

lated for this purpose. It is used especially in the treatment of soggy athlete's foot, to promote drying and, hence, to enhance the efficacy of specific antifungal drugs. For ordinary antiperspirant use the basic salt *aluminum chlorohydroxide*, $Al_2Cl(OH)_5$, is preferable as it is less irritating and causes less deterioration of clothing than does this drug. It may have a special use in the treatment of *hyperhidrosis of the palms, soles or axillae*, for which a 20% solution in absolute ethanol is used. In the presence of water, it hydrolyzes to aluminum chlorohydroxide and hydrochloric acid, which can cause irritation, especially in fissures, discomfort and also deterioration of clothing. Concentrations below 15% cause a low incidence of irritation. Consequently, it is essential that the area to be treated is completely dry before application. To protect bedclothes, the treated area is sometimes covered with plastic wrap, but such occlusion of the axillae may result in boils or furuncles. It should not be applied to the axillae immediately after shaving or used where the skin is irritated or broken. Concentrations above 15% are used as caustics.

Dose—*Topical*, to the skin, as 6.25 to 30% solution. The 20% alcoholic solution may be applied on 2 successive days and twice a week thereafter, except that it may be applied twice a day for athlete's foot.

Aluminum Chlorohydrates

The hydrate of aluminum chloride hydroxide [1327-41-9] $Al_2Cl(OH)_5$.

Uses—Mainly employed in antiperspirant products, for which they have been rated safe and effective in concentrations of 25% (as anhydride) or less. Since solutions or suspensions are less acidic than those of aluminum chloride, they cause a lower incidence of irritation to the skin.

Dose—*Topical*, to the axilla, as a 2.5 to 25% cake, ointment, solution or suspension.

Aluminum Sulfate

Sulfuric acid, aluminum salt (3:2), hydrate; Cake Alum; Patent Alum; Pearl Alum; Pickle Alum; "Papermaker's Alum"

Aluminum sulfate (2:3) hydrate [17927-65-0] $Al_2(SO_4)_3.xH_2O$; anhydrous [10043-01-3] (342.14).

Preparation—By reacting freshly precipitated aluminum hydroxide with an appropriate quantity of sulfuric acid. The resulting solution is evaporated and allowed to crystallize.

Description—White crystalline powder, shining plates or crystalline fragments; stable in air; odorless and has a sweet, mildly astringent taste; aqueous solution (1 in 20) is acid and has a pH not less than 2.9.

Solubility—1 g in about 1 mL water; insoluble in alcohol.

Uses—A powerful *astringent*, acting much like alum. It is used widely as a *local antiperspirant* and is the effective ingredient in some commercial antiperspirant products. Solutions usually are buffered with sodium aluminum lactate to make them less irritating. It is used for water purification in the "alum flocculation" process. It is a *pharmaceutical necessity* for *Aluminum Subacetate Solution*.

Dose—*Topical*, to the skin, as an 8% solution.

Bismuth Subcarbonate—page 799.

Bismuth Subnitrate—page 775.

Calamine

Iron oxide (Fe_2O_3), mixt. with zinc oxide; Prepared Calamine; Lapis Calaminaris; Artificial Calamine

Calamine [8011-96-9]; contains, after ignition, not less than 98.0% ZnO (81.38).

Preparation—By thoroughly mixing zinc oxide with sufficient ferric oxide (usually 0.5 to 1%) to obtain a product of the desired color.

It originally was obtained by roasting a native zinc carbonate, then known as *calamine*, hence, the name. This name also is applied by mineralogists to a native form of zinc silicate, which is not suitable for making medicinal calamine.

Description—Pink powder, all of which passes through a No 100 standard mesh sieve. It is odorless and almost tasteless.

Solubility—Insoluble in water; dissolves almost completely in mineral acids.

Uses—Similar to those of zinc oxide, being employed chiefly as an *astringent* and in *protective* and soothing ointments and lotions for *sunburn, ivy poisoning*, etc. It often is prescribed by dermatologists to give opacity and a flesh-like color to lotions or ointments.

Dose—*Topical*, to the skin, in various concentrations in lotions and ointments.

Calamine Lotion [Lotio Calaminae]—*Preparation:* Dilute bentonite magma (250 mL) with an equal volume of calcium hydroxide solution. Mix calamine (80 g) and zinc oxide (80 g) intimately with glycerin (20 mL) and about 100 mL of the diluted magma, triturating until a smooth, uniform paste is formed. Gradually incorporate the remainder of the diluted magma. Finally add calcium hydroxide solution (qs) to make 1000 mL, and shake well. If a more viscous consistency in the Lotion is desired, the quantity of bentonite magma may be increased to not more than 400 mL. *Note: Shake thoroughly before dispensing.*

Phenolated Calamine Lotion [Lotio Calaminae Composita; Compound Calamine Lotion]—*Preparation:* Mix liquefied phenol (10 mL) and calamine lotion (990 mL) to make 1000 mL. Commercial preparations also contain 8.4% isopropyl alcohol and have various other modifications. See *Calamine*. *Note: Shake thoroughly before dispensing.*

Glutaral—page 1165.

Potassium Permanganate—page 1173.

Resorcinol—RPS-16, page 1107.

Silver Nitrate—page 766.

White Lotion

Lotio Alba; Lotio Sulfurata

Zinc Sulfate	40 g
Sulfurated Potash	40 g
Purified Water, a sufficient quantity, To make	1000 mL

Dissolve zinc sulfate and sulfurated potash separately, each in 450 mL purified water, and filter each solution. Add slowly the sulfurated potash solution to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

Note—Prepare freshly and shake thoroughly before dispensing. For further discussion see *Sulfurated Potash* (page 1327).

Uses—An *astringent, protective* and mild antimicrobial preparation. The astringency is attributable to the zinc ion. The thiosulfates and polysulfides in it exert antibacterial and antifungal actions (see *Sodium Thiosulfate*, RPS-16, page 1176). White lotion is used in the treatment of acne vulgaris.

Dose—*Topical*, to the skin, as required.

Zinc Oxide

Flowers of Zinc; Zinc White; Pompholyx; Nihil Album; Lana Philosophica

Zinc oxide [1314-13-2] ZnO (81.38).

Preparation—By heating zinc carbonate at a low red heat until the carbon dioxide and water are expelled.

Description—Very fine, odorless, amorphous, white or yellowish white powder, free from gritty particles; gradually absorbs carbon dioxide from the air; when strongly heated it assumes a yellow color which disappears on cooling; its suspension in water is practically neutral.

Solubility—Insoluble in water or alcohol; soluble in dilute acids, solutions of the alkali hydroxides or ammonium carbonate solution.

Incompatibilities—Reacts slowly with fatty acids in *oils* and *fats* to produce lumpy masses of zinc oleate, stearate, etc. *Vanishing creams* tend to dry out and crumble. Whenever permissible, it is advisable to levigate it to a smooth paste with a little mineral oil before incorporation into an ointment.

Uses—Has a mild *astringent, protective* and *antiseptic* action. In the form of its various official ointments and pastes it is employed widely in the treatment of dry skin and such skin disorders and infections as *acne vulgaris, prickly heat, insect stings and bites, ivy poisoning, diaper rash, dandruff, seborrhea, eczema, impetigo, ringworm, psoriasis, varicose ulcers* and *pruritus*. It is contained in some sunscreens. It is included in some vulvovaginal deodorant preparations and in preparations for the treatment of hemorrhoids.

It also is used in dental cements and temporary fillings. It is the essential ingredient in *Calamine* (page 762).

Dose—*Topical*, as a 5 to 25% cream, lotion, ointment, paste, baby powder or rectal suppository.

Dosage Forms—Ointment: 20%; Paste: 25%. In numerous combinations: 2 to 15%.

Zinc Pyrithione—page 1173.

Zinc Sulfate—page 1170.

Zinc Undecylenate—page 1237.

Other Astringents and Antiperspirants

Aluminum Zirconium Chlorhydrate—*Uses:* Mainly in antiperspirant products. Because of the propensity of the zirconium to elicit allergic reactions and sarcoid-like granulomas, the compound is not included in aerosols, because of possible pulmonary complications if inhaled. *Dose:* To the axilla, in a concentration not to exceed 20% (as anhydride).

Tannic Acid [Gallotannic Acid; Tannin; Digallic Acid] [1401-55-4]—A tannin usually obtained from nutgalls, the excrescences produced on the young twigs of *Quercus infectoria* Olivier and allied species of *Quercus* Linné (Fam *Fagaceae*). Yellowish white to light brown amorphous powder, glistening scales or spongy masses; usually odorless with a strong astringent taste; gradually darkens on exposure to air and light. 1 g dissolves in about 0.35 mL water or 1 mL warm glycerin; very soluble in alcohol; practically insoluble in chloroform or ether. *Incompatibilities:* Solutions gradually darken on exposure to air and light through oxidation of phenolic groups to quinoid structures. It is incompatible with most enzymes, gums, salts of many metals and many other substances.

Uses: On an open sore or denuded surface, it forms a film of protein tannate that acts as a mechanical protective which excludes external irritants and infectives and, thus, provides some relief from pain. However, it is not antibacterial and not only does not inhibit the growth of bacteria entrained beneath the film but actually may create favorable conditions for the growth of certain anaerobes. For this reason, and also the fact that it is absorbed sufficiently from large denuded areas to cause liver damage, it is no longer used in the treatment of burns and should not be used on any large lesion. Nevertheless, it is incorporated in 8 to 10% concentration in several products to treat ivy or oak poisoning. As a 7% gel it is used on cold sores, fever blisters and cankers. It is included in 2.16% concentration in a hemorrhoidal preparation and in 4% concentration in a keratolytic product for removing corns, calluses and warts, these concentrations probably being too low to contribute significantly to the supposed efficacies. In 25% solution it is used to reduce inflammation and harden skin around ingrown toenails, thus increasing comfort and making nail-cutting easier.

Its content in tea accounts for the use of strong tea as an internal antidote, presumably for the dual purpose of precipitating toxic alkaloids and hardening the surface of the gastrointestinal mucosa and its mucous layer.

Zinc Caprylate [Zinc octanoate [557-09-5] $C_{16}H_{30}O_4Zn$ (351.79)]—Lustrous scales. Sparingly soluble in boiling water; moderately soluble in boiling alcohol. *Uses:* In the treatment of athlete's foot. The astringency of the zinc decreases inflammation and wetness. The caprylate has a weak antifungal action. *Dose:* As a 5% ointment.

Zinc Chloride [Zinc chloride [7646-85-7] $ZnCl_2$ (136.29)]—Prepared by reacting metallic zinc or zinc oxide with hydrochloric acid and evaporating the solution to dryness. White, or nearly white, odorless, crystalline powder, or as porcelain-like masses, or in moulded pencils; very deliquescent; aqueous solution (1 in 10) is acid to litmus. 1 g dissolves in 0.5 mL water, about 1.5 mL alcohol or about 2 mL glycerin; solution in water or alcohol is usually slightly turbid, but the turbidity disappears on addition of a small quantity of HCl. *Incompatibilities:* Soluble zinc salts are precipitated as zinc hydroxide by alkali hydroxides, including ammonium hydroxide; the precipitate is soluble in an excess of either the fixed or the ammonium hydroxide. *Carbonates, phosphates, oxalates, arsenates,* and *tannin* cause precipitation. The precipitation with sodium borate can be prevented by addition of an amount of glycerin equal in weight to the sodium borate. In weak aqueous solutions, it has a tendency to form the insoluble basic salt by hydrolysis and about one-half its weight of ammonium chloride has been used for the purpose of stabilization. It is very *deliquescent*. It has the incompatibilities of chlorides, being precipitated by *silver* and *lead salts*. *Uses:* In high concentrations it is caustic and has been used as a caustic agent to treat corns, calluses and warts. In the low concentrations in which it is marketed it is astringent and mildly antibacterial and probably does not contribute to keratolysis. Although it is used in mouthwashes, the contact time is too short, and only an astringent and not an antibacterial action results. *Dose: Topical*, to the teeth, as a 10% solution; to skin and mucous membranes for astringency and antimicrobial actions, as a 0.1 to 2% solution.

Zinc Ricinoleate [Zinc [*R*-(*Z*)]-12-hydroxy-9-octadecenoate $(C_{18}H_{33}O_3)_2Zn$ (660.24)]—Only as a deodorant for ostomies.

Zirconium Oxide [Zirconium Dioxide; Zirconic Anhydride; Zircomia; [1314-23-4] ZrO_2 (123.22)]—White powder or crystals. Insoluble in water; soluble in acids. *Uses:* Has weak astringent and adsorptive activity, for which it is employed in topical preparations for treating thus dermatitis (ivy and oak poisoning). However, it is not only poorly effective for this purpose but it also can cause allergic reactions that may give rise to sarcoid-like granulomas. Consequently, its use should be condemned. Zirconium salts also are subject to the same criticisms.

Irritants, Rubefacients and Vesicants

The *irritants* are drugs that act locally on the skin and mucous membranes to induce hyperemia, inflammation and, when the action is severe, vesication. Agents that induce only hyperemia are known as *rubefacients*. Rubefaction is accompanied by a feeling of comfort, warmth and, sometimes, itching and hyperesthesia. Appropriately low concentrations of directly applied or inhaled vapors of volatile aromatic irritants, such as camphor or menthol, induce a sensation of coolness rather than warmth. When the irritation is more severe, plasma escapes from the damaged capillaries and forms blisters (vesicles). Agents that induce blisters are known as *vesicants*. Most rubefacients also are vesicants in higher concentrations. Certain irritants may be relatively selective for various tissues or cell types, so that hypersecretion of the surface, seborrheic abscesses, paresthesia or other effects may be noted in the absence of appreciable hyperemia.

Irritants have been used empirically for many centuries, probably even prehistorically. They may be employed for counterirritation, the mechanism of which is poorly understood. A moderate to severe pain may be obscured by a milder pain arising from areas of irritation appropriately placed to induce reflex stimulation of certain organs or systems, especially respiratory. Sensory and visible effects of irritation sometimes give the patient assurance that he is receiving effective medication. Taken internally, many irritants exert either an emetic or laxative action. Irritant laxatives are listed on page 783. A few irritants, especially cantharides, on absorption into the blood stream, irritate the urogenital tract and, consequently, have been dangerously employed as *aphrodisiacs*. Certain irritants also possess a healing action on wounds, possibly the result of local stimulation. Many condiments are irritants. In high concentrations, many irritants are corrosive.

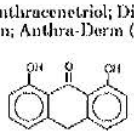
Alcohol—page 1314.

Alcohol, Rubbing—page 1164.

Ammonia Spirit, Aromatic—RPS-17, page 15.

Anthralin

1,8,9-Anthracenetriol; Dithranol; Dioxyanthranol; Cignolin; Anthra-Derm (*Dermik*); Lasan (*Stiefel*)



1,8-Dihydroxyanthranol [480-22-8] $C_{14}H_{10}O_3$ (226.23).

Preparation—Anthraquinone is sulfonated to the 1,8-disulfonic acid, which is isolated from the reaction mixture and then heated with a calcium hydroxide-calcium chloride mixture to form 1,8-dihydroxy-9,10-anthraquinone, which is reduced with tin and HCl to anthralin.

Description—Yellowish brown, crystalline powder; odorless and tasteless; melts between 175° and 181°.

Solubility—Insoluble in water; slightly soluble in alcohol; soluble in chloroform; slightly soluble in ether.

Uses—Although long considered to be an irritant, its principal therapeutic action is the reduction of epidermal DNA synthesis and mitotic activity. It is used in the treatment of *psoriasis, alopecia areata, eczema* and other *chronic dermatoses*. It usually is used in

combination with ultraviolet light and a daily coal tar "bath." To avoid harmful irritation, medicaments containing it should not be used on the face, scalp, genitalia or intertriginous skin areas; they should not be applied to blistered, raw or oozing areas of the skin, and should be kept from the eyes, since they may cause severe conjunctivitis, keratitis or corneal opacity. Renal irritation, casts and albuminuria may result when the drug is absorbed systemically. The hands should be washed immediately after applying medication. A reversible slight discoloration of the skin may occur.

Dose—*Topical*, to the skin, as a 0.1 to 1% cream or ointment, once a day with cream and once or twice a day with ointment. The concentration should be low initially and increased only as necessary.

Dosage Forms—Cream: 0.1, 0.2, 0.25, 0.4, 0.5 and 1%; Ointment: 0.1, 0.25, 0.4, 0.5, 1 and 2%.

Benzoin Tincture, Compound—page 760.

Coal Tar

Pix Carbonis; Prepared Coal Tar BP; Pix Lithanthracis; Gas Tar

The tar obtained as a by-product during the destructive distillation of bituminous coal.

Description—Nearly black, viscous liquid, heavier than water, with a characteristic naphthalene-like odor and a sharp burning taste; on ignition it burns with a reddish, luminous and very sooty flame, leaving not more than 2% of residue.

Solubility—Only slightly soluble in water, to which it imparts its characteristic odor and taste and a faintly alkaline reaction; partially dissolved by alcohol, acetone, methanol, solvent hexane, carbon disulfide, chloroform or ether; to the extent of about 95% by benzene, and entirely by nitrobenzene with the exception of a small amount of suspended matter.

Uses—A *local irritant* used in the treatment of *chronic skin diseases*. Like anthralin, its primary action is to decrease the epidermal synthesis of DNA and, hence, to suppress hyperplasia. Occasionally, it may cause rash, burning sensation or other manifestations of excessive irritation or sensitization. Since photosensitization may occur, the treated area should be protected from sunlight. It should be kept away from the eyes and from raw, weeping or blistered surfaces. Temporary discoloration of the skin may occur.

Dose—*Topical*, to the skin: *cleansing bar*, 2% once or twice a day; *cream*, 1.6 to 5%, 2 or 3 times a day; *gel*, 5 to 7.5% once or twice a day; *lotion*, 2 to 5%, 2 to 4 times a day; *ointment*, 1 to 5%, 2 or 3 times a day; *paste*, 5% once or twice a day; *shampoo*, 0.5 to 10% twice a week; *solution*, 2.5 to 20% straight or diluted 1:3 with water 1 to 3 times a day; *suspension*, 7.5 to 33.3% diluted in lukewarm water at intervals directed by the physician.

Dosage Forms—Cleansing Bar: 2%; Cream: 1.6 and 5%; Gel: 5 and 7.5%; Lotion: 2 and 5%; Ointment: 1 and 5%; Paste: 5%; Shampoo: 0.5, 1, 2, 3, 4.3, 5, 9 and 10%; Topical Solution: 2.5, 5 and 20%; Topical Suspension: 7.5, 30 and 33.3%.

Green Soap—RPS-17, page 786.

Green Soap Tincture—RPS-17, page 766.

Methyl Salicylate—page 1295.

Resorcinol—RPS-16, page 1107.

Resorcinol Ointment, Compound—RPS-16, page 1107.

Resorcinol Monoacetate—RPS-16, page 1107.

Storax—page 1326.

Tolu Balsam—page 1299.

Turpentine Oil, Rectified—RPS-16, page 808.

Other Irritants, Rubefacients and Vesicants

Camphor [Bicyclo [2.2.1] heptane-2-one, 1,7,7-trimethyl-, 2-Camphanone; 2-Bornanone [76-22-2] $C_{10}H_{16}O$ (152.24); Gum Camphor; Laurel Camphor]—A ketone obtained from *Cinnamomum camphora* (Linné) Nees et Ebermaier (Fam *Lauraceae*) (Natural Camphor) or produced synthetically (Synthetic Camphor). *Preparation:* Natural crude camphor may be obtained by steam distilling chips of the camphor tree; the crude camphor so obtained is purified, usually by sublimation. One method of producing synthetic camphor starts with *pinene* [$C_{10}H_{16}$], a hydrocarbon obtained from turpentine oil. The pinene is saturated with hydrogen chloride at 0° forming bornyl chloride [$C_{10}H_{17}Cl$]. On heating the bornyl chloride with sodium acetate and glacial acetic acid, it is converted into isobornyl acetate, which is subsequently hydrolyzed to isobornyl alcohol [$C_{10}H_{17}OH$] and oxidized with chromic acid to camphor. Synthetic camphor resembles natural camphor in most of its properties except that it is a racemic mixture and, therefore, lacks optical activity. When camphor is mixed in approximately molecular proportions with chloral hydrate, menthol, phenol or thymol, liquefaction ensues; such mixtures are known as *eutectic mixtures* (see page 176).

Description: Colorless or white crystals, granules or crystalline masses; or as colorless to white, translucent, tough masses; a penetrating, characteristic odor, a pungent, aromatic taste and is readily pulverizable in the presence of a little alcohol, ether or chloroform; specific gravity about 0.99; melts between 174° and 179° and slowly volatilizes at ordinary temperature and in steam. *Solubility:* 1 g in about 800 mL water, 1 mL alcohol, about 0.5 mL chloroform or 1 mL ether; freely soluble in carbon disulfide, solvent hexane or fixed and volatile oils. *Incompatibilities:* Forms a liquid or a soft mass when rubbed with *chloral hydrate, hydroquinone, menthol, phenol, phenyl salicylate, resorcinol, salicylic acid, thymol* or other substances. It is precipitated from its alcoholic solution by the addition of water. It is precipitated from camphor water by the addition of soluble salts.

Uses: Locally, weakly *analgesic*, mildly *analgesic (antipruritic)* and *rubefacient* when rubbed on the skin. The spirit is applied locally to allay itching caused by insect stings. It also is used as a counterirritant in humans for *inflamed joints, sprains* and *rheumatic* and other *inflammatory* conditions such as colds in the throat and chest. Although the patient may feel improved, the inflammation is not affected. However, reflexly induced local vasoconstriction may mediate a mild nasopharyngeal decongestant effect. When taken internally in small amounts it produces a feeling of warmth and comfort in the gastrointestinal tract, and, therefore, formerly was much used as a *carminative*. Systemically, it is a reflexly active *circulatory* and *respiratory stimulant*. However, its use as a stimulant is obsolete. It also possesses a slight *expectorant* action and is included in some cough-suppressant mixtures. Concentrations above 11% are not safe. Toxicity consists of nausea and vomiting, headache, feeling of warmth, confusion, delirium, convulsions, coma or respiratory arrest. Camphor is a pharmaceutical necessity for *Flexible Collodion* and *Camphorated Opium Tincture*. *Dose: Topical*, to the skin, rectum or throat, as a 0.1 to 3% lotion, cream, spray or ointment, or 10% tincture (spirit), no more than 3 to 4 times a day. For topical analgesia, concentrations of 0.1 to 3% are used; for counterirritation, 3 to 11%.

Cantharidin [(3aα,4β,7β,7aα-Hexahydro-3a,7a-dimethyl-4,7-epoxyisobenzofuran-1,3-dione[56-25-7] $C_{10}H_{12}O_4$ (196.21)]—The active principle of *Cantharides*. White platelets soluble 1 g in 40 mL acetone, 65 mL chloroform, 560 mL ether or 150 mL ethyl acetate; soluble in oils. *Uses:* Produces intradermal vesiculation. It is used to remove warts, particularly the periungual type. It is applied under an occlusive bandage. The vesicle eventually breaks, becomes encrusted and falls off in 1 to 2 weeks. *Dose:* Topical, to the wart, as a 0.7% solution.

Capsicum—The dried ripe fruit of *Capsicum frutescens* Linné, *Solanaceae*, which contains less than 1% of capsaicin [(*E*)-*N*-[4-Hydroxy-3-methoxyphenyl)methyl]-8-methyl-6-nonenaamide[404-86-4] $C_{18}H_{27}NO_3$ (305.40), which is the active ingredient. *Uses:* Its active ingredients are mildly irritant, causing erythemia and a feeling of warmth without vesication. Its preparations are used as counterirritants. *Dose:* The equivalent of 0.025 to 0.25% of capsicum applied to the skin no more than 3 or 4 times a day.

Ichthammol [Ammonium Ichthosulfonate; Sulfonated Bitumen; fetid; Ichthymall (*Mallinckrodt*), Ichthyol (*Stiefel*) [8029-68-3]]—It is obtained by the destructive distillation of certain bituminous schists, sulfonating the distillate and neutralizing the product with ammonia.

It yields not less than 2.5% of NH_3 (ammonia) and not less than 10% of total sulfur.

Constituents: It belongs to a class of preparations containing, as essential constituents, salts or compounds of a mixture of acids designated by the group name *sulfoichthyolic acid*, formed by sulfonation of the oil obtained in the destructive distillation of certain bituminous shales. Sulfoichthyolic acid is characterized by a high sulfur content, the sulfur existing largely in the form of sulfonates, sulfones and sulfides. *Description* and *Solubility:* Reddish brown to brownish black, viscous fluid, with a strong, characteristic, empyreumatic odor. Miscible with water, glycerin fixed oils or fats; partially soluble in alcohol or ether. *Incompatibilities:* Becomes granular in the presence of *acids* or under the influence of *heat*. In solution, it is precipitated by acids and *acid salts* as a dark, sticky mass; *alkalies* liberate ammonia; many *metallic salts* cause precipitation. *Uses:* A mildly astringent irritant and local antibacterial agent with moderate emollient and demulcent properties. It is used alone or in combination with other antiseptics for the treatment of skin disorders such as *insect stings and bites, erysipelas, psoria-*

sis and *lupus erythematosus* and to produce healing in *chronic inflammations*. It also is used to treat *inflammation* and *boils* in the external ear canal. Medical opinion is divided as to whether this agent is useful. In higher concentrations, irritation is frequent and rashes may develop. It should be kept away from the eyes and other sensitive surfaces. It has been reported to cause hyperepithelialization, an action that would be counterproductive in the treatment of psoriasis. *Dose: Topical*, to the skin as a 10 or 20% ointment or external ear canal as a 10% ointment.

Juniper Tar [Cade Oil]—The empyreumatic volatile oil obtained from the woody portions of *Juniperus oxycedrus* Linné (Fam *Pinaceae*). Dark brown, clear, thick liquid, having a tarry odor and a faintly aromatic, bitter taste. Very slightly soluble in water; 1 volume dissolves in 9 volumes of alcohol; dissolves in 3 volumes of ether, leaving a slight, flocculent residue; miscible with chloroform. *Uses:* A mildly irritant oil that is employed as a topical antipruritic in several chronic dermatologic disorders, such as *psoriasis, atopic dermatitis, pruritus, eczema* and *seborrhea*. Since it is irritant to the conjunctiva and also may cause chemosis of the cornea, care should be taken to keep it out of the eyes. Systemic absorption may result in renal damage. *Dose: Topical*, as 1 to 5% ointment applied once a day; it also is used as a 4% shampoo or 34% bath.

Menthol [Cyclohexanol, 5-methyl-2-(1-methylethyl)-, *p*-Menthan-3-ol; Peppermint Camphor [1490-04-6] $C_{10}H_{20}O$ (156.27)]—An alcohol obtained from diverse mint oils or prepared synthetically. It may be levorotatory [(−)-Menthol] from natural or synthetic sources, or racemic [(±)-Menthol].

Preparation: It owes its odor chiefly to menthol, which is obtained from it by fractional distillation and allowing the proper fraction to crystallize, or by chromatographic processes. Among numerous methods of synthesis of an optically inactive menthol, the most popular involves the catalytic hydrogenation of thymol (obtained from natural sources or synthesized from *m*-cresol or cresylic acid). The difficulty in the synthesis of (−)-menthol arises from the fact that menthol contains three asymmetric carbon atoms, and there are thus eight stereoisomers, designated as (−)- and (+)-menthol, (−)- and (+)-isomenthol, (−)- and (+)-neomenthol, and (−)- and (+)-neoisomenthol. To obtain a product meeting USP requirements, it is necessary to separate (−)-menthol from its stereoisomers, for which purpose fractional crystallization, distillation under reduced pressure or esterification may be used. The other stereoisomers differ from the official (−)-menthol in physical properties and possibly to some extent in pharmacologic action.

Description: Colorless, hexagonal, usually needle-like crystals, or fused masses, or a crystalline powder, with a pleasant, peppermint-like odor; (−)-menthol melts between 41° and 44°; (±)-menthol congeals at 27° to 28°. *Solubility:* Very soluble in alcohol, chloroform or ether; freely soluble in glacial acetic acid, mineral oil or in fixed and volatile oils; slightly soluble in water. *Identification:* When mixed with about an equal weight of camphor, chloral hydrate, phenol or thymol, it forms a "eutectic" mixture liquefying at room temperature. *Incompatibilities:* Produces a liquid or soft mass when triturated with *camphor, phenol, chloral hydrate, resorcinol, thymol* or numerous other substances. *Labeling:* The label on the container indicates whether it is levorotatory or racemic.

Uses: In low concentrations, selectively stimulates the sensory nerve endings for cold and, hence, causes a sensation of coolness. Some local analgesic effects also accompany this effect. Higher concentrations not only stimulate sensory endings for heat and other pain, but also may cause some irritation. Consequently, there may first be a sensation of coolness, then a slight prickly and burning sensation. The local analgesia and sensation of coolness are employed in the treatment of insect bites and stings, itching (antipruretic effect), minor burns and sunburn, hemorrhoids, toothache, cankers, cold sores and sore throat. The local analgesic effect also is the probable basis of the antitussive use, although the value of the drug as an antitussive remains unproved. Care must be taken to avoid the inhalation of irritant concentrations. The contribution of a placebo effect to some of these effects cannot be discounted. It is incorporated into irritant products used to treat acne vulgaris, dandruff, seborrhea, calluses, corns, warts and athlete's foot and in vaginal preparations to lessen the sense of irritation. Whatever effects the rubbing of menthol-containing ointment on the chest possess to relieve pulmonary congestion in colds and allergy are attributable to counterirritation and placebo effects. It also is contained in counterirritants for the treatment of muscle aches. *Dose: Topical*, to the skin, as a 0.1 to 2% lotion or ointment; to the throat, as a 0.08 to 0.12% lozenge. *Inhalation*, 15 mL of 1% liquid or 10 mL of 2% ointment per quart of water, to be dispensed by steam inhalation.

Peruvian Balsam [Peru Balsam; Balsam of Peru; Indian Balsam; Black Balsam]—Obtained from *Myroxylon pereirae* (Royle) Klotzsch (Fam *Leguminosae*). Contains from 60 to 64% of a volatile oil termed *cinnamein* and from 20 to 28% of *resin*. Cinnamein is a mixture of compounds, among which the following have been identified: the esters *benzyl benzoate, benzyl cinnamate, cinnamyl cinnamate (styracin)* and the alcohol *peruviol* (considered by some to be identical with the sesquiterpene alcohol *nerolidol*, $C_{15}H_{26}O$) as ester, free *cinnamic acid;* about 0.05% of *vanillin;* and a trace of *coumarin*. The resin consists of benzoic and cinnamic acid. *Description* and *Solubility:* Dark brown, viscid liquid; transparent and appears reddish brown in thin layers; agreeable odor resembling vanilla, a bitter, acrid taste, with a persistent after-taste and free from stringiness or stickiness. It does not harden on exposure to air; specific gravity 1.150 to 1.170. Nearly insoluble in water, but soluble in alcohol, chloroform or glacial acetic acid, with not more than an opalescence; partly soluble in ether or solvent hexane. *Uses: A local irritant and vulnerary.* It once was used as a dressing to promote growth of epithelial cells in the treatment of *indolent ulcers, wounds* and certain *skin diseases*, eg, scabies. It presently is an ingredient in suppositories used in the treatment of hemorrhoids and anal pruritus. Allergic reactions to it occasionally occur. Ointments containing both this and sulfur present a problem in compounding, since the resinous part of the balsam tends to separate. This difficulty may be overcome by mixing the balsam with an equal amount of castor oil, prior to incorporating it into the base; or alternatively, by mixing it with solid petroxolin [An ointment vehicle (oxygenated petroleum) consisting of liquid paraffin, oleic acid and ammoniated alcohol]. *Dose: Topical, rectal*, 1.8 to 30 mg in suppositories.

Pine Tar [Pix Pini; Pix Liquida; Tar]—The product obtained by the destructive distillation of the wood of *Pinus palustris* Miller, or of other species of *Pinus* Linné (Fam *Pinaceae*). Usually obtained as a by-product in the manufacture of charcoal or acetic acid from wood. It is a complex mixture of phenolic bodies for the most part insoluble in water. Among these are *cresol, phlorol, guaiacol, pyrocatechol, caeruligual* and *pyrogallol* others. Traces of *phenol* and *cresols* also are present as well as hydrocarbons of the paraffin and benzene series. *Description* and *Solubility:* Very viscid, blackish brown liquid; translucent in thin layers, but becomes granular and opaque with age; has an empyreumatic, terebinthinate odor, a sharp, empyreumatic taste and is more dense than water; solution is acid to litmus. Miscible with alcohol, ether, chloroform, glacial acetic acid or with fixed and volatile oils; slightly soluble in water, the solution being pale yellowish to yellowish brown. *Uses:* Externally as a mild *irritant* and *local antibacterial* agent in chronic *skin diseases*, especially eczema and psoriasis. Its volatile constituents are claimed to be *expectorant* but their efficacy is unproven; its inhalations were formerly used for this purpose. *Dose: Topical*, as a 1.8 to 30% shampoo.

Sclerosing Agents

A number of irritant drugs are of sufficient activity to damage cells but are not so potent as to destroy large numbers of cells at the site of application. Such agents promote fibrosis and are used to strengthen supporting structures, close inguinal rings, etc. The intimal surface of blood vessels may break down under attack by such agents and thus initiate thrombosis, which may be an undesirable side effect. This action is the basis of the use of sclerosing agents in the reduction of varicose veins and hemorrhoids. Sclerosing agents generally are regarded as obsolete. They can be harmful when improperly used and sometimes even when used with caution.

Sclerosing Agents

Morrhuate Sodium Injection—A sterile solution of the sodium salts of the fatty acids of cod liver oil. It contains 50 mg of sodium morrhuate/mL. A suitable antimicrobial agent, not to exceed 0.5%, and ethyl or benzyl alcohol, not to exceed 3%, may be added. *Note: It may show a separation of solid matter on standing. Do not use the material if such solid does not dissolve completely upon warming.* Prepared by heating cod liver oil with alcoholic sodium hydroxide until completely saponified. After dilution with water the alcohol is removed by distillation. Dilute H_2SO_4 is then added to the aqueous solution, and the liberated organic acids are separated or preferably extracted with a suitable immiscible solvent such as ether. Just-sufficient aqueous NaOH then is added to neutralize the acids. About 20 mg of benzyl alcohol/mL of the injection usually is added to lessen the pain of injection. *Uses:* Formerly, widely used as a *sclerosing* and *fibrosing agent* for obliterating *varicose veins*. Irritants of this type once were employed for closure of hernial rings, fibrosing of uncomplicated hemorrhoids, removal of condylomata acuminata and in other conditions where the ultimate objective was production of fibrous tissue. *Dose: Intravenous*, by special injection, 0.5 to 5 mL of a 5% injection to a localized area; *usual*, 1 mL. *Dosage Forms:* 5 and 30 mL.

Sodium Tetradecyl Sulfate [7-Ethyl-2-methyl-4-undecanol hydrogen sulfate sodium salt [139-88-8] $C_{14}H_{29}NaO_4S$ (316.43); STS; Sotradecol Sodium (*Elkins-Sinn*)]—One method of preparation reacts the corresponding alcohol with $ClSO_3H$ and neutralizes the resulting hydrogen sulfate ester with Na_2CO_3. Occurs as a white, waxy, odorless solid. Soluble in water, alcohol or ether. *Uses:* A *sclerosing agent* similar in action to sodium morrhuate. It formerly was used widely as a buffered solution in the *obliteration of varicose veins and internal hemorrhoids*. For such purposes, the solution is injected directly into the vein. Injection outside of the vein may cause sloughing. For this reason, the substance is not used to close inguinal rings. The principal untoward effect is pain immediately upon injection, although brief; mild anaphylactoid and idiosyncratic responses rarely occur. Because the substance is an anionic surface-active agent, it also is used as a wetting agent to promote spreading of certain topical antiseptics. *Dose:* By injection directly into the target vein, as a 1 or 3% solution, depending on the size of the vein. The volume then to be injected at any one site varies from 0.2 to 2.0 mL, depending on the concentration and the number of previous injections at the site, the larger volumes being given only after several previous injections. No more than 10 mL of the 3% solution or 6 mL of the 5% solution should be given at any one time. The interval between injections varies from 5 to 7 days. *Dosage Form:* Injection: 1 and 3% in 2-mL ampuls.

Caustics and Escharotics

Any topical agent that causes destruction of tissues at the site of application is a *caustic* (or corrosive).

Caustics may be used to induce desquamation of cornified epithelium ("keratolytic" action) and, therefore, are used to destroy warts, condylomata, keratoses, certain moles and hyperplastic tissues.

If the agent also precipitates the proteins of the cell and the inflammation exudate, there is formed a scab (or eschar), which later is organized into a scar; such an agent is an *escharotic* (or cauterizant). Most, but not all, caustics are also escharotic. Furthermore, certain caustics, especially the alkalies, redissolve precipitated proteins, partly by hydrolysis, so that no scab or only a soft scab forms; such agents penetrate deeply and generally are unsuitable for therapeutic use. Escharotics sometimes are employed to seal cutaneous and aphthous ulcers, wounds, etc. Since most escharotics are bactericidal, it formerly was thought that chemical cauterization effected sterilization; however, sterilization is not achieved always, especially by those agents which remain bound to the protein precipitate. The growth of certain bacteria even may be favored by the chemically induced necrosis and by the protection of the scab.

Acetic Acid, Glacial—page 1317.
Alum—page 761.
Aluminum Chloride—page 761.
Phenol—page 1323.

Podophyllum

Mandrake; May Apple

The dried rhizome and roots of *Podophyllum peltatum* Linné (Fam *Berberidaceae*); it yields not less than 5% of podophyllum resin.

Constituents—From 3 to 6% of resin along with up to 1% of quercetin and podophyllotoxin and peltatin glucosides. At least 16 different compounds have been isolated and characterized. The aglycone *podophyllotoxin* [$C_{22}H_{22}O_8$] is the lactone of 1-hydroxy-2-(hydroxymethyl) - 6,7 -methylenedioxy -4- (3',4',6'-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid. Hydrolytic rupture of the lactone ring yields *podophyllic acid* [$C_{22}H_{24}O_9$], the 2,3-*trans* form of which is *podophyllinic acid* while the 2,3-*cis* form is *picropodophyllinic acid*.

Although podophyllotoxin has been demonstrated to possess marked caustic, cathartic and toxic properties, it is believed that not it, but an amorphous *resin*, called *podophylloresin*, is the chief cathartic principle of the drug. However, podophyllotoxin is safer and ultimately probably will replace the crude preparations.

Uses and Dose—See *Podophyllum Resin*.

Podophyllum Resin

Uses—Supersedes podophyllum (above). Certain glycosides and polynuclear lactones in the resin interact with tubulin and, thus, interfere with cell cycling and intracellular dynamics such as to cause the eventual death of affected cells. Applied topically, it is corrosive in the region of contact. It mainly is used in the treatment of *condyloma accuminatum* but also of *juvenile papilloma of the larynx*, *multiple superficial epitheliomatoses* (basal cell and squamous cell carcinomas), *precancerous keratoses* (seborrheic, actinic and radiation keratoses), *verrucae fibroids* and *calluses*. Some pain usually occurs at the site of application; if it is excessive, the drug should be removed with ethanol or isopropyl alcohol. Resin on adjacent normal tissues also should be removed. Pain may be avoided somewhat by treating only a small area of surface at any one time. *It especially is irritating to the eyes and mucous membranes*. Treatment of large surfaces also may result in excessive absorption and systemic effects, such as nausea and vomiting, tachycardia, shallow respiration, leukopenia, thrombocytopenia, renal damage, paralytic ileus, lethargy, stupor, psychotic confusional states and peripheral neuropathy, including flaccid paralysis. Systemic absorption is enhanced by occlusion. The drug is contraindicated in pregnancy and lactation.

Dose—*Topical, adults* and *children*, to the *skin*, *condyloma accuminata*, as a 25% solution, the resin to remain in place for 6 hr; application may be repeated weekly for up to 4 weeks, if necessary; *superficial epitheliomatoses* and *precancerous keratoses*, as a 25% solution once a day, to be continued until several days after a slough has occurred; *to laryngeal lesions*, *juvenile laryngeal papilloma*, as a 12.5% solution to the papilloma, initially once a day, but progressively longer intervals may be elected as the lesions shrink (medical authorities hold that short intervals are more effective); the 12.5% solution is to be extemporized by diluting the 25% solution in 95% ethanol.

Dosage Form—Topical Solution: 25%.

Salicylic Acid—page 768.
Silver Nitrate—page 766.

Silver Nitrate

Nitric acid silver(1+) salt; Argenti Nitras

Silver(1+) nitrate [7761-88-8] $AgNO_3$ (169.87).

Preparation—By the action of nitric acid on metallic silver.

Description—Colorless or white crystals; on exposure to light in the presence of organic matter, it becomes gray or grayish black; pH of solutions about 5.5.

Solubility—1 g in 0.4 mL water, 30 mL alcohol, about 250 mL acetone, slightly more than 0.1 mL boiling water or about 6.5 mL of boiling alcohol; slightly soluble in ether.

Incompatibilities—Easily reduced to metallic silver by most *reducing agents*, including *ferrous salts*, *arsenites*, *hypophosphites*, *tartrates*, *sugars*, *tannins*, *volatile oils* and other *organic substances*. In neutral or alkaline solutions, precipitated by *chlorides*, *bromides*, *iodides*, *borax*, *hydroxides*, *carbonates*, *phosphates*, *sulfates*, *arsenites* and *arsenates*. *Potassium permanganate*, *tannic acid* and *soluble citrates and sulfates* may cause a precipitate if sufficiently concentrated. In acid solution, only the *chloride*, *bromide* and *iodide* are insoluble. *Ammonia water* dissolves many of the insoluble silver salts through formation of the silver diammine complex, $Ag(NH_3)_2^+$.

Uses—Silver ions combine with proteins and cause denaturation and precipitation. As a result, silver ions have astringent, caustic, bactericidal and antiviral properties. In low concentrations, silver-denatured protein is confined to the interstitial spaces and the surface of denuded, weeping areas, so that only astringent and antimicrobial effects occur; with higher concentrations, cell membranes are disrupted, so that caustic effects result. The corroded site will become covered with a scab of silver protein precipitate.

It is used mainly in podiatry as a caustic to *destroy excessive granulation tissue*, such as *corns*, *calluses*, *granuloma pyogenicum* and *plantar warts*, to *reduce neurovascular helomas*, *remove papillomas* and *cauterize small nerve endings* and *blood vessels*. As an astringent, it is used to treat *impetigo vulgaris* and *pruritis* as well as *indolent ulcers*, *wounds* and *fissures*. It also is used as a *styptic*, especially in dentistry.

As an antiseptic, it mainly is employed prophylactically against *ophthalmia neonatorum*. It formerly was applied regularly to

burned surfaces because of its high efficacy against both staphylococci and pseudomonas. However, the precipitation of AgCl at the site of application and in dressing depletes plasma chloride and can cause serious electrolyte disturbances; consequently, the drug seldom is used in burn therapy today. Refer to RPS-17, page 1165, for a discussion of its prior uses as an antiseptic.

Excessive corrosion at the target site and corrosion from inadvertent application or leakage away from the intended site can occur. Dental cones or pieces of toughened silver nitrate that are accidentally ingested can cause death. Elemental silver from the bioreduction of silver ion may reside permanently at the site of application and cause a bluish-to-black discoloration called argyria. Locally injected sodium thiosulfate sometimes can remove the silver. Nitrate ion absorbed from large, denuded surfaces can cause methemoglobinemia. Only concentrations 0.5% or below should be applied to raw wounds, fresh cuts or broken skin.

Dose—*Topical, antiseptic*, to the *conjunctiva*, 0.1 mL of a 1% solution; to the *burned skin* or *open lesion* (neither advised), 0.1 to 0.5% solution as a wet dressing. *Astringent*, to the *affected skin*, as a 10% solution for *impetigo vulgaris* and as a 10 or 25% solution for *pruritis*. *Caustic*, to the *lesion* only, as a 10% solution or ointment for *helomas* and to *cauterize small nerve endings* and *blood vessels*, as a 25 or 50% solution for *plantar warts* and as a 50% solution for *granulation tissue, granuloma pyogenica* and *papillomatous growths*.

Dosage Forms—Ointment: 10%; Topical Solution: 10, 25 and 50%. For *Toughened Silver Nitrate*, see RPS-17, page 784.

Other Caustics and Escharotics

Dichloroacetic Acid [Dichloroacetic acid $C_2H_2Cl_2O_2$ (128.95)]—Pungent liquid miscible with water, alcohol or ether. *Uses:* See *Trichloroacetic Acid*.

Nitric Acid—Contains 67–71% HNO_3. A fuming liquid, very caustic, with a characteristic, highly irritating odor; boils at 120°; specific gravity about 1.41. Miscible with water. *Uses:* As a cauterizing agent for the immediate sterilization of dangerously infected wounds, such as the bite from a rabid animal; it does not penetrate too deeply and forms a firm eschar.

Podophyllotoxin—[(5*R*,5a*R*,9*R*)-5,5a,6,8,8a,9-Hexahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6-one [518-28-5] $C_{22}H_{22}O_8$ (414.41)]—Found in the rhizomes of several species of plants, principally *Podophyllum peltatum* L. *Berberidaceae, P emodi* and *Juniperus virginiana* L, *Coniferae*. For the synthesis see *JACS 103:* 6208, 1981. Occurs as hydrated crystals; melts about 115° (dec) and about 184° after drying; a number of polymorphic forms exist. Very slightly soluble in water; soluble in alcohol, chloroform or acetone. *Uses:* Actions, uses and adverse effects are those of *Podophyllum Resin* (page 766), except that the therapeutic index is greater. It is several times more potent. It is an investigational drug. *Dose: Topical*, to the *skin, adults* and *children*, as a 0.5 to 1% solution twice a day for 3 days.

Potassium Hydroxide [Potassium hydroxide; Caustic Potash; Lye; Potash Lye [1310-58-3] contains not less than 85.0% of total alkali, calculated as KOH (56.11), including not more than 3.5% of K_2CO_3 (138.21)] *Caution—Exercise great care in handling, as it rapidly destroys tissues. Do not handle it with bare hands.* Prepared by electrolysis of a solution of potassium chloride in a diaphragm cell that does not allow liberated chlorine to react with it. It is prepared in the form of sticks, pellets, flakes or fused masses. Sticks or pellets are made by evaporating a solution of it to a fluid of oily consistency and then pouring the hot liquid into suitable molds in which it solidifies. *Description* and *Solubility:* White, or nearly white, fused masses, small pellets, flakes, sticks, and other forms; hard and brittle and shows a crystalline fracture; exposed to air it rapidly absorbs carbon dioxide and moisture, and deliquesces; melts at about 360–380°; when dissolved in water or alcohol, or when its solution is treated with an acid, much heat is generated; solutions, even when highly diluted, are strongly alkaline. 1 g dissolves in 1 mL water, 3 mL alcohol or 2.5 mL glycerin at 25°; very soluble in boiling alcohol. *Incompatibilities:* Bases react with *acids* to form salts, liberate alkaloids from aqueous solutions of *alkaloidal salts*, and promote various hydrolysis reactions such as the decomposition of *chloral hydrate* into chloroform and a formate or the breakdown of *salol* into phenol and a salicylate. Only the alkali hydroxides are appreciably soluble in water. Nearly all common *metals* will be precipitated as hydroxides when solutions of their salts are added to solutions of the alkali hydroxides. Certain hydroxides, however, notably those of aluminum, zinc, arsenic or lead, will dissolve in excess of sodium or potassium hydroxide. *Uses:* A *caustic*, principally in veterinary practice. The end of a stick of potassium hydroxide may be inserted into a section of rubber tubing, or wrapped several times with tin foil, to avoid cauterizing the fingers of the operator. It is used also as a *pharmaceutical necessity* in several pharmacopoeial preparations.

Trichloroacetic Acid [Acetic acid, trichloro-, Trichloroacetic acid [76-03-9] $C_2HCl_3O_2$ (163.39)]—Usually made by oxidizing chloral hydrate with fuming nitric acid. Colorless, deliquescent crystals having a slight, characteristic odor; melts at about 58° and boils at 196°–197°. *Solubility:* 1 g in about 0.1 mL water; soluble in alcohol or ether. *Uses:* Precipitates proteins and used as a *caustic* on the skin or mucous membranes to destroy local lesions and for treatment of various dermatologic diseases. Its chief use is to destroy ordinary warts and juvenile flat warts. It is employed extensively as a precipitant of protein in the chemical analysis of body fluids and tissue extracts, as well as a decalcifier and fixative in microscopy. *Caution—Trichloroacetic Acid is highly corrosive to the skin. Dose: Topical*, to the skin, as a 15 to 100% *w/v* solution, carefully applied with a cotton-tipped applicator or glass rod. Concentrations above 50% are not recommended.

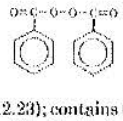
Zinc Chloride—page 763.

Keratolytics (Desquamating Agents)

The epidermis consists of layers of flat cells, called *stratified squamous epithelial cells*. They are bound together by desmosomes and penetrating tonofibrils, both of which largely consist of keratin. The outer layer of the epidermis, the cornified epithelium or stratum corneum, is made up of the collapsed ghosts of the squamous cells and, as such, is principally a tight network of keratin and lipoprotein. Certain fungi, especially the dermatophytes, utilize keratin and, therefore, reside in the stratum corneum in those places where the degree of hydration and the pH are sufficiently high. One way such mycoses may be suppressed is that of removal of the stratum corneum, a process that is called *desquamation*. Certain chemical substances, especially among phenols and sulfhydryl compounds, loosen the keratin and, thus, facilitate desquamation. These substances are called *keratolytics*. Aqueous maceration of the stratum corneum also favors desquamation. In addition to the treatment of epidermophytosis, keratolytics are used to thin hyperkeratotic areas. Most keratolytics are irritant. Irritants also can cause desquamation by causing damage to and swelling of the basal cells.

Benzoyl Peroxide

(Various Mfrs)



[94-36-0] $C_{14}H_{10}O_4$ (242.23); contains 65–82% of benzoyl peroxide; also contains about 26% of water for the purpose of reducing flammability and shock sensitivity.

Preparation—Benzoyl chloride is reacted with a cold solution of sodium peroxide.

Description—White, granular powder, having a characteristic odor; melts about 104°; *may explode with heat*.

Solubility—Sparingly soluble in water or alcohol; soluble in acetone, chloroform or ether.

Caution (For the drug entity—not the dosage forms)—It may explode at temperatures higher than 60° or cause fires in the presence of reducing substances. Store it in the original container, treated to reduce static charges. Do not transfer it to metal or glass containers fitted with friction tops. Do not return unused material to its original container, but destroy it by treatment with NaOH solution (1 in 10) until addition of a crystal of KI results in no release of free iodine.

Uses—Possesses mild antibacterial properties, especially against anaerobic bacteria. It is also mildly irritant, and it exerts moderate keratolytic and antiseborrheic actions. Its principal use is in the treatment of mild *acne vulgaris* (in which it is comedolytic) and *acne rosaceae*, but it also is used in the treatment of decubital and stasis ulcers.

It causes stinging or burning sensations for a brief time after application; with continued use these effects mostly disappear. After 1 or 2 weeks of use there may be a sudden excess dryness of the

skin and peeling. The drug must be kept away from the eyes, and from inflamed, denuded or highly sensitive skin, such as the circumoral areas, neck and skin of children. It should not be used in conjunction with harsh abrasive skin cleansers. It can cause contact dermatitis. It can bleach hair and fabrics.

Dose—*Topical*, to the *skin*, *adults* and *children 12 yr or older*, as a 5 or 10% cleansing bar 2 or 3 times a day, 5 to 10% cream or gel 1 or 2 times a day, 5 to 20% lotion 1 to 4 times a day, 5 or 10% cleansing lotion 1 or 2 times a day, 5% facial mask once a day, 10% soap 1 or 2 times a day or 10% stick 1 to 3 times a day. The 20% lotion is used only for the treatment of decubital and stasis ulcers.

Dosage Forms—Cleansing Bar: 5 and 10%; Cream: 5, 7 and 10%; Gel: 2.5, 5 and 10%; Lotion: 5, 5.5, 10 and 20%; Cleansing Lotion: 5 and 10%; Facial Mask: 5%; Stick: 10%.

Fluorouracil—page 1151.

Resorcinol—RPS-16, page 1107.

Resorcinol Ointment, Compound—RPS-16, page 1107.

Salicylic Acid

Benzoic acid, 2-hydroxy-, *o*-Hydroxybenzoic Acid

Salicylic acid [69-72-7] $C_7H_6O_3$ (138.12).

Preparation—Mostly by the Kolbe-Schmidt process in which CO_2 is reacted with sodium phenolate under pressure at about 130° to form sodium salicylate, followed by treatment with mineral acid.

Description—White, fine, needle-like crystals or as a fluffy, white, crystalline powder; the synthetic acid is white and odorless; sweetish, afterward acrid, taste; stable in the air; melts between 158° and 161°.

Solubility—1 g in 460 mL water, 3 mL alcohol, 45 mL chloroform, 3 mL ether, 135 mL benzene or about 15 mL boiling water.

Uses—Used *externally* on the skin, where it exerts a slight *antiseptic* action and considerable *keratolytic* action. The latter property makes it a beneficial agent in the local treatment of certain forms of *eczematoid dermatitis*. It also is included in products for the treatment of *psoriasis*, for which the FDA classification is Category I. Tissue cells swell, soften and ultimately desquamate. Salicylic Acid Plaster often is used for this purpose. The drug is especially useful in the treatment of *tinea pedis* (athlete's foot) and *tinea capitis* (ringworm of the scalp), since the fungus grows and thrives in the stratum corneum. Keratolysis both removes the infected horny layer and aids in penetration by antifungal drugs. It is combined with benzoic acid in an ointment long known as Whitfield's Ointment. It also is combined commonly with zinc oxide, sulfur or sulfur and coal tar. It is incorporated into mixtures for the treatment of acne, dandruff and seborrhea, insect bites and stings and into soaps and vaginal douches, but efficacy remains to be established. In high concentrations it is *caustic* and may be used to remove *corns*, *calluses*, *warts* and other growths.

Collodions or solutions of 17% or higher and other forms above 25% concentration should not be employed if the patient has diabetes mellitus, peripheral vascular disease or inflammation or infection at the intended site of application. Continuous application of the drug to the skin can cause dermatitis. Systemic toxicity resulting from application to large areas of the skin has been reported. It is not employed internally as an analgesic because of its local irritating effect on the gastrointestinal tract.

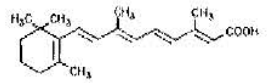
Dose—*Topical*, to the *skin*, *keratolytic*, as a 16.7 or 17% collodion once a day, 2.5 to 10% cream under occlusion once every 3 to 5 days, 2% foam once or twice a day, 5 or 6% gel under occlusion once a day, 1.8% lotion once or twice a day, 3 to 10% ointment once a day, 2 or 4% shampoo once or twice a week, 3.5% soap once a day or 17% solution once a day; *antipsoriatic*, as a 5 or 6% gel under occlusion or 3 to 10% ointment once a day; *antiseborrheic*, as a 1.8% lotion, 3 to 10% ointment or 2 or 4% shampoo once a day; *antiacne*, as a 2% foam once or twice a day, 5 or 6% gel under occlusion once a day, 3 to 6% ointment once a day or 3.5% soap once a day; *caustic*, as a 25% cream once every 3 to 5 days, 25 to 60% ointment under occlusion every 3 to 5 days, or 40% plaster once a day.

Dosage Forms—Flexible Collodion: 16.7 and 17%; Cream: 2.5, 10 and 25%; Gel: 5 and 6%; Lotion: 1.8%; Ointment: 25, 40 and 60% (3 to 10% ointments must be extemporized); Plaster: 40%; Shampoo: 2 and 4%; Soap: 3.5%; Topical Solution: 17%.

Sulfur, Precipitated—page 1247.

Tretinoin

Retinoic acid; Retin-A (*Ortho*)



all *trans*-Retinoic acid [302-79-4] $C_{20}H_{28}O_2$ (300.44).

Preparation—By oxidation of vitamin A aldehyde which may be obtained by oxidation of vitamin A. *Biochem J 90*: 569, 1964.

Description—Yellow to light-orange crystals or crystalline powder with the odor of ensilage; should be stored in cold and protected from light and air; melts between 176 and 181°.

Solubility—Insoluble in water; slightly soluble in alcohol; slightly soluble in chloroform; 1 g in 10 mL boiling benzene.

Uses—It is retinoic acid, or so-called *vitamin A acid*, which is formed when the aldehyde group of retinene (retinal) is oxidized to a carboxyl group. It is not known whether retinoic acid has a physiologic function, but some authorities consider it to be the form of vitamin A that acts in the skin. This view is supported by the fact that retinol and retinal have very little action on the skin but large systemic doses of vitamin A evoke prominent dermatologic changes.

Topically, it causes inflammation, thickening of the epidermis (acanthosis) and local intercellular edema, which leads to some separation of the epidermal cells. Follicular epithelial cells become less adhesive, the stratum corneum loosens and exfoliation may occur. High concentrations can cause vesiculation. These actions are used in the treatment of *acne vulgaris*. The loosened horny layer makes it easier for the comedo to rise up and discharge, and the inflammatory response mobilizes white cells which attack the bacteria in the follicle. In the early stages of treatment, the sudden surfacing of obscured preexisting comedones makes it appear that the acne has been exacerbated, but the new comedones do not coalesce into cysts or nodules and scarring does not occur. The exaggerated stage may last for as long as 6 weeks, after which improvement comes rapidly. Shortly after discontinuation of treatment, relapses readily occur. Deep cystic nodular acne (acne conglobata) or severe cases usually are not improved by the drug.

Various hyperkeratotic conditions are reported to respond to it, responses being sometimes exceptionally dramatic. *Solar* and *follicular keratosis*, *lamellar ichthyosis*, *keratosis palmaris* and *plantaris* and other hyperplastic dermatoses have been treated successfully with the drug. It also has been used in the treatment of some skin cancers. Recent reports indicate that it may somewhat rejuvenate sun-aged skin.

It is an antioxidant and free-radical scavenger. There is some evidence not only that topical applications may provide some protection from actinic and other radiation effects on the skin, including cancer, but that internally it may be protective against carcinogenesis from radiation and carcinogens. Systemically, it does not cause the toxic effects of large doses of vitamin A.

In concentrations of 0.05 to 0.1%, it causes a transient feeling of warmth or mild stinging, and erythema follows. Peeling of the skin may occur. Irritation and peeling are marked more when the concentration exceeds 0.1%. When peeling, crusting or blistering occurs, medication should be withheld until the skin recovers, or the concentration should be reduced. The drug should not be applied around the eyes, nose or angles of the mouth, because the mucosae are much more sensitive than the skin to the irritant effects. It also may cause severe irritation on eczematous skin. It should not be applied along with, or closely following, other irritants or keratolytic drugs. Exposure to sunlight should be avoided if possible. Both hypo- and hyperpigmentation have been reported, but the conditions appear to be reversible and temporary.

Dose—*Topical*, *usual*, to the skin, 0.01 to 0.1% once a day at bedtime.

Dosage Forms—Cream: 0.05 and 0.1%; Gel: 0.01 and 0.025%; Topical Solution: 0.05%.

Trichloroacetic Acid—page 767.

Urea—page 931.

Cleansing Preparations

The skin may be cleansed with detergents, solvents or abrasives, singly or in combination. Among the detergents, the soaps have enjoyed the greatest official status, more through custom than through special merit. The nonsoap detergents became important, not only as household hand cleansers, but also in dermatologic and surgical practice as well. However, because many nonsoap detergents do not decompose in sewage disposal plants, there has been a return to real soap. Some of the antiseptic "soaps" still contain synthetic detergents. Soap interferes with the action of many antiseptics, which is one reason synthetic detergents often are used in antiseptic cleansing preparations. However, synthetic detergents also interact with some antiseptics. Anionic nonsoap skin detergents rarely sensitize the skin and, thus, are prescribed when the user is allergic to soap.

Ordinary soaps tend to be alkaline, with pH ranging from 9.5 to 10.5. Superfatted soaps have a pH in the lower end of the range. Synthetic detergents usually have a pH of 7.5 or less. Neutral toilet bars contain synthetic detergents.

Shampoos are liquid soaps or detergents used to clean the hair and scalp. Both soaps and shampoos often are used as vehicles for dermatologic agents.

Many bar soaps contain either triclosan or triclocarban as antiseptics in concentrations which suppress bacterial production of body odors but which effectively are not antiseptic. A number of soaps and shampoos contain keratolytic and antiacne ingredients. Abrasive soaps contain particles of alumina, polyethylene or sodium tetraborate decahydrate.

It commonly, but erroneously, is believed that soap has an antiseptic action. The promotion of either soap or synthetic detergents alone for the control of acne is unwarranted; antiseptic substances must be added to the cleansing material or be used separately. Quantitative studies of the cutaneous flora before and after cleansing with soap or with other anionic detergents show a negligible antiseptic effect. However, the removal of loose epidermis lessens the likelihood that cutaneous bacteria will be transferred from the skin to other structures. Certain cationic detergents employed in dermatology are antiseptic. Detergents are treated under *Surface-Active Agents* (page 267).

The choice of organic solvents to cleanse the skin depends largely upon the nature of the material to be removed. In medical practice ethanol and isopropyl alcohol are the most frequently employed organic solvents. Cleansing creams act both as solvents and as detergents. Other soapless cleansers variously contain petrolatum, vegetable oils, lanolin, high-molecular-weight alcohols, various carbohydrate derivatives, oatmeal and other ingredients.

Alcohol—page 1314.
Alcohol, Rubbing—page 1164.
Benzalkonium Chloride—page 1164.
Green Soap—RPS-17, page 786.
Hexachlorophene Cleansing Emulsion—page 1166.
Isopropyl Rubbing Alcohol—page 1167.
Sodium Lauryl Sulfate—page 1307.

Miscellaneous Dermatologics

Gargles, nasal washes, douches, enemata, etc generally contain as basic ingredients substances described under other categories in this chapter. These preparations are described under *Aqueous Solutions*, page 1521.

Antiphlogistics include alcohol and several creams and lotions that cool the skin by evaporation. Many antiphlogistic preparations also contain an astringent and a local anesthetic or camphor or menthol.

Commonly employed *antipruritics* also depend largely upon local anesthetics and the soothing effect of cooling, although emollients or demulcents may be included, especially depending upon the etiology of the pruritus. The antipruritic properties of phenol preparations largely derive from superficial local anesthesia.

Vulnerary and *epithelizing* properties are attributed to numerous irritants and to several dyes; however, few reliable data exist to support most claims to vulnerary action.

Sunscreens contain aromatic compounds, like aminobenzoic acid, which efficiently absorb the harmful ultraviolet (UV) rays from the incident sunlight and transmit mainly the less harmful wavelengths, or titanium dioxide, which reflects sunlight from the surface of application. UV light in the spectral range of 290–320 nm causes suntan and sunburn; therefore, a sunscreen to prevent tan or burn should have a high molar absorptivity in this range. However, *photosensitization* (ie, the photoactivation of chemicals to make them toxic or allergenic) may occur with wavelengths as high as 500 nm; consequently, to protect recipients of certain drugs (tetracyclines, sulfonamides, erythromycin, promazine, chlorpromazine, promethazine, psoralens), sunscreens with a broader absorption spectrum are required. An adequate broad spectrum is usually achieved with combinations of sunscreens (eg, dioxybenzone and oxybenzone).

Melanizers are substances that promote the pigmentation of the skin. Most melanizers produce their effect by sensitizing the skin to UV light,* so that the effect is principally the same as if the subject had been exposed for a long time to the sun.

Skin bleaches, or *demelanizers*, mostly contain hydroquinone derivatives.

Hair bleaches generally contain peroxides.

There is a large variety of *depilatories* on the market. Many of them are sulfhydryl compounds, especially thioglycollates, which reduce the disulfide bonds of keratin, thus softening the hair to the point where it can be separated easily from the epidermis. Some of the same compounds are used in lower concentrations in hairwaving preparations. There is one drug, minoxidil, an antihypertensive drug, which can *increase hair growth* and *treat baldness*. Diazoxide probably will prove to have similar activity.

Antiperspirants have been included among the astringents.

Aminobenzoic Acid

Benzoic acid, 4-amino-, PABA

p-Aminobenzoic acid [150-13-0] $C_7H_7NO_2$ (137.14).

Preparation—*p*-Nitrotoluene is oxidized with permanganate to *p*-nitrobenzoic acid, and the nitro group is then reduced to amino with iron and hydrochloric acid.

Description—White or slightly yellow, odorless crystals or crystalline powder; melts between 186° and 189°; discolors on exposure to air or light.

* This action is termed a *photodynamic action*. The term has been used loosely to include all instances of enhanced sensitivity to light, but in strict definition it is confined to photosensitization in which the participation of oxygen is required. In the photodynamic process, light of wavelengths too long to be ordinarily effective may be used, so that the activating spectrum may be shifted toward longer wavelengths.

Solubility—Slightly soluble in water or chloroform; freely soluble in alcohol or solutions of alkali hydroxides and carbonates; sparingly soluble in ether.

Uses—A *sunscreen*. It absorbs UV light of wavelengths in the region of 260 to 313 nm; its molar absorptivity at 288.5 nm is 18,300. However, it does not absorb throughout the near UV range, so that drug-related photosensitivity and phototoxicity may not be prevented by it, but in combination with benzophenone it does protect against some drug-induced phototoxicities. Nevertheless, in the 260–313 nm range, it has the highest protection index of current sunscreen agents.

For animal species that do not use preformed folic acid, which contains the *p*-aminobenzoyl moiety, it is a B-vitamin. However, man does not use it, and its promotion in vitamin preparations preys on the ignorance of the consumer. It or its potassium salt is promoted as an agent that softens or regresses fibrotic tissue in Peyronie's disease, scleroderma, dermatomyositis, morphea and pemphigus. The claims for the antifibrotic actions are substantiated poorly, and the actions and uses are not mentioned in major works on pharmacology and therapeutics.

Topically, it is rarely allergenic to recipients but phototoxicity and photoallergenicity occur. Systemic side effects include nausea, anorexia, fever and rash.

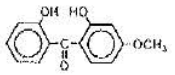
Dose—*Topical*, as a sunscreen, 4 to 15% in solutions, lotions, creams and lipsticks. *Oral, adults*, 12 g a day in 4 to 6 divided doses; *children*, 1 g/10 lb a day in divided doses, to be diluted and taken with food.

Dosage Forms—Capsules: 500 mg; Cream: 4% (may also contain sodium PABA); Gel: 5%; Lotion: 5%; Powder: 2, 100 and 453 g; Solution: 5%; Stick: 5% (may contain red petrolatum); Tablets: 30, 100 and 500 mg.

Cetyl Alcohol—page 1312.

Dioxybenzone

Methanone, (2-hydroxy-4-methoxyphenyl)(2-hydroxyphenyl)-, Spectra-Sorb UV 24 (*American Cyanamid*); Solaquin (*Elder*)



2,2′-Dihydroxy-4-methoxybenzophenone [131-53-3] $C_{14}H_{12}O_4$ (244.25).

Preparation—By a Friedel-Crafts reaction in which *o*-methoxybenzoyl chloride is added gradually to a mixture of 1,3-dimethoxybenzene, chlorobenzene and aluminum chloride. The reaction conditions are such that both methoxy groups ortho to the carbonyl bridge in the initial condensation product are demethylated. US Pat 2,853,521.

Description—Off-white to yellow powder; congeals not lower than 68°.

Solubility—Practically insoluble in water; freely soluble in alcohol or toluene.

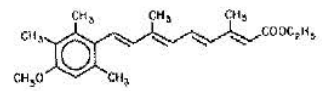
Uses—A *sunscreen* of intermediate molar absorptivity (11,950 at 282 nm), but it absorbs throughout the UV spectrum and, hence, affords protection not only against sunburn but also against the photodynamic, photosensitizing and phototoxic effects of drugs. At present, it is marketed in combination with the closely related *Oxybenzone* (page 771).

Dose—*Topical*, as a 3% lotion.

Dosage Forms—Dioxybenzone and Oxybenzone Cream: 3% of each ingredient.

Etretinate

2,4,6,8-Nonatetraenoic acid, 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-, ethyl ester (*all-E*); Tegison (*Roche*)



[54350-48-0] $C_{23}H_{30}O_3$ (354.49).

Preparation—One scheme involves the Wittig condensation of diphenyl 2,3,6-trimethyl-4-methoxybenzylphosphonium chloride and 8-oxo-3,7-dimethyl-2,4,6-octane-trienoic acid (*all-trans*) in the presence of butylene oxide; *Experientia 34*: 1113, 1978.

Description—Crystalline solid melting about 104°.

Uses—Although not a topical drug, it is a retinoid closely related to tretinoin and is used only for its dermatologic actions; consequently, it is included in this chapter. It is used in the treatment of recalcitrant *psoriasis*, especially the severe pustular erythrodermic type. It decreases scaling, erythema and the thickness of lesions and causes epithelial and dermal cells to redifferentiate to normal cells. Sometimes, dramatic improvement occurs within 2 weeks and complete clearing in 1.5 to 4.5 mo. However, relapses are frequent once treatment is discontinued and sometimes even during chronic maintenance. It can be used alone or in low-dose combination with PUVA therapy. The mechanism of action is unknown, but it is undoubtedly like that of vitamin A. Activity resides in the acid metabolite.

Adverse effects occur in more than 75% of recipients. They include chapped lips, peeling of the palms, soles and fingertips, dryness of the mucous membranes, sore tongue, cheilitis, rhinorrhea, nosebleed, gingival bleeding, loss of hair, nail abnormalities, dry and irritated cornea, sclera and conjunctiva (50%), epidermal fragility, easy sunburning and other effects. Occasionally, pseudotumor cerebri, metastatic calcification of ligaments and tendons, and liver dysfunction or necrosis occur. In children and adolescents there may be premature closure of the epiphyses. Plasma cholesterol and triglycerides rise and high-density lipoprotein decreases. The drug is also teratogenic. Adverse effects are less with the low doses used with PUVA.

Absorption after oral administration is incomplete. It is increased by whole milk and other lipid-containing foods. There is a rapid metabolism during which it is deesterified to the acid metabolite. A much slower degradation and conjugation follows, the metabolites being secreted into bile and urine. Nearly all of the circulating drug is bound to plasma lipoproteins, but the active metabolite is bound to albumin. Ultimately, it is taken up into fat, where it may be found even as long as 2 yr after the last dose. The apparent elimination half-life is about 120 days. This persistence of drug in the body militates against the use of the drug in fertile women of child-bearing age, since the incidence of congenital defects is high even when conception occurs months after the drug is discontinued. The drug also is excreted into milk; effects in the nursing infant are not known.

Dose—*Oral, adult, initially* 0.25 to 1.5 mg/kg a day in divided doses, the dose depending upon the type and seriousness of the disorder; with erythrodermic psoriasis, the initial dose is 0.25 mg/kg a day, increased weekly with increments of 0.25 mg/kg a day until a response occurs; *maintenance*, 0.5 to 0.75 mg/kg a day. Maintenance usually is not begun until after 8 to 16 weeks of treatment. The above doses are higher than those used concurrently with PUVA treatment.

Dosage Form—Capsules: 10 and 25 mg.

Hydrogen Peroxide Solution—page 1171.

Hydroquinone

1,4-Benzenediol; *p*-Dihydroxybenzene; Hydroquinol; Quinol; Eldoquin and Eldopaque (*Elder*)

Hydroquinone [123-31-9] $C_6H_6O_2$ (110.11).

Preparation—Various processes are employed. One involves reacting a sulfuric acid solution of aniline with manganese dioxide and reducing the resulting *p*-benzoquinone with sodium bisulfite.

Description—Fine, white needles; darkens on exposure to air; melts between 172 and 174°.

Solubility—1 g in about 17 mL water, 4 mL alcohol, 51 mL chloroform or 16.5 mL ether.

Uses—A *hypopigmenting* agent employed percutaneously to lighten localized areas of hyperpigmented skin, such as skin blem-

ishes, lentigo, melasma, chloasma, freckles, etc. Its action is temporary, so that it is necessary to repeat the application at frequent intervals. It is a mild irritant, and erythema or rash may develop, which requires discontinuation of the drug. It should not be used near the eyes or in open cuts. It is contraindicated in the presence of sunburn, miliaria or irritated skin. It is not to be used in children.

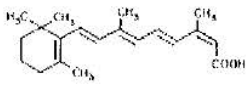
Dose—*Topical*, to the skin, *adults* and *children over 12 yr* as a 2 to 4% cream, gel, lotion or ointment to the affected area once or twice a day.

Dosage Forms—Cream: 2 and 4%; Gel: 4%; Lotion: 2%; Ointment: 2 and 4%.

Hydroxyurea—page 1158.

Isotretinoin

13-*cis*-Retinoic Acid; Accutane (*Roche*)



3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-*cis*-4-*trans*-6-*trans*-8-*trans*-nonatetraenoic acid [4759-48-2] $C_{20}H_{28}O_2$ (300.44). Differs from tretinoin (vitamin A) only in the configuration of the unsaturation at the α and β carbon atoms, which is *cis* rather than *trans*.

Uses—Although not a topical drug, it is a dermatologic agent and, hence, is described here. Its primary action is to decrease the production of sebum, which lends itself to the treatment of severe *nodular* and *cystic acne* (acne conglobata). The size of the sebaceous gland is decreased and there is a change in the morphology and secretory capacity of the cells (dedifferentiation). Complete clearing of lesions is seen in about 90% of cases. A single course of treatment usually brings about long-lasting, sometimes permanent, remissions.

It also appears to diminish hyperkeratosis and has been reported to be effective in *rosacea*, gram-negative *folliculitis*, *lamellar ichthyosis*, *Darier's disease*, *pityriasis rubra pilaris* and *keratocanthoma*.

Adverse effects include facial dermatitis, fragile skin, thinning and drying of the hair, reversible cheilitis and dry skin, mouth, eyes and conjunctivitis in 25 to 80% of recipients. Peeling of the palms and soles and sensitivity to sunburn occur in about 5% of users. Urethral inflammation also occurs frequently. Joint pains and exacerbation of rheumatoid arthritis also has been reported to occur in about 16% of patients. Sedimentation rate, serum triglyceride concentration and serum levels of alanine and aspartate transaminases transiently occur in about 25% of users. In spite of the relatively high incidence of side effects, treatment rarely has to be discontinued.

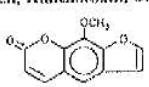
After oral administration, peak blood concentrations occur within 1 to 4 hr. The compound is oxidized to 4-hydroxy-13-*cis*-retinoic acid, which is then glucuronidated and is secreted into the bile. The elimination half-life is 11 to 39 (mean 20) hr. Isotretinoin should not be given during pregnancy or nursing.

Dose—*Oral*, *adult*, for *acne*, 1 to 2 mg/kg a day in 2 divided doses for 15 to 20 weeks. If the cyst count has not been reduced by more than 70%, a second course of treatment may be given after a wait of 2 months. Persons over 70 kg or who have severe chest and back involvement usually require doses at the high end of the range. For *severe rosacea* or gram-negative *folliculitis*, 0.25 to 0.5 mg/kg twice a day. For *hyperkeratoses*, up to 4 mg/kg.

Dosage Forms—Capsules: 10, 20 and 40 mg.

Methoxsalen

7*H*-Furo [3,2-*g*][1]benzopyran-7-one, 9-methoxy-, Ammoidin; 9-Methoxypsoralen; Xanthotoxin; Oxsoralen (*Elder*)



[298-81-7] $C_{12}H_8O_4$ (216.19).

Preparation—Occurs naturally in *Psorales coryfolia*, *Ammi majus*, *Ruta chalepensis* and various other plants. It may be synthesized by methods described in *JACS 79*: 3491, 1957, and in US Pat 2,889,337.

Description—White to cream-colored, odorless, fluffy, needle-like crystals; melts between 143° and 148°.

Solubility—Practically insoluble in cold water, sparingly soluble in boiling water; freely soluble in chloroform; soluble in boiling alcohol, acetone or acetic acid; soluble in aqueous alkalies with ring cleavage; reconstitution occurs on neutralization.

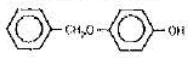
Uses—A psoralen melanizer. It increases the photodynamic pigmentation of skin; it does not induce pigmentation in the absence of UV light or melanocytes. It is used in the treatment of *vitiligo* and to *desensitize to sunlight*. Severe sunburning can occur with topical application; it is customary to protect the surrounding skin with a sunscreen. It also is used in PUVA treatment of *psoriasis*, *mycosis fungoides* and *cutaneous T-cell lymphoma*; in these, irradiation activates it to cross-link DNA. It may have value in the PUVA treatment of *alopecia areata*, *inflammatory dermatoses*, *eczema* and *lichen planus*. After oral administration gastrointestinal upset and central nervous system toxicities, such as vertigo and excitement, also occur. Consequently, the drug should be used orally only under medical supervision. It is additive with other photosensitizing drugs and the furocumarin pigments in carrots, celery, figs, limes, mustard, parsley and parsnips. It inhibits the metabolism of caffeine.

Dose—*Topical*, as a 1% lotion (see the package literature for details of application and use). *Oral*, *adults* and *children over 12 yr*, for *vitiligo*, 30 to 40 mg once a day 2 to 4 hr before exposure to ultraviolet light or at longer than 48-hr intervals 2 or 3 times a week; for *psoriasis*, *mycosis fungoides* or *cutaneous T-cell lymphoma*, 0.6 mg/kg 2 or 3 hr before UVA exposure (see the package literature for details).

Dosage Forms—Capsules: 10 mg; Lotion: 1%.

Monobenzone

Phenol, 4-(phenylmethoxy)-, Monobenzyl Ether of Hydroquinone; Benoquin (*Elder*)



p-(Benzyloxy)phenol [103-16-2] $C_{13}H_{12}O_2$ (200.24).

Preparation—Prepared in various ways. One method involves condensing sodium *p*-nitrophenolate with benzyl chloride to produce benzyl *p*-nitrophenyl ether followed by (1) reduction of nitro to amino, (2) diazotization of amino and (3) hydrolytic decomposition of the diazonium compound to the corresponding phenol.

Description—White, odorless, crystalline powder possessing very little taste; melts between 117° and 120°.

Solubility—1 g in >10,000 mL water, 14.5 mL alcohol, 29 mL chloroform or 14 mL ether.

Uses—A *depigmenting agent* or *demelanizer*. It acts by interfering with the formation of melanin, which is the principal cutaneous pigment. It is recommended only for the final depigmentation in *vitiligo*. It is not recommended for treatment of lentigo, severe freckling and other types of hyperpigmentation. It is not effective against pigmented moles or malignant melanoma. Its pigment-decreasing action is somewhat erratic. Irritation of varying degrees occurs in a considerable number of patients.

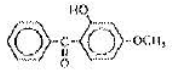
Dose—*Topical*, *adults* and *children over 12 yr*, to the skin, as a 20% cream 2 or 3 times a day.

Dosage Forms—Cream: 20%.

Minoxidil—page 837.

Oxybenzone

Methanone, (2-hydroxy-4-methoxyphenyl)phenyl-, (*Various Mfrs*)



2-Hydroxy-4-methoxybenzophenone [131-57-7] $C_{14}H_{12}O_3$ (228.25).

Preparation—Benzoic acid is condensed with resorcinol monomethyl ether by heating in the presence of $ZnCl_2$ or polyphosphoric acid (103% H_3PO_4 equivalent), and PCl_3. US Pat 3,073,866.

Description—White to off-white powder; congeals not lower than 62°.

Solubility—Practically insoluble in water; freely soluble in alcohol or toluene.

Uses—A *sunscreen* with a high molar absorptivity (20,381 at 290 nm), and it absorbs in both the long and short UV spectrum 270–350 nm. Therefore, it serves not only to prevent sunburn but also to protect against the photodynamic, photosensitizing and phototoxic effects of various drugs. Contact with the eyes should be avoided. At present, it is marketed only in combination with other sunscreens.

Dose—*Topical*, as a 3 to 5% cream, 0.5% lipstick and 2 or 3% lotion in combination with other sunscreens.

Ringer's Irrigation—RPS-16, page 762.
Sodium Bicarbonate—page 777.

Sodium Fluoride

Sodium fluoride [7681-49-4] NaF (41.99).

Preparation—By interaction of 40% HF with an equivalent quantity of NaOH or Na_2CO_3.

Description—White, odorless powder.

Solubility—1 g in 25 mL water; insoluble in alcohol.

Uses—A *dental caries prophylactic*. Fluoridation of municipal water supplies is considered a safe and practical public health measure, a concentration of about 1 ppm of fluoride in the water supply resulting in a 50 to 65% reduction in the incidence of dental caries in permanent teeth. Ingested fluoride is effective only while teeth are being formed. The fluoride is incorporated into tooth salts as fluorapatite. Excessive intake during development of teeth may cause mottling; hence, mottling of newly erupted teeth is an indication to reduce fluoride intake. Where drinking water contains less than 0.7 ppm of fluoride, dietary supplements for children with unerupted teeth may provide some future protection.

Topical application results in changes only in the outer layers of enamel or exposed dentin. In children, repeated application of a 2% solution of the drug to cleaned teeth results in a 16 to 49% reduction of dental caries; adult teeth are protected to a lesser extent by topical application. Topical application also is used to *densensitize* teeth.

Orally administered, it produces new bone formation in some patients with osteoporosis, especially when calcium and vitamin D (and estrogens in women) are administered concomitantly to facilitate mineralization of the new bone. However, the bone may become brittle.

It removes calcium from tissues and also poisons certain enzymes. Large oral doses may cause nausea and vomiting, which usually can be prevented by taking the substance with food. Pastes, rinses, solutions and gels for topical applications should not be swallowed.

Dose (as sodium fluoride)—*Topical*, to the teeth, as a 0.02 to 2% solution, 1.1 or 2.71% gel or 0.22 to 2.3% toothpaste. *Oral*, 1.5 to 3 ppm (equivalent to 0.7 to 1.3 ppm of fluoride ion) in drinking water; as a supplement, when the drinking water contains less than 0.3 ppm of fluoride ion, 0.55 mg a day for infants from 2 wk to 2 yr of age, 1.1 mg once a day for children from 2 to 3 yr and 2.2 mg for those from 3 to 13 yr, and when the drinking water contains 0.3 to 0.7 ppm of fluoride ion, 550 μg once a day for children 2 to 3 yr and 1.1 mg for those 3 to 13 yr. The fluoride ion equivalents of 550 μg, 1.1 mg, and 2.2 mg of the drug are 250 μg, 500 μg, and 1 mg, respectively. For *osteoporosis*, up to 60 mg a day. *Caution: It is poisonous.*

Dosage Forms—Drops: 0.275, 0.55 and 1.1 mg/drop; Gel: 1.1 and 2.71%; Rinse: 0.02, 0.05, 0.2 and 0.44%; Solution: 1.1, 3.3, 5.5, and 20 mg/mL; Chewable Tablets: 0.55, 1.1 and 2.2 mg. Sodium Fluoride and Orthophosphoric Acid: Gel: 1.23% fluoride ion and 1% phosphoric acid.

Sodium Monofluorophosphate

Phosphorofluoridic acid, sodium salt

$FPO(ONa)_2$

Disodium phosphorofluoridate [10163-15-2] (143.95).

Preparation—Substantially pure drug is produced by fusing a mixture of sodium metaphosphate and sodium fluoride, in stoichiometric proportion, in a closed vessel from which moist air is excluded.

Description—White to slightly gray, odorless powder.

Solubility—Freely soluble in water.

Uses—Like *Sodium Fluoride*, above, it promotes the replacement of the hydroxyapatite by fluorapatite in the tooth salts and, hence, is used as a *dental prophylactic* against dental caries. It has the advantage over sodium fluoride in that the teeth do not require special preparation before application, it is effective when included in dentifrices and in dentifrices there is no hazard with respect to local toxicity to the gingivae or systemic intoxication from ingestion.

Dose—*Topical*, to the teeth, in dentifrice containing 0.76%.

Stannous Fluoride

Tin Difluoride; Fluoristan

Tin fluoride (SnF_2) [7783-47-3] (156.69); contains not less than 71.2% Sn^{2+} (stannous tin), and about 24% F^- (fluoride).

Preparation—Stannous oxide is dissolved in 40% HF and the solution is evaporated out of contact with air.

Description—White, crystalline powder with a bitter, salty taste; melts at about 213°.

Solubility—Freely soluble in water; practically insoluble in alcohol, ether or chloroform.

Uses—Alters the composition and crystalline structure of the hydroxyapatite-like salts that make up the bulk of enamel and dentin, so that the tooth material is more resistant to acidic erosion and dental caries (decay). The substance is applied only topically, so that the tooth substance is only affected in the superficial layers, and it must be applied periodically. It is most effective when applied to the tooth surface after the teeth have been cleaned thoroughly by a dentist. However, there is good evidence that even when incorporated into tooth pastes the drug has a retardant effect on the development of dental caries.

Dose—*Topical*, to the teeth, generally as 0.4% gel or 0.1% rinse.

Dosage Forms—Capsules (for solution): 0.4, 0.65 and 0.8 g; Concentrate: 30%; Gel: 0.4%.

Titanium Dioxide

Titanic Anhydride

Titanium oxide (TiO_2) [13463-67-7] TiO_2 (79.88).

Preparation—By adding ammonia or an alkali carbonate to a solution of titanyl sulfate ($TiOSO_4$). Titanic acid [$Ti(OH)_4$ or $TiO(OH)_2$] is precipitated and, after filtration and washing, is dried and ignited.

Description—White, amorphous, tasteless, odorless, infusible powder; density about 4; suspension in water (1 in 10) neutral to litmus.

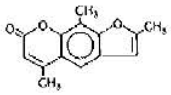
Solubility—Insoluble in water, HCl, HNO_3 or dilute H_2SO_4.

Uses—Its powder has a very high reflectance at visible and UV wavelengths, and, hence, it serves as an excellent white pigment. In ointments or lotions it reflects a very high proportion of incident sunlight, hence, protecting the skin from sunburn and serving as a *sunblock*. It also is used in cosmetics and as a dusting powder. Topically, it is devoid of toxicity.

Dose—*Topical*, as 2 to 25% cream, lotion or ointment as required.

Trioxsalen

7*H*-Furo[3,2-*g*][1]benzopyran-7-one, 2,5,9-trimethyl-, 6-Hydroxy-β,2,7-trimethyl-5-benzofuranacrylic Acid δ-Lactone; Trisoralen (*Elder*)



[3902-71-4] $C_{14}H_{12}O_3$ (228.25).

Caution: Avoid contact with the skin.

Preparation—2-Methylresorcinol is cyclized with ethyl acetoacetate with the aid of sulfuric acid to 7-hydroxy-4,8-dimethylcoumarin (I). Treatment with allyl bromide in the presence of potassium carbonate transforms I into the 7-allyloxy compound which, on reacting with acetic anhydride in the presence of *N,N*-diethylaniline and anhydrous sodium acetate, rearranges and esterifies to give the 7-acetoxy-6-allyl compound (II). Bromination of II followed by reaction with sodium methoxide yields trioxsalen. US Pat 3,201,421.

Description—White to off-white, odorless, tasteless crystalline solid; stable in light, air and heat; melts at about 230°.

Solubility—1 g in 1150 mL alcohol, 84 mL chloroform or 43 mL methylenedichloride; practically insoluble in water.

Uses—Although not a topical drug, it closely relates to other drugs in this section. It facilitates the action of near UV light to induce melanin (skin pigment) formation. It is used to cause repigmentation in idiopathic *vitiligo* and to enhance pigmentation to *increase tolerance to sunlight* or for *cosmetic purposes*. The increased tolerance to sunlight does not occur until enhanced pigmentation has occurred, and the user must be cautioned that severe sunburning with less than normal exposure can occur early during the course of treatment. The increase in dermal pigment occurs gradually over a period of several days of repeated exposure. Care must be taken to protect the eyes and lips during treatment. The manufacturer's recommended schedule of exposure should be used except at high altitudes, where exposure times should be appropriately reduced.

It is contraindicated in persons with photosensitizing diseases, such as infectious leukoderma, porphyria or lupus erythematosus and when photosensitizing drugs are being given. The drug sometimes may cause gastric irritation and emesis. Children under 12 should not take it.

Dose—*Oral, adults* and *children over 12 yr*, 5 to 10 mg 2 hr before exposure to sunlight. For the treatment of vitiligo the exposure should be repeated once a day for 4 days, and subsequent exposures should be determined according to the results of the initial 4 days. For the enhancement of pigmentation, treatment should not exceed 2 weeks, and the total accumulated dose in any one treatment course should not exceed 140 mg. Persons who show side effects of the drug should take only 5 mg; the duration of use will be necessarily prolonged over that in persons taking the usual dose of 10 mg.

Dosage Forms—Tablets: 5 mg.

Urea—page 931.

Other Miscellaneous Topical Drugs

Allantoin [2,5-Dioxo-4-imidazolidinylurea [97-59-6]; $C_4H_6N_4O_3$ (158.12)]—Prepared by oxidation of uric acid. Colorless crystals melting at 238°. 1 g dissolves in 190 mL water or 500 mL alcohol; nearly insoluble in ether. *Uses:* In World War I it was noticed that maggot-infested wounds seemed to heal better than uninfested wounds, an effect attributed to this drug produced by maggots. It is used topically as a vulnerary to stimulate tissue repair in suppurating wounds, resistant ulcers, acne, seborrhea, cold sores, hemorrhoids and various dermatologic infections and psoriasis. It frequently is combined with astringents, keratolytics, coal tar, antiseptics and antifungal drugs. The silver salt has been used in the topical treatment of extensive burns. *Dose: Topical*, 0.2 to 2% in creams, lotions or shampoos and 0.3 to 0.5% in ointments for hemorrhoids.

Cinoxate [2-Ethoxyethyl *p*-methoxycinnamate [104-28-9]; $C_{14}H_{18}O_4$ (250.29)]—A viscous liquid that may have a slightly yellow tinge; boils at about 185°. Practically insoluble in water; miscible with alcohols. *Uses:* A *sunscreen* that absorbs UV light at 270 to 328 nm and has a relatively high molar absorptivity (19,400 at 306 nm) but not absorbing well throughout the entire offending range of UV light. Consequently, it is used principally in preparations intended to promote tanning rather than to protect against photosensitivity and phototoxicity. *Dose: Topical*, 1.75 to 4% in creams, gels or lotions.

Dextranomer [Dextran 2,3-dihydroxypropyl-2-hydroxy-1,3-propanediyl ether [56087-11-7] Dextran polymer; Debrisan (*Pharmacia*)]—Small, dry beads of a three-dimensional dextran polymer; highly hygroscopic. 1 g absorbs about 4 g water. *Uses:* For drying, cleansing and debridement of exudative *venous stasis ulcers, infected wounds* and *burns*; it is not useful for cleansing nonexudative wounds or lesions. The beads not only absorb water but also proteins, including fibrin/fibrinogen degradation products and, thus, prevent encrustation. The beads are poured into the cleansed wound, which is circumscribed with petroleum jelly, and a compress is taped in place to retain the material. Changes may be made up to 3 or 4 times a day, as needed. The beads must be removed before skin grafting is attempted. Care must be taken to prevent cross-contamination from patient to patient. On the floor the beads are slippery and, thus, hazardous.

Digalloyl Trioleate [[17048-39-4; 27436-80-2] $C_{96}H_{166}O_{17}$ (1415.59)]—*Uses:* A sunscreen with an absorption band at 270 to 320 nm. It is used topically as a 3.5% cream or 2.5% lipstick.

Dihydroxyacetone [1,3-Dihydroxydimethyl ketone [96-26-4] $C_3H_6O_3$ (90.08)]—The ketone resulting from oxidation of the secondary alcohol group of glycerin. A crystalline powder; fairly hygroscopic; characteristic odor and sweet taste. The normal form is the dimer, slowly soluble in 1 part water or 15 parts alcohol; the monomer formed in solution is very soluble in water, alcohol or ether. *Uses:* Interacts with keratin in the stratum corneum to form a dark pigment that simulates the appearance of a suntan. It is incorporated in several sunscreen preparations. Since the sunscreen component is usually present in a concentration lower than optimal, such preparations may not provide protection to photosensitive persons.

Ethyl Dihydroxypropylaminobenzoate [Ethyl 4-[bis(hydroxypropyl)]aminobenzoate [58882-17-0] $C_{15}H_{23}NO_4$ (281.35); Amerscreen (*Amerchol*)]—*Uses:* A sunscreen with a limited absorption spectrum (280 to 330 nm) characteristic of *p*-aminobenzoates but a relatively high molar absorptivity. It is used mainly in suntan products. *Dose: Topical*, in concentrations of 1 to 5%.

Ethylhexyl Methoxycinnamate [2-Ethylhexyl *p*-methoxycinnamate [5466-77-3] $C_{18}H_{26}O_3$ (290.40)]—*Uses:* A sunscreen with a narrow absorption band of 290 to 320 nm and a moderate molar absorptivity. *Dose: Topical*, in 2 to 7.5% concentration in creams, lotions and oils.

Glyceryl *p*-Aminobenzoate [1,2,3-Propanetriol 1-(4-aminobenzoate) [136-44-7] $C_{10}H_{13}NO_4$ (211.21)]—Prepared by esterification of aminobenzoic acid with glycerin. A waxy semisolid or syrup. Insoluble in water, oils or fats; soluble in ethanol, isopropanol or propylene glycol. *Uses:* A sunscreen that absorbs UV light at 264 to 315 nm and which has a relatively high molar absorptivity (17,197 at 295 nm) but a limited spectrum, therefore used primarily to promote tanning rather than to protect sensitive persons. *Dose: Topical*, 2 to 3% in lotions.

Homosalate [3,3,5-Trimethylcyclohexyl salicylate; homomenthyl salicylate [118-56-9] $C_{16}H_{22}O_3$ (262.36); ing of Coppertone (*Plough*); Filtrosol "A" (*Norda*); Heliophan (*Greeff*)]—*Uses:* A liquid with relatively low molar absorptivity (6,720 at 310 nm) and limited absorption in the near ultraviolet range (290 to 315 nm), so that it is used mainly to promote tanning. Photosensitive persons may not be protected from burns and phototoxicity. *Dose: Topical*, 4 to 10% in creams, lotions or oils.

Methyl Anthranilate [Methyl 2-aminobenzoate [134-20-3] $C_8H_9NO_2$ (151.16)]—A constituent of several essential oils; also obtained by esterifying anthranilic acid with methyl alcohol. A crystalline substance; melts at 25°. Slightly soluble in water; freely soluble in alcohol or ether. *Uses:* A sunscreen, with the lowest molar absorptivity of all sunscreens (941 at 315 nm); also, it does not absorb throughout the near UV range (absorption band, 290 to 320 nm) and, therefore, is used in combination with other sunscreens or light-protectives. It also is used as a perfume in ointments and cosmetics. *Dose: Topical*, to the skin, 5% in creams, lotions or ointments.

Octyl salicylate—*Uses:* A sunscreen with an absorption band at 280 to 320 nm and a moderate absorptivity. It is used primarily in conjunction with other sunscreens in suntan products.

Padimate A [Pentyl *p*-(dimethylamino)benzoate [14779-78-3] $C_{14}H_{21}NO_2$ (235.33); (*Various Mfrs*)]—A mixture of pentyl, isopentyl and 2-methylbutyl esters of *p*-aminobenzoic acid. Yellow liquid with a faint, aromatic odor. Practically insoluble in water or glycerin; soluble in alcohol, chloroform, isopropyl alcohol or mineral oil. *Uses:* A sunscreen of moderate molar absorptivity but relatively narrow UV absorption spectrum (290 to 315 nm) characteristic of other aminobenzoic acid derivatives. *Dose: Topical*, to the skin, as a 1.4 to 8% cream, foam, lotion or stick.

Padimate O [2-Ethylhexyl 4-(dimethylamino)benzoate [21245-02-3] $C_{17}H_{27}NO_2$ (277.41); (*Various Mfrs*)]—A light-yellow mobile liquid with a faint, aromatic odor. Practically insoluble in water, alcohol or mineral oil. *Uses:* See *Padimate A*.

Red Petrolatum—*Uses:* Owing to its opacity, it is used in sunblock creams, ointments and sticks. Concentrations range from 30 to 100%.

CHAPTER 66

Pharmaceutical Necessities

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This chapter describes substances that are of little or no therapeutic value, but which are useful in the manufacture and compounding of various pharmaceutical preparations. Hence, they are referred to as pharmaceutical necessities. The substances described include antioxidants and preservatives; coloring, flavoring and diluting agents; emulsifying and suspending agents; ointment bases; pharmaceutical solvents and miscellaneous agents. For a more detailed review of the uses of these agents, the interested reader is referred to the various chapters in Part 8 of this book.

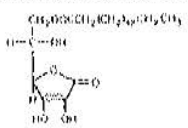
Antioxidants and Preservatives

An antioxidant is a substance capable of inhibiting oxidation and that may be added for this purpose to pharmaceutical products subject to deterioration by oxidative processes as, for example, the development of rancidity in oils and fats or the inactivation of some medicinals in the environment of their dosage forms. A preservative is, in the common pharmaceutical sense, a substance that prevents or inhibits microbial growth and may be added to pharmaceutical preparations for this purpose to avoid consequent spoilage of the preparations by microorganisms. Both antioxidants and preservatives have many applications in making medicinal products.

Alcohol—page 1314.

Ascorbyl Palmitate

L-Ascorbic acid, 6-hexadecanoate; Ascorbic Acid Palmitate (ester)



L-Ascorbic acid 6-palmitate [137-66-6] $C_{22}H_{38}O_7$ (414.54).

Preparation—By condensing palmitoyl chloride with ascorbic acid in the presence of a suitable dehydrochlorinating agent such as pyridine.

Description—White to yellowish white powder having a characteristic odor; melts 107° and 117°.

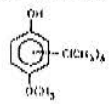
Solubility—1 g in >1000 mL of water, 125 mL of alcohol, >1000 mL of chloroform or >1000 mL of ether.

Uses—An *antioxidant* used in foods and pharmaceuticals. It also is used to prevent rancidity, to prevent the browning of cut apples, in meat curing and in the preservation of canned or frozen foods.

Benzoic Acid—page 1235.
Benzalkonium Chloride—page 1104.
Benzethonium Chloride—page 1170.
Benzyl Alcohol—page 1056.

Butylated Hydroxyanisole

Phenol, (1,1-dimethylethyl)-4-methoxy-; Tenox BHA (*Eastman*)



tert-Butyl-4-methoxyphenol [25013-16-5] $C_{11}H_{16}O_2$ (180.25).

Preparation—By an addition interaction of *p*-methoxyphenol and 2-methylpropene. US Pat 2,428,745.

Description—White or slightly yellow, waxy solid having a faint, characteristic odor.

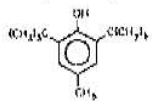
Solubility—Insoluble in water; 1 g in 4 mL of alcohol, 2 mL of chloroform or 1.2 mL of ether.

Uses—An *antioxidant* in cosmetics and pharmaceuticals containing fats and oils.

Butylparaben—page 1170.

Butylated Hydroxytoluene

Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-, Butylated Hydroxytoluene Crystalline (*Diamond-Shamrock*); Tenox BHT (*Eastman*)



2,6-Di-*tert*-butyl-*p*-cresol [128-37-0] $C_{15}H_{24}O$ (220.35).

Preparation—By an addition interaction of *p*-cresol and 2-methylpropene. US Pat 2,428,745.

Description—White, tasteless crystals with a mild odor; stable in light and air; melts at 70°.

Solubility—Insoluble in water; 1 g in 4 mL of alcohol, 1.1 mL of chloroform or 1.1 mL of ether.

Uses—An *antioxidant* employed to retard oxidative degradation of oils and fats in various cosmetics and pharmaceuticals.

Cetylpyridinium Chloride—page 1171.

Chlorobutanol

2-Propanol, 1,1,1-trichloro-2-methyl-, Chlorbutol; Chlorbutanol; Acetone chloroform; Chloretone (*Parke-Davis*)

$(CCl_3)C(CH_3)_2OH$

1,1,1-Trichloro-2-methyl-2-propanol [57-15-8] $C_4H_7Cl_3O$ (177.46); *hemihydrate* [6001-64-6] (186.46).

Preparation—Chloroform undergoes chemical addition to acetone under the catalytic influence of powdered potassium hydroxide.

Description—Colorless to white crystals, of a characteristic, somewhat camphoraceous odor and taste; anhydrous melts about 96°; hydrous melts about 76°; boils with some decomposition 165 and 168°.

Solubility—1 g in 125 mL of water, 1 mL of alcohol or about 10 mL of glycerin; freely soluble in chloroform, ether or volatile oils.

Incompatibilities—The anhydrous form must be used in order to prepare a clear solution in liquid petrolatum. It is decomposed by *alkalies; ephedrine* is sufficiently alkaline to cause its breakdown with the formation of ephedrine hydrochloride which will separate from a liquid petrolatum solution. It is only slightly soluble in water, hence alcohol must be used to dissolve the required amount in certain vehicles. A soft mass is produced by trituration with *antipyrine, menthol, phenol* and other substances.

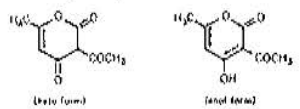
Uses—Topically, as a solution in clove oil as a *dental analgesic*. It has *local anesthetic* potency to a mild degree and has been employed as an anesthetic dusting powder (1 to 5%) or ointment (10%). It has antibacterial and germicidal properties. It is used chiefly as a *preservative* in solutions of epinephrine, posterior pituitary, etc. When administered orally, it has much the same therapeutic use as chloral hydrate. Hence, it has been employed as a sedative and hypnotic. It has been taken orally to allay vomiting due to gastritis.

Dose—*Topical*, as a 25% solution in clove oil.

Other Dose Information—The oral dose is 300 mg to 1 g, given in tablets or capsules.

Dehydroacetic Acid

Keto form: 2*H*-Pyran-2,4(3*H*)-dione, 3-acetyl-6-methyl-,



Enol form: 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one [520-45-6 (Keto)], [771-03-9 (enol)] $C_8H_8O_4$ (168.15).

Preparation—By fractional distillation of a mixture of ethyl acetoacetate and sodium bicarbonate, maintaining almost total reflux conditions, allowing only ethanol to be removed. The residue is distilled under vacuum. *Org Syn Coll Vol III:* 231, 1955.

Description—White to creamy-white crystalline powder melting about 110° with sublimation.

Solubility—One g dissolves in 25 g of acetone, 18 g of benzene, 5 g of methanol or 3 g of ethanol.

Uses—Preservative.

Ethylenediamine

1,2-Ethanediamine

$H_2NCH_2CH_2NH_2$

Ethylenediamine [107-15-3] $C_2H_8N_2$ (60.10).

Caution—Use care in handling because of its caustic nature and the irritating properties of its vapor.

Note—It is strongly alkaline and may readily absorb carbon dioxide from the air to form a nonvolatile carbonate. Protect it against undue exposure to the atmosphere.

Preparation—By reacting ethylene dichloride with ammonia, then adding NaOH and distilling.

Description—Clear, colorless or only slightly yellow liquid, having an ammonia-like odor and strong alkaline reaction; miscible with water and alcohol; anhydrous boils 116 to 117° and solidifies at about 8°; volatile with steam; a strong base and readily combines with acids to form salts with the evolution of much heat.

Uses—A *pharmaceutical necessity* for *Aminophylline Injection*. It is irritating to skin and mucous membranes. It also may cause sensitization characterized by asthma and allergic dermatitis.

Ethylparaben—page 1171.
Ethyl Vanillin—page 1294.
Glycerin—page 1027.
Hypophosphorus Acid—page 1322.
Methylparaben—page 1172.

Monothioglycerol

1,2-Propanediol, 3-mercapto-,

$HSCH_2CH(OH)CH_2OH$

3-Mercapto-1,2-propanediol [96-27-5] $C_3H_8O_2S$ (108.15).

Preparation—An ethanolic solution of 3-chloro-1,2-propanediol is heated with potassium bisulfide.

Description—Colorless or pale yellow, viscous liquid having a slight sulfidic odor; hygroscopic; specific gravity 1.241 to 1.250; pH (1 in 10 solution) 3.6 to 7.

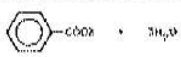
Solubility—Freely soluble in water; miscible with alcohol; insoluble in ether.

Uses—A pharmaceutic aid stated to be used as a preservative. It has been used in 1:5000 solution to stimulate healing of wounds, and as a 1:1000 jelly in atrophic rhinitis.

Phenol—page 1323.
Phenylethyl Alcohol—page 1297.
Phenylmercuric Nitrate—page 1172.

Potassium Benzoate

Benzoic acid, potassium salt



[582-25-2] $C_7H_5KO_2$ (160.21) (anhydrous).

Description—Crystalline powder.

Solubility—Soluble in water or alcohol.

Uses—Preservative.

Potassium Metabisulfite

Dipotassium pyrosulfite

[16731-55-8] $K_2S_2O_5$ (222.31).

Description—White crystals or crystalline powder with an odor of SO_2. Oxidizes in air to the sulfate. May ignite on powdering in a mortar if too much heat develops.

Solubility—Freely soluble in water; insoluble in alcohol.

Uses—Antioxidant.

Potassium Sorbate

2,4-Hexadienoic acid, (*E,E*)-, potassium salt; 2,4-Hexadienoic acid, potassium salt; Potassium 2,4-Hexadienoate

Potassium (*E,E*)-sorbate; potassium sorbate [590-00-1] [24634-61-5] $C_6H_7KO_2$ (150.22).

Preparation—Sorbic Acid is reacted with an equimolar portion of KOH. The resulting potassium sorbate may be crystallized from aqueous ethanol. US Pat 3,173,948.

Description—White crystals or powder with a characteristic odor; melts about 270° with decomposition.

Solubility—1 g in 4.6 mL of water, 35 mL of alcohol, >1000 mL of chloroform or >1000 mL of ether.

Uses—A water-soluble salt of sorbic acid used in pharmaceuticals to *inhibit the growth of molds and yeasts*. Its toxicity is low, but it may irritate the skin.

Propylparaben—page 1173.
Sassafras Oil—page 1300.
Sodium Benzoate—page 1173.

Sodium Disulfite

Sulfurous acid, monosodium salt; Sodium Hydrogen Sulfite; Sodium Acid Sulfite; Leucogen

Monosodium sulfite [7631-90-5] $NaHSO_3$ and sodium metabisulfite ($Na_2S_2O_5$) in varying proportions; yields 58.5–67.4% of SO_2.

Description—White or yellowish white crystals or granular powder having the odor of sulfur dioxide; unstable in air.
Solubility—1 g in 4 mL of water; slightly soluble in alcohol.

Uses—An *antioxidant* and *stabilizing agent*. Epinephrine hydrochloride solutions may be stabilized by the addition of small quantities of the salt. It also is used to help solubilize kidney stones. It is useful for removing permanganate stains and for solubilizing certain dyes and other chemicals (see *Menadione Sodium Bisulfite*, RPS-17, page 1011).

Sodium Metabisulfite

Disulfurous acid, disodium salt

Disodium pyrosulfite [7681-57-4] $Na_2S_2O_5$ (190.10).
Preparation—Formed when sodium bisulfite undergoes thermal dehydration. It also may be prepared by passing sulfur dioxide over sodium carbonate.

Description—White crystals or white to yellowish crystalline powder having an odor of sulfur dioxide; on exposure to air and moisture, it is slowly oxidized to sulfate.
Solubility—1 g in 2 mL of water; slightly soluble in alcohol; freely soluble in glycerin.

Uses—*A reducing agent*. It is used in easily oxidized pharmaceuticals, such as epinephrine hydrochloride and phenylephrine hydrochloride injections, to retard oxidation.

Sodium Propionate—page 1236.

Sorbic Acid

2,4-Hexadienoic acid, (*E,E*)-, 2,4-Hexadienoic acid

(*E,E*)-Sorbic acid; Sorbic acid [22500-92-1] [110-44-1] $C_6H_8O_2$ (112.13).
Preparation—By various processes. Refer to US Pat 2,021,090.

Description—Free-flowing, white, crystalline powder, having a characteristic odor; melts about 133°.
Solubility—1 g in 1000 mL of water, 10 mL of alcohol, 16 mL of chloroform, 30 mL of ether or 19 mL of propylene glycol.

Uses—*A mold and yeast inhibitor*. It also is used as a fungistatic agent for foods, especially cheeses.

Sulfur Dioxide

Sulfur dioxide [7446-09-5] SO_2 (64.06).
Preparation—By burning sulfur or sulfides and by reacting a bisulfite or a sulfite with a strong acid.

Description—Colorless, nonflammable gas, with a strong, suffocating, odor characteristic of burning sulfur; 1 L weighs 2.927 g at 760 mm and 0°; readily liquefies under pressure forming a colorless liquid with a density of approximately 1.5 g/mL, and a boiling point of −10°.
Solubility—1 volume of water dissolves approximately 39 volumes of it at 760 mm and 20°; 1 volume of alcohol dissolves approximately 114 volumes under the same conditions; soluble in ether or chloroform.
Note—It is used mostly in the form of a gas in pharmaceutical applications, and is described herein for such purposes. However, it is usually packaged under pressure, hence the USP specifications (Water, Nonvolatile residue and *Sulfuric acid), are designed for the testing of its liquid form.*

Uses—The gas in the presence of moisture forms sulfurous acid which is a *bleaching agent*, *fungicide* and *bactericide*. For this reason fruits often are exposed to the gas before drying to prevent darkening and the growth of molds and bacteria. The gas is also an *antioxidant* and a pharmaceutical necessity for *Injections*. It may be intensely irritating to the eyes and respiratory tract.

Thimerosal—page 1173.

Other Antioxidants and Preservatives

Anoxomer [1,4-Benzenediol, 2-(1,1-dimethylethyl)-, polymer with diethenyl benzene, 4-(1,1-dimethylethyl)phenol, 4-methoxyphenol, 4,4′-(1-methylethylidene)bis[phenol] and 4-methylphenol [60837-57-2] $(C_{10}H_{14}O_2)_x(C_{10}H_{10})_y(C_{10}H_{14}O)_w(C_7H_8O_2)_x(C_{16}H_{18}O_2)_y(C_7H_8O)_z$. *Uses:* Antioxidant and food additive.
Maleic Acid BP [*cis*-Butanedioic acid $C_4H_4O_4$ (116.07); Toxic acid] —*Preparation:* Benzene vapor is oxidized by passage over heated vanadium pentoxide. Odorless, white, crystalline powder having a strongly acid taste; melts about 130°. Soluble in 1.6 parts of water, 2 parts of alcohol or 12 parts of ether. *Uses:* In the preparation of ergometrine maleate injection or as a rancidity retardant in fats and oils (1:10,000).
Propyl Gallate BP [Propyl 3,4,5-Trihydroxybenzoate]—White to creamy-white crystalline powder; odorless; slightly bitter taste. Soluble in 1000 parts of water or 3 parts of alcohol. *Uses:* A preservative.

Coloring, Flavoring and Diluting Agents

The use of properly colored and flavored medicinal substances, although offering no particular therapeutic advantage, is of considerable importance psychologically. A water-clear medicine is not particularly acceptable to most patients, and, in general, is thought to be inert. Many very active medicinal substances are quite unpalatable, and the patient may fail to take the medicine simply because the taste or appearance is objectionable. Disagreeable medication can be made both pleasing to the taste and attractive by careful selection of the appropriate coloring, flavoring and diluting agents. Therefore, judicious use of these substances is important in securing patient cooperation in taking or using the prescribed medication and continued compliance with the prescriber's intent.

Coloring Agents or Colorants

Coloring agents may be defined as compounds employed in pharmacy solely for the purpose of imparting color. They may be classified in various ways, eg, inorganic or organic. For the purpose of this discussion two subdivisions are used: *Natural Coloring Principles* and *Synthetic Coloring Principles*. The members of these groups are used as colors for pharmaceutical preparations, cosmetics, foods and as bacteriological stains and diagnostic agents.

Natural Coloring Principles

Natural coloring principles are obtained from mineral, plant and animal sources. They are used primarily for artistic purposes, as symbolic adornments of natives, as colors for foods, drugs and cosmetics and for other psychological effects.

Mineral colors frequently are termed *pigments* and are

used to color lotions, cosmetics and other preparations, usually for external application. Examples are *Red Ferric Oxide* (page 1328) and *Yellow Ferric Oxide* (page 1328), titanium dioxide (page 772) and carbon black.

The term pigment also is applied generically to plant colors by phytochemists. Many plants contain coloring principles that may be extracted and used as colorants, eg, chlorophyll. Anattenes are obtained from annatto seeds and give yellow to orange water-soluble dyes. Natural beta-carotene is a yellow color extracted from carrots and used to color margarine. Alizarin is a reddish-yellow dye obtained from the madder plant. The indigo plant is the source of a blue pigment called indigo. Flavones, such as riboflavin, rutin, hesperidin and quercetin, are yellow pigments. Saffron is a glycoside that gives a yellow color to drugs and foods. Cudbear and red saunders are two other dyes obtained from plants. Most plant colors now have been characterized and synthesized, however, and those with the desirable qualities of stability, fastness and pleasing hue are available commercially as synthetic products.

Animals have been a source of coloring principles from the earliest periods of recorded history. For example, *Tyrian purple*, once a sign of royalty, was prepared by air oxidation of a colorless secretion obtained from the glands of a snail (*Murex brandaris*). This dye now is known to be 6,6'-dibromoindigo, and has been synthesized, but cheaper dyes of the same color are available. Cochineal from the insect *Coccus cacti* contains the bright-red coloring principle *carminic acid*, a derivative of anthraquinone. This dye is no longer used in foods and pharmaceuticals due to *Salmonella* contamination.

Synthetic Coloring Principles

Synthetic coloring principles date from 1856 when W H Perkin accidentally discovered *mauveine*, also known as a *Perkin's purple*, while engaged in unsuccessful attempts to synthesize quinine. He obtained the dye by oxidizing aniline containing *o*- and *p*-toluidines as impurities. Other discoveries of this kind followed soon after, and a major industry grew up in the field of coal-tar chemistry.

The earliest colors were prepared from aniline and for many years all coal-tar dyes were called aniline colors, irrespective of their origin. The coal-tar dyes include more than a dozen well-defined groups among which are *nitroso-dyes, nitro-dyes, azo-dyes, oxazines, thiazines, pyrazolones, xanthenes, indigoids, anthraquinones, acridines, rosanilines, phthaleins, quinolines* and others. These in turn are classified, according to their method of use, as *acid dyes* and *basic dyes*, or *direct dyes* and *mordant dyes*.

Certain structural elements in organic molecules, called chromophore groups, give color to the molecules, eg, azo (—N=N—), nitroso (—N=O), nitro (—NO_2), azoxy (—N=N—O—), carbonyl (>C=O) and ethylene (>C=C<). Other such elements augment the chromophore groups, eg, methoxy, hydroxy and amino groups.

Stability—Most dyes are relatively unstable chemicals due to their unsaturated structures. They are subject to fading due to light, metals, heat, microorganisms, oxidizing and reducing agents plus strong acids and bases. In tablets, fading may appear as spotting and specking.

Uses—Most synthetic coloring principles are used in coloring fabrics and for various artistic purposes. They also find application as indicators, bacteriological stains, diagnostic aids, reagents in microscopy, etc.

Many coal-tar dyes originally were used in foodstuffs and beverages without careful selection or discrimination between those that were harmless and those that were toxic and without any supervision as to purity or freedom from poisonous constituents derived from their manufacture.

After the passage of the Food and Drugs Act in 1906, the US Department of Agriculture established regulations by which a few colors came to be known as *permitted colors*. Certain of these colors may be used in foods, drugs and cosmetics, but only after certification by the FDA that they meet certain specifications. From this list of permitted colors may be produced, by skillful blending and mixing, other colors that may be used in foods, beverages and pharmaceutical preparations. Blends of certified dyes must be recertified.

The word "permitted" is used in a restricted sense. It does not carry with it the right to use colors for purposes of deception, even though they are "permitted" colors, for all food laws have clauses prohibiting the coloring of foods and beverages in a manner so as to conceal inferiority or to give a false appearance of value.

The certified colors are classified into three groups: FD&C dyes which legally may be used in foods, drugs and cosmetics, D&C dyes which legally may be used in drugs and cosmetics and External D&C dyes which legally may be used only in externally applied drugs and cosmetics. There are specific limits for the pure dye, sulfated ash, other extractives, soluble and insoluble matter, uncombined intermediates, oxides, chlorides and sulfates. As the use status of these colors is subject to change, the latest regulations of the FDA should be consulted to determine how they may be used—especially since several FD&C dyes formerly widely used have been found to be carcinogenic even when "pure" and, therefore, have been banned from use.

The Coal-Tar Color Regulations specify that the term "externally applied drugs and cosmetics" means drugs and cosmetics which are applied only to external parts of the body and not to the lips or any body surface covered by mucous membrane. No certified dye, regardless of its category, legally may be used in any article which is to be applied to the area of the eye.

Lakes are calcium or aluminum salts of certified dyes extended on a substrate of alumina. They are insoluble in water and organic solvents, hence are used to color powders, pharmaceuticals, foods, hard candies and food packaging.

The application of dyes to pharmaceutical preparations is an art that can be acquired only after an understanding of the characteristics of dyes and knowledge of the composition of the products to be colored has been obtained. Specific rules for the choice or application of dyes to pharmaceutical preparations are difficult to formulate. Each preparation may present unique problems.

Preparations which may be colored include most liquid pharmaceuticals, powders, ointments and emulsions. Some general hints may be offered in connection with solutions and powders, but desired results usually can be obtained only by a series of trials. In general, an inexperienced operator tends to use a much higher concentration of the dye than is necessary, resulting in a dull color. The amount of dye present in any pharmaceutical preparation should be of a concentration high enough to give the desired color and low enough to prevent toxic reactions and permanent staining of fabrics and tissues.

Liquids (Solutions)—The dye concentration in liquid preparations and solutions usually should come within a range of 0.0005% (1 in 200,000) and 0.001% (1 in 100,000), depending upon the depth of color wanted and the thickness of column to be viewed in the container. With some dyes, concentrations as low as 0.0001% (1 in 1,000,000) may have a distinct tinting effect. Dyes are used most conveniently in the form of stock solutions.

Powders—White powders usually require the incorporation of 0.1% (1 in 1000) of a dye to impart a pastel color. The dyes may be incorporated into the powder by dry-blending in a ball mill or, on a small scale, with a mortar and pestle.

The dye is incorporated by trituration and geometric dilution. Powders also may be colored evenly by adding a solution of the dye in alcohol or some other volatile solvent having only a slight solvent action on the powder being colored. When this procedure is employed, the solution is added in portions, with thorough mixing after each addition, after which the solvent is allowed to evaporate from the mixture.

Many of the syrups and elixirs used as flavoring and diluting agents are colored. When such agents are used no further coloring matter is necessary. The use of colored flavoring agents is discussed in a subsequent section. However, when it is desired to add color to an otherwise colorless mixture, one of the agents described in the first section may be used.

Incompatibilities—FD&C dyes are mainly anionic (sodium salts), hence are incompatible with cationic substances. Since the concentrations of these substances are generally very low, no precipitate is evident. Polyvalent ions such as calcium, magnesium and aluminum also may form insoluble compounds with dyes. A pH change may cause the color to change. Acids may release the insoluble acid form of the dye.

Caramel

Burnt Sugar Coloring

A concentrated solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark brown mass results, a small amount of alkali, alkaline carbonate or a trace of mineral acid being added while heating.

Description—Thick, dark brown liquid with the characteristic odor of burnt sugar, and a pleasant, bitter taste; specific gravity not less than 1.30; 1 part dissolved in 1000 parts of water yields a clear solution having a distinct yellowish orange color which is not changed and no precipitate is formed after exposure to sunlight for 6 hr; when spread in a thin layer on a glass plate, it appears homogeneous, reddish brown and transparent.

Solubility—Miscible with water in all proportions and with dilute alcohol up to 55% by volume; immiscible with ether, chloroform, acetone, benzene, solvent hexane or turpentine oil.

Uses—To produce a brown color in elixirs, syrups and other preparations.

Flavoring Agents

Flavor

The word flavor refers to a mixed sensation of taste, touch, smell, sight and sound, all of which combine to produce an infinite number of gradations in the perception of a substance. The four primary tastes—*sweet*, *bitter*, *sour* and *saline*—appear to be the result partly of physicochemical and partly of psychological action. Taste buds (Fig 66-1), located mainly on the tongue, contain very sensitive nerve endings that react, in the presence of moisture, with the flavors in the mouth and as a result of physicochemical activity electrical impulses are produced and transmitted via the seventh, ninth and tenth cranial nerves to the areas of the brain which are devoted to the perception of taste. Some of the taste buds are specialized in their function, giving rise to areas on the tongue which are sensitive to only one type of taste. The brain, however, usually perceives taste as a composite sensation, and accordingly the components of any flavor are not readily discernible. Children have more taste buds than adults, hence are more sensitive to tastes.

Taste partly depends on the ions which are produced in the mouth, but psychologists have demonstrated that sight (color) and sound also play a definite role when certain reflexes become conditioned through custom and association of sense perceptions. Thus, in the classic experiments of Pavlov demonstrating "conditioned reflexes," the ringing of a bell or the showing of a circle of light caused the gastric juices of a dog to flow although no food was placed before it, and much of the enjoyment derived from eating celery is due to its crunchy crispness as the fibrovascular bundles are crushed. The effect of color is just as pronounced; oleomargarine is unpalatable to most people when it is uncolored, but once the dye has been incorporated gourmets frequently cannot distinguish it from butter. Color and taste must coincide, eg, cherry flavor is associated with a red color.

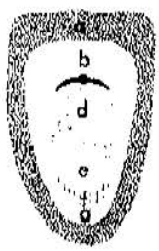


Fig 66-1. Upper Surface of the tongue. a: Taste receptors for all tastes; b: sweet, salty and sour; c: salty and sour; d: sour only; e: no taste sensation; f: sweet and sour and g: bitter, sweet and sour (adapted from Crocker EC: *Flavor*, McGraw-Hill, New York, 22, 1945).

A person suffering from a head cold finds his food much less palatable than usual because his sense of smell is impaired, and, if the nostrils are held closed, raw onions taste sweet and it is much easier to ingest castor oil and other nauseating medicines. The volatility of a substance is an important factor that is influenced by the warmth and moisture of the mouth since the more volatile a compound, the more pronounced its odor. The sense of smell detects very minute amounts of material and is usually much more sensitive in detecting the presence of volatile chemicals, but the tongue is able to detect infinitesimal amounts of some vapors if it is protruded from the mouth so that solution of the gases in the saliva may take place. In this manner traces of sulfur dioxide can be detected in the air since it dissolves in the saliva and creates a sour taste.

Flavors described as hot are those that exert a mild counterirritant effect on the mucosa of the mouth, those that are astringent and pucker the mouth contain tannins and acids that produce this effect by reacting with the lining of the mouth and wines possess a bouquet due to the odor of the volatile constituents. Indian turnip (Jack-in-the-pulpit) owes its flavor largely to the stinging sensation caused by the minute acicular crystals of calcium oxalate which penetrate the mucous membrane.

Other physiological and physical factors that also may affect taste are coarseness or grittiness due to small particles, eg, ion-exchange resins. Antidiarrheal preparations have a chalky taste. Menthol imparts a cool taste because it affects the coldness receptors. Mannitol gives a cool sensation when it dissolves because its negative of heat of solution will cause the temperature to drop. For this reason, mannitol often is used as the base for chewable tablets.

There is a definite threshold of taste for every substance, which varies somewhat with the individual and with the environment. The experienced chef tastes his delicacies at the temperature at which they will be served since heat and cold alter the flavor of many preparations. Thus, lemon

loses its sour taste entirely at an elevated temperature and other flavors become almost nonvolatile, tasteless and odorless when cooled sufficiently. In addition to the influence of temperature, the sensitivity of each individual must be considered. For example, it has been determined by experiment that the amount of sugar that can just be detected by the average individual is about 7 mg. However, this amount cannot be tasted by some and it is definitely sweet to others.

People are more sensitive to odor than to taste. There are about 10,000 to 30,000 identifiable scents, of which the average person can identify about 4000. Women are more sensitive to odors than men. Additional insights can be obtained by reading Cagan RH, Kare MR: *Biochemistry of Taste and Olfaction*, Academic, 1981, and Beidler LM (ed): *Handbook of Sensory Physiology*, vol IV, pts 1 and 2, Springer-Verlag, 1971.

Preservation of Flavors—Most monographs of official products contain specific directions for storage. Proper methods of storage are essential to prevent deterioration which in many instances results in destruction of odor and taste. Under adverse conditions undesirable changes occur due to one or a combination of the following: enzymatic activity, oxidation, change in moisture content, absorption of odors, activity of microorganisms and effects of heat and light. In certain products some of the changes wrought by these factors are desirable, as when esters are formed due to the activity of enzymes and when blending and mellowing results from the interchange of the radicals of esters (*transesterification*).

One method for protecting readily oxidizable substances, such as lemon oil, from deteriorating, and thus preserving their original delicate flavor, is to microencapsulate them by spray-drying. The capsules containing the flavors then are enclosed in various packaged products (eg, powdered gelatins) or tablets which are flavored deliciously when the capsule is disintegrated by mixing and warming with water or saliva.

Correlation of Chemical Structure with Flavor and Odor—The compounds employed as flavors in vehicles vary considerably in their chemical structure, ranging from simple esters (methyl salicylate), alcohols (glycerin) and aldehydes (vanillin) to carbohydrates (honey) and the complex volatile oils (anise oil). Synthetic flavors of almost any desired type are now available. These frequently possess the delicate flavor and aroma of the natural products and also the desirable characteristics of stability, reproducibility and comparatively low cost. Synthetic products such as cinnamaldehyde and benzaldehyde, first officially recognized when several of the essential oils became scarce during World War II, have been used widely.

There is a close relationship between chemical structure and taste. Solubility, the degree of ionization and the type of ions produced in the saliva definitely influence the sensation interpreted by the brain.

Sour taste is caused by hydrogen ions and it is proportional to the hydrogen-ion concentration and the lipid solubility of the compound. It is characteristic of acids, tannins, alum, phenols and lactones. Saltiness is due to simultaneous presence of anions and cations, eg, KBr, NH_4Cl and sodium salicylate. High-molecular-weight salts may have a bitter taste. Sweet taste is due to polyhydroxy compounds, polyhalogenated aliphatic compounds and α-amino acids. Amino and amide groups, especially if the positive effect is balanced by the proximity of a negative group, may produce a sweet taste. Sweetness increases with the number of hydroxy groups, possibly due to increase in solubility. Imides such as saccharin and sulfamates such as cyclamates are intensely sweet. Cyclamates have been removed from the market because they reportedly cause bladder tumors in rats. Free bases such as alkaloids and amides such as amphetamines give bitter tastes. Polyhydroxy compounds with a molecular weight greater than 300, halogenated substances and aliphatic thio compounds also may have bitter tastes. Unsaturation frequently bestows a sharp, biting odor and taste upon compounds.

No precise relationship between chemical structure and odor has been found. There are no primary odors, and odors blend into each other. Polymerization reduces or destroys odor; high valency gives odor and unsaturation enhances odor. A tertiary carbon atom often will give a camphoraceous odor, esters and lactones have a fruity odor and ketones have a pleasant odor. Strong odors often are accompanied by volatility and chemical reactivity.

Selection of Flavors

The proper selection of flavors for disguising nauseating medicines aids in their ingestion. Occasionally, sensitive patients have become nauseated sufficiently to vomit at the thought of having to take disagreeable medication, and it is particularly difficult to persuade children to continue to use and retain distasteful preparations. There is a need to know the allergies and idiosyncrasies of the patient; thus, it is foolish to use a chocolate-flavored vehicle for the patient who dislikes the flavor or who is allergic to it, notwithstanding the fact that this flavor is generally acceptable.

Flavoring Methodology

Each flavoring problem is unique and requires an individual solution. The problem of flavoring is further complicated because flavor and taste depend on individual preferences. In solving flavoring problems the following techniques have been used:

1. *Blending*—Fruit flavors blend with sour taste; bitter tastes can be blended with salty, sweet and sour tastes; salt reduces sourness and increases sweetness; chemicals such as vanillin, monosodium glutamate and benzaldehyde are used for blending.
2. *Overshadow*—Addition of a flavor whose intensity is longer and stronger than the obvious taste, eg, methyl salicylate, glycyrrhiza and oleoresins.
3. *Physical*—Formation of insoluble compounds of the offending drug, eg, sulfonamides; emulsification of oils; effervescence, eg, magnesium citrate solution; high viscosity of fluids to limit contact of drug with the tongue, and mechanical procedures such as coating tablets, are physical methods to reduce flavoring problems.
4. *Chemical*—Adsorption of the drug on a substrate, or formation of a complex of the drug with ion-exchange resins or complexing agents.
5. *Physiological*—The taste buds may be anesthetized by menthol or mint flavors.

Flavors, as used by the pharmacist in compounding prescriptions, may be divided into four main categories according to the type of taste which is to be masked, as follows:

1. *Salty Taste*—Cinnamon syrup has been found to be the best vehicle for ammonium chloride, and other salty drugs such as sodium salicylate and ferric ammonium citrate. In a study of the comparative efficiency of flavoring agents for disguising salty taste, the following additional vehicles were arranged in descending order of usefulness: orange syrup, citric acid syrup, cherry syrup, cocoa syrup, wild cherry syrup, raspberry syrup, glycyrrhiza elixir, aromatic elixir and glycyrrhiza syrup. The last-named is particularly useful as a vehicle for the salines by virtue of its colloidal properties and the sweetness of both glycyrrhizin and sucrose.
2. *Bitter Taste*—Cocoa syrup was found to be the best vehicle for disguising the bitter taste of quinine bisulfate, followed, in descending order of usefulness, by raspberry syrup, cocoa syrup, cherry syrup, cinnamon syrup, compound sarsaparilla syrup, citric acid syrup, licorice syrup, aromatic elixir, orange syrup and wild cherry syrup.
3. *Acrid or Sour Taste*—Raspberry syrup and other fruit syrups are especially efficient in masking the taste of sour substances such as hydrochloric acid. Acacia syrup and other mucilaginous vehicles are best for disguising the acrid taste of substances, such as capsicum, since they tend to form a colloidal protective coating over the taste buds of the tongue. Tragacanth, unlike acacia, may be used in an alcoholic vehicle.

4. *Oily Taste*—Castor oil may be made palatable by emulsifying with an equal volume of aromatic rhubarb syrup or with compound sarsaparilla syrup. Cod liver oil is disguised effectively by adding wintergreen oil or peppermint oil. Lemon, orange and anise or combinations of these are also useful. It is better to mix most of the flavor with the oil before emulsifying it, and then the small remaining quantity can be added after the primary emulsion is formed.

Those flavors that are most pleasing to the majority of people are associated with some stimulant of a physical or physiological nature. This may be a central nervous stimulant such as caffeine, which is the reason so many enjoy tea and coffee as a beverage, or it may be a counterirritant such as one of the spices that produce a "biting" sensation or an agent which "tickles" the throat such as soda water. Sherry owes its sharp flavor to its acetaldehyde content, and some of the volatile oils contain terpenes that are stimulating to the mucous surfaces.

Selection of Vehicles

Too few pharmacists realize the unique opportunity they have in acquainting physicians with a knowledge of how to increase both the palatability and efficacy of their prescribed medicines through the judicious selection of vehicles. Because of the training a pharmacist receives, his knowledge of the characteristics of various pharmaceuticals and therapeutic agents and his technique and skill in preparing elegant preparations are well-developed, so that he is qualified admirably to advise concerning the proper use of vehicles.

A large selection of flavors is available as well as a choice of colors, so that one may prescribe a basic drug for a prolonged period, but by changing the vehicle from time to time, the taste and appearance are so altered that the patient does not tire of the prescription or show other psychological reactions to it.

The statement of the late Dr Bernard Fantus that "the best solvent is the best vehicle" helps to explain the proper use of a flavoring vehicle. For example, a substance that is soluble in alcohol, eg, phenobarbital, will not leave an alcoholic vehicle readily to dissolve in the aqueous saliva.

Waters—These are the simplest of the vehicles and are available with several flavors. They contain no sucrose, a fact to be considered at times, since sucrose under certain circumstances may be undesirable. They are likewise nonalcoholic, another fact which frequently influences vehicle selection.

Elixirs—These have added sweetness that waters lack, and they usually contain alcohol, which imparts an added sharpness to the flavor of certain preparations, making the latter more pleasing to the taste. Elixirs are suitable for alcohol-soluble drugs.

Syrups—These vehicles, like elixirs, offer a wide selection of flavors and colors from which to choose. Their specific value, however, lies particularly in the fact that they are intensely sweet and contain little or no alcohol, a combination which makes them of singular value as masking agents for water-soluble drugs.

Vehicles consisting of a solution of pleasantly flavored volatile oils in syrup or glycerin (1:500) have been employed successfully in producing uniform and stable preparations. These vehicles are prepared by adding 2 mL of the volatile oil, diluted with 6 mL of alcohol, to 500 mL of glycerin or syrup, which has been warmed gently. The solution is added a little at a time with continuous shaking, and then sufficient glycerin or syrup is added to make 1000 mL, and mixed well.

Alcohol solutions of volatile oils are sometimes used as "stock solutions" for flavoring pharmaceuticals.

A listing of substances, most of them official, used as flavors, flavored vehicles or as sweeteners, is given in Table I. Additional information on flavoring ingredients may be obtained in Furia TE, Bellanca A: *Fenaroli's Handbook of Flavor Ingredients*, Chemical Rubber, Cleveland, 1971.

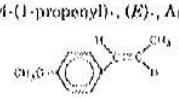
Table I—Flavoring Agents

Acacia syrup	Honey
Anethole	Iso-Alcoholic elixir
Anise oil	Lavender oil
Aromatic elixir	Lemon oil
Benzaldehyde	Lemon tincture
Benzaldehyde elixir, compound	Mannitol
Caraway	Methyl salicylate
Caraway oil	Nutmeg oil
Cardamom oil	Orange, bitter, elixir
Cardamom seed	Orange, bitter, oil
Cardamom spirit, compound	Orange flower oil
Cardamom tincture, compound	Orange flower water
Cherry juice	Orange oil
Cherry syrup	Orange peel, bitter
Cinnamon	Orange peel, sweet, tincture
Cinnamon oil	Orange spirit, compound
Cinnamon water	Orange syrup
Citric acid	Peppermint
Citric acid syrup	Peppermint oil
Clove oil	Peppermint spirit
Cocoa	Peppermint water
Cocoa syrup	Phenylethyl alcohol
Coriander oil	Raspberry juice
Dextrose	Raspberry syrup
Eriodictyon	Rosemary oil
Eriodictyon fluidextract	Rose oil
Eriodictyon syrup, aromatic	Rose water
Ethyl acetate	Rose water, stronger
Ethyl vanillin	Saccharin
Fennel oil	Saccharin calcium
Ginger	Saccharin sodium
Ginger fluidextract	Sarsaparilla syrup, compound
Ginger oleoresin	Sorbitol solution
Glucose	Spearmint
Glycerin	Spearmint oil
Glycyrrhiza	Sucrose
Glycyrrhiza elixir	Syrup
Glycyrrhiza extract	Thyme oil
Glycyrrhiza extract, pure	Tolu balsam
Glycyrrhiza fluidextract	Tolu balsam syrup
Glycyrrhiza syrup	Vanilla
	Vanilla tincture
	Vanillin
	Wild cherry syrup

Acacia Syrup—see page 1301.

Anethole

Benzene, 1-methoxy-4-(1-propenyl)-, (*E*)-, Anethol; Anise Camphor



(*E*)-*p*-Proponylanisole [4180-23-8] $C_{10}H_{12}O$ (148.20); obtained from anise oil and other sources, or prepared synthetically.

Preparation—It is the principal constituent of anise and fennel oil and usually is obtained from these sources by fractionating and chilling the proper fraction whereby it crystallizes out.

Description—Colorless or faintly yellow liquid at or above 23°; aromatic odor of anise and a sweet taste; affected by light; specific gravity 0.983 to 0.988; distils completely 231 to 237° and congeals at not less than 20°; its alcohol solution is neutral to litmus.

Solubility—Very slightly soluble in water; freely soluble in alcohol; miscible with chloroform or ether; yields a clear solution with 2 volumes of alcohol.

Uses—A *flavoring agent*. Its uses are similar to those of anise oil. It sometimes is sold as *Synthetic* or *Artificial Anise Oil* for flavoring and is a licorice-like flavor used in *Diphenhydramine Hydrochloride Elixir*.

Anise Oil

Aniseed Oil; Star Anise Oil

The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* Linné (Fam *Umbelliferae*) or from the dried, ripe fruit of *Illicium verum* Hooker filius (Fam *Magnoliaceae*).

Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.

Constituents—The official oil varies somewhat in composition, depending upon whether it was obtained from *Pimpinella anisum* or the star anise, *Illicium verum*. *Anethole* is the chief constituent of both oils, occurring to the extent of 80 to 90%. *Methyl chavicol*, an isomer of anethole, and *anisic ketone* [$C_{10}H_{10}O_2$] are also found in both oils, as are small amounts of many other constituents.

Description—Colorless or pale yellow, strongly refractive liquid, having the characteristic odor and taste of anise; specific gravity 0.978 to 0.988; congeals not below 15°.

Solubility—Soluble in 3 volumes of 90% alcohol.

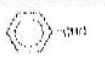
Uses—Extensively as *a flavoring agent*, particularly for licorice candies. It has been given as *a carminative* in a dose of about 0.1 mL.

Aromatic Elixir—page 1302.

Aromatic Elixir, Red—RPS-15, page 1240.

Benzaldehyde

Artificial Essential Almond Oil



Benzaldehyde [100-52-7] C_7H_6O (106.12).

Preparation—By the interaction of benzal chloride with lime in the presence of water. Benzal chloride is obtained by treating boiling toluene with chlorine.

Description—Colorless, strongly refractive liquid, having an odor resembling that of bitter almond oil, and a burning aromatic taste; affected by light; specific gravity 1.041 to 1.046; boils about 180°, solidifies about −56.5° and on exposure to air it gradually oxidizes to benzoic acid.

Solubility—Dissolves in about 350 volumes of water; miscible with alcohol, ether, chloroform or fixed and volatile oils.

Uses—In place of bitter almond oil for *flavoring* purposes; it is much safer than the latter because it contains no hydrocyanic acid. It also is used extensively in *perfumery* and in the manufacture of dyestuffs and many other organic compounds, such as aniline, acetanilid or mandelic acid.

Compound Benzaldehyde Elixir—*Preparation:* Dissolve benzaldehyde (0.5 mL) and vanillin (1 g) in alcohol (50 mL); add syrup (600 mL), orange flower water (150 mL) and sufficient purified water, in several portions, shaking the mixture thoroughly after each addition, to make the product measure 1000 mL; then filter, if necessary, until the product is clear. *Alcohol Content:* 3 to 5%. *Uses:* A useful vehicle for administering bromides and other salts, especially when a low alcoholic content is desired.

Camphor Water—RPS-13, page 436.

Caraway

Carum; Caraway Seed; Caraway Fruit; Kimmel

The dried ripe fruit of *Carum carvi* Linné (Fam *Umbelliferae*).

Constituents—About 6% of *volatile oil*, with a little *fixed oil* and other constituents.

Uses—A *flavor*. It also has been used empirically as *a carminative* and *stimulant*.

Caraway Oil [Oleum Cari]—A volatile oil distilled from the dried, ripe fruit of *Carum carvi* Linné (Fam *Umbelliferae*); yields not less than 50% (*v/v*) of $C_{10}H_{14}O$ (carvone). The chief odoriferous component of the oil is the ketone *d-carvone* [$C_{10}H_{14}O$], which is the optical isomer of the levorotatory variety occurring in spearmint oil. The remainder of the oil consists mainly of the terpene *d-limonene* [$C_{10}H_{16}$]. Colorless or pale yellow liquid, with the characteristic odor and taste of caraway; specific gravity 0.900 to 0.910. *Uses:* In making caraway water and as a flavor and *carminative* in other pharmaceutical preparations.

Cardamom Seed

Cardamom Fruit; Cardamom; Ceylon or Malabar Cardamom

The dried ripe seed of *Elettaria cardamomum* (Linné) Maton (Fam. *Zingiberaceae*).

It should be removed recently from the capsule.

Constituents—A *volatile oil*, the yield of which is 1.3% from Malabar Ceylon Seeds and 2.6% from Mysore-Ceylon Seeds. *Fixed oil* is present to the extent of 10%, also starch, mucilage, etc.

Uses—A *flavor*. For many years it was employed empirically as a *carminative*.

Cardamom Oil—The volatile oil distilled from the seed of *Elettaria cardamomum* (Linné) Maton (Fam *Zingiberaceae*). Varieties of the oil contain *d-α-terpineol* [$C_{10}H_{17}OH$] both free and as the acetate, 5 to 10% *cineol* [$C_{10}H_{18}O$] and *limonene* [$C_{10}H_{16}$]. The Ceylon Oil, however, contains the alcohol *4-terpineol* (*4-carbomenthenol*) [$C_{10}H_{17}OH$], the terpenes *terpinene* and *sabinene*, and *acetic* and *formic acids*, probably combined as esters. Colorless or very pale yellow liquid possessing the aromatic, penetrating and somewhat camphoraceous odor of cardamom, and a persistently pungent, strongly aromatic taste; affected by light. Specific gravity 0.917 to 0.947; miscible with alcohol; dissolves in 5 volumes of 70% alcohol. *Uses:* A *flavor*.

Cardamom Tincture, Compound—page 1302.

Cherry Juice—page 1320.

Cherry Syrup—page 1301.

Cinnamon

Saigon Cinnamon; True Cinnamon; Saigon Cassia

The dried bark of *Cinnamomum loureirii* Nees (Fam. *Lauraceae*).

It contains, in each 100 g, not less than 2.5 mL of volatile oil.

Uses—A *flavoring agent*. Formerly, it was used as a carminative.

Cinnamon Oil [Cassia Oil; Oil of Chinese Cinnamon]—The volatile oil distilled with steam from the leaves and twigs of *Cinnamomum cassia* (Nees) Nees ex Blume (Fam *Lauraceae*), rectified by distillation; contains not less than 80%, by volume, of the total aldehydes of cinnamon oil. Cinnamaldehyde is the chief constituent. Yellowish or brownish liquid, becoming darker and thicker on aging or exposure to the air, and having the characteristic odor and taste of cassia cinnamon; specific gravity 1.045 to 1.063. Soluble in an equal volume of alcohol, 2 volumes of 70% alcohol or an equal volume of glacial acetic acid. *Uses:* A *flavor*. It formerly was used in a dose of 0.1 mL for flatulent colic.

Cocoa

Cacao USP XVI; Prepared Cocoa; Powdered Cocoa; Cocoa Powder; Medium-Fat Cocoa

A powder prepared from the roasted, cured kernels of the ripe seed of *Theobroma cacao* Linné (Fam *Sterculiaceae*).

It yields 10 to 22% of nonvolatile, ether-soluble extractive.

Preparation—The cocoa bean is dark as the result of a fermentation and roasting process which it undergoes. *Plain chocolate* consists of shelled cocoa beans (*cocoa nibs*) ground to a smooth paste which forms a hard cake when it cools because of the high fat content (50 to 58%).

It is the food prepared by pulverizing the residue remaining after part of the fat has been removed by expression from plain chocolate. It may be flavored by the addition of ground spice, ground vanilla bean, vanillin, ethylvanillin, coumarin, salt and other flavors as long as they do not imitate the flavor of chocolate, milk or butter. Three types are recognized depending on fat content: *breakfast cocoa* or *high fat cocoa* (22% minimum), *cocoa* or *medium-fat cocoa* (10 to 22%) and *low-fat cocoa* (less than 10%).

Sweet chocolate is plain chocolate plus added sugar and flavor (usually vanilla).

Milk chocolate is a mixture of sweet chocolate and milk powder or other dairy product. Chocolate and the products described above contain the purines theobromine and caffeine, and considerable quantities of fat (cocoa butter or theobroma oil), as well as protein and starch. These factors are lowered in sweet chocolate because of the large amount of added sugar (more than 50% of the final product).

Description—Weak reddish to purplish brown to moderate brown powder having a chocolate-like odor and taste, free from sweetness.

Uses—A food and pharmaceutically as a flavor in tablets, syrups, pill and tablet coatings, troches, etc.

Cocoa Syrup—page 1301.

Coriander—page 1200.

Coriander Oil

The volatile oil distilled with steam from the dried ripe fruit of *Coriandrum sativum* Linné (Fam *Umbelliferae*).

Constituents—The alcohol *d-linaloöl* (formerly termed *"coriandrol"*) is the chief constituent of this oil, occurring in amounts varying from 60 to 80%. Other constituents include *l-borneol, geraniol, pinenes, terpinenes* and *p-cymene*.

Description—Colorless or pale yellow liquid, having the characteristic odor and taste of coriander; specific gravity 0.863 to 0.875.
Solubility—Soluble in 3 volumes of 70% alcohol.

Uses—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative*.

Denatonium Benzoate—page 1321.

Eriodictyon

Consumptives' Weed; Mountain Balm; Yerba Santa

The dried leaf of *Eriodictyon californicum* (Hooker et Arnott) Torrey (Fam *Hydrophyllaceae*).

Constituents—A bitter *resin, volatile oil, eriodictyonone* [$C_{16}H_{14}O_6$, also called *homoeriodictyol*], *fixed oil, tannin, gum*, etc.

Uses—A pharmaceutical necessity. It is used in the preparation of *Eriodictyon Fluidextract*.

Eriodictyon Fluidextract [Yerba Santa Fluidextract]—*Preparation:* Using Eriodictyon (in moderately coarse powder, 1000 g), prepare the fluidextract by Process A (page 1543), using a mixture of 4 volumes of alcohol and 1 volume of water as the menstruum. Macerate the drug during 48 hr, then percolate at a moderate rate and reserve the first 800 mL of percolate. *Alcohol Content:* 57 to 62%. *Uses:* A peculiar, aromatic *flavor* used in syrups and elixirs, especially for masking the taste of bitter drugs like quinine. Because of its resinous character it requires an alkali to render it soluble in aqueous mixtures.

Eriodictyon Syrup, Aromatic—page 1301.

Ethyl Acetate

Acetic acid, ethyl ester; Acetic Ether

$CH_3COOC_2H_5$

Ethyl acetate [141-78-6] $C_4H_8O_2$ (88.11).
Preparation—By slow distillation of a mixture of alcohol and acetic acid in the presence of sulfuric acid.

Description—Transparent, colorless liquid with a fragrant and refreshing, slightly acetous odor, and a peculiar acetone, burning taste; specific gravity 0.894 to 0.898; distills 76 to 77.5°.
Solubility—1 mL in about 10 mL of water; miscible with alcohol, acetone, ether, chloroform or fixed and volatile oils.

Uses—Chiefly as a *flavoring agent*. It is used industrially in artificial fruit essence, *as a solvent* for nitrocellulose varnishes and lacquers and as a solvent in organic chemistry.

Ethyl Vanillin

Benzaldehyde, 3-ethoxy-4-hydroxy-; Bourbonal; Ethovan; Vanillal; Vanirome

3-Ethoxy-4-hydroxybenzaldehyde [121-32-4] $C_9H_{10}O_3$ (166.18).
Preparation—By reacting *o*-ethoxyphenol with formaldehyde and *p*-nitrosodimethylaniline in the presence of aluminum and water.

Description—Fine, white or slightly yellowish crystals; odor and taste similar to vanillin; affected by light; solutions are acid to litmus; melts about 77°.
Solubility—1 g in about 100 mL of water at 50°; freely soluble in alcohol, chloroform, ether or solutions of fixed alkali hydroxides.

Uses—A *flavor*, like vanillin, but stronger.

Eucalyptus Oil

The volatile oil distilled with steam from the fresh leaf of *Eucalyptus globulus* Labillardière or of some other species of *Eucalyptus* L'Heritier (Fam *Myrtaceae*). It contains not less than 70% of $C_{10}H_{18}O$ (eucalyptol).

Constituents—The most important constituent is *eucalyptol (cineol)*. Other compounds include *d-α-pinene, globulol, pinocarveol, pinocarvone* and several aldehydes.

Description—Colorless or pale yellow liquid, having a characteristic, aromatic, somewhat camphoraceous odor, and a pungent, spicy, cooling taste; specific gravity 0.905 to 0.925 at 25°.
Solubility—Soluble in 5 volumes of 70% alcohol.

Uses—A *flavoring agent* and an *expectorant* in chronic bronchitis. It also has *bacteriostatic* properties. This oil may be toxic.

Fennel Oil

The volatile oil distilled with steam from the dried ripe fruit of *Foeniculum vulgare* Miller (Fam *Umbelliferae*).

Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.

Constituents—*Anethole* [$C_{10}H_{12}O$] is the chief constituent, occurring to the extent of 50 to 60%. Some of the other constituents are *d*-pinene, phellandrene, dipentene, fenchone, methylchavicol, anisaldehyde and anisic acid.

Description—Colorless or pale yellow liquid, having the characteristic odor and taste of fennel; specific gravity 0.953 to 0.973; congealing temperature is not below 3°.
Solubility—Soluble in 8 volumes of 80% alcohol or in 1 volume of 90% alcohol.

Uses—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative*.

Glycyrrhiza

Licorice Root; Liquorice Root; Sweetwood; Italian Juice Root; Spanish Juice Root

The dried rhizome and roots of *Glycyrrhiza glabra* Linné, known in commerce as Spanish Licorice, or of *Glycyrrhiza glabra* Linné var *glandulifera* Waldstein et Kitaibel, known in commerce as Russian Licorice, or of other varieties of *Glycyrrhiza glabra* Linné, yielding a yellow and sweet wood (Fam. *Leguminosae*).

Constituents—This well-known root contains 5 to 7% of the sweet principle *glycyrrhizin*, or *glycyrrhizic acid* which is 50 times as sweet as cane sugar. There also is present an oleoresinous substance to which its slight acridity is due. If alcohol or an alkali is used as a menstruum for the root and the preparation not treated to deprive it of acridity, it will have a disagreeable aftertaste. For this reason boiling water is used for its extraction in both the extract and the fluidextract.

Description—The USP/NF provides descriptions of *Unground Spanish and Russian Glycyrrhizas, Histology* and *Powdered Glycyrrhiza*.

Uses—Valuable in pharmacy chiefly for its *sweet flavor*. It is one of the most efficient substances known for masking the taste of bitter substances, like quinine. Acids precipitate the glycyrrhizin and should not be added to mixtures in which glycyrrhiza is intended to mask disagreeable taste. Most of the imported licorice is used

by tobacco manufacturers to flavor tobacco. It also is used in making candy.

Pure Glycyrrhiza Extract [Pure Licorice Root Extract]—*Preparation:* Moisten 1000 g of glycyrrhiza, in granular powder, with boiling water, transfer it to a percolator, and percolate with boiling water until the glycyrrhiza is exhausted. Add enough diluted ammonia solution to the percolate to impart a distinctly ammoniacal odor, then boil the liquid under normal atmospheric pressure until it is reduced to a volume of about 1500 mL. Filter the liquid, and immediately evaporate the filtrate until the residue has a pilular consistency. Pure extract of glycyrrhiza differs from the commercial extract in that it is almost completely soluble in aqueous mixtures. The large amount of filler used in the commercial extract to give it firmness renders it unfit to use as a substitute for the pure extract. *Description:* Black, pilular mass having a characteristic, sweet taste. *Uses:* A *flavoring agent*. One of the ingredients in *Aromatic Cascara Sagrada Fluidextract*.

Glycyrrhiza Fluidextract [Licorice Root Fluidextract; Liquid Extract of Liquorice]—*Preparation:* To 1000 g of *coarsely* ground glycyrrhiza add about 3000 mL of boiling water, mix, and allow to macerate in a suitable, covered percolator for 2 hr. Then allow the percolation to proceed at a rate of 1 to 3 mL/min, gradually adding boiling water until the glycyrrhiza is exhausted. Add enough diluted ammonia solution to the percolate to impart a distinctly ammoniacal odor, then boil the liquid actively under normal atmospheric pressure until it is reduced to a volume of about 1500 mL. Filter the liquid, evaporate the filtrate on a steam bath until the residue measures 750 mL, cool, gradually add 250 mL of alcohol and enough water to make the product measure 1000 mL, and mix. *Alcohol Content:* 20 to 24%, by volume. *Uses:* A pleasant *flavor* for use in syrups and elixirs to be employed as vehicles and correctives.

Glycyrrhiza Elixir—page 1302.
Glycyrrhiza Syrup—page 1302.
Honey—page 1302.
Hydriodic Acid Syrup—page 1302.
Iso-Alcoholic Elixir—page 1328.

Lavender Oil

Lavender Flowers Oil

The volatile oil distilled with steam from the fresh flowering tops of *Lavandula officinalis* Chaix ex Villars (*Lavandula vera* DeCandolle) (Fam *Labiatae*) or produced synthetically. It contains not less than 35% of esters calculated as $C_{12}H_{20}O_2$ (linalyl acetate).

Constituents—It is a product of considerable importance in perfumery. *Linalyl acetate* is the chief constituent. *Cineol* appears to be a normal constituent of English oils. Other constituents include *amyl alcohol, d-borneol* (small amount); *geraniol, lavandulol* ($C_{10}H_{18}O$); *linalool; nerol; acetic, butyric, valeric,* and *caprylic acids* (as esters); traces of *d-pinene, limonene* (in English oils only) and the sesquiterpene *caryophyllene; ethyl n-amyl ketone;* an aldehyde (probably *valeric aldehyde*) and *coumarin*.

Description—Colorless or yellow liquid, having the characteristic odor and taste of lavender flowers; specific gravity 0.875 to 0.889.
Solubility—1 volume dissolves in 4 volumes of 70% alcohol.

Uses—Primarily as a *perfume*. It formerly was used in doses of 0.1 mL as a *carminative*.

Lemon Oil

The volatile oil obtained by expression, without the aid of heat, from the fresh peel of the fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), with or without the previous separation of the pulp and the peel. The total aldehyde content, calculated as citral ($C_{10}H_{16}O$), is 2.2–3.8% for California-type oil, and 3.0–5.5% for Italian-type oil.

Note—Do not use oil that has a terebinthine odor.

Constituents—From the standpoint of odor and flavor, the most noteworthy constituent is the aldehyde *citral*, which is present to the extent of about 4%. About 90% of *d-limonene* is present; small amounts of *l-α-pinene, β-pinene, camphene, β-phellandrene* and γ-terpinene also occur. About 2% of a solid, nonvolatile substance called *citroptene, linettin* or *lemon-camphor*, which is dissolved out of the peel, also is present. In addition, there are traces of several other compounds: *α-terpineol*; the *acetates of linalool* and *geranial; citronellal, octyl* and *nonyl aldehydes;* the sesquiterpenes *bisabolene* and *cadinene* and the ketone *methylheptenone*.

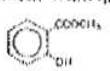
When fresh, the oil has the fragrant odor of lemons. Because of the instability of the terpenes present, the oil readily undergoes deterioration by oxidation, acquiring a terebinthinate odor.

Description—Pale yellow to deep yellow or greenish yellow liquid, with the characteristic odor and taste of the outer part of fresh lemon peel; specific gravity 0.849 to 0.855.
Solubility—Soluble in 3 volumes of alcohol; miscible in all proportions with dehydrated alcohol, carbon disulfide or glacial acetic acid.

Uses—A *flavor* in pharmaceutical preparations and in certain candies and foods.

Methyl Salicylate

Benzoic acid, 2-hydroxy-, methyl ester; Gaultheria Oil; Wintergreen Oil; Betula Oil; Sweet Birch Oil; Teaberry Oil; Artificial Wintergreen Oil; Synthetic Wintergreen Oil



Methyl salicylate [119-36-8] $C_6H_4(OH)COOCH_3$ (152.15); produced synthetically or obtained by maceration and subsequent distillation with steam from the leaves of *Gaultheria procumbens* Linné (Fam *Ericaceae*) or from the bark of *Betula lenta* Linné (Fam *Betulaceae*).

Note—It must be labeled to indicate whether it was made synthetically or distilled from either of the plants mentioned above.

Preparation—Found naturally in gaultheria and betula oils and in many other plants but the commercial product is usually synthetic, made by esterifying salicylic acid with methyl alcohol in the presence of sulfuric acid and distilling.

Description—Colorless, yellowish or reddish liquid, having the characteristic odor and taste of wintergreen; specific gravity (synthetic), 1.180 to 1.185, (from gaultheria or betula), 1.176 to 1.182; boils between 219 to 224° with some decomposition.
Solubility—Slightly soluble in water; soluble in alcohol or glacial acetic acid.

Uses—A pharmaceutical necessity and *counterirritant* (local analgesic). As a pharmaceutical necessity, it is used to flavor the official *Aromatic Cascara Sagrada Fluidextract*, and it is equal in every respect to wintergreen oil or sweet birch oil. As a counterirritant, it is applied to the skin in the form of a liniment, ointment or cream; care should be exercised since salicylate is absorbed through the skin.

Caution—Because it smells like wintergreen candy, it is ingested frequently by children and has caused many fatalities. *Keep out of the reach of children.*

Dose—*Topical*, in lotions and solutions in 10 to 25% concentration.

Monosodium Glutamate

Glutamic acid, monosodium salt, monohydrate

[142-47-2] $C_5H_8NNaO_4 \cdot H_2O$ (187.13)

Preparation—From the fermentation of beet sugar or molasses or by hydrolysis of vegetable proteins.

Description—White, crystalline powder. The pentahydrate effloresces in air to form the monohydrate.
Solubility—Very soluble in water; sparingly soluble in alcohol.

Uses—Flavoring agent and perfume.

Nutmeg Oil

Myristica Oil NF XIII; East Indian Nutmeg Oil; West Indian Nutmeg Oil

The volatile oil distilled with steam from the dried kernels of the ripe seeds of *Myristica fragrans* Houttuyn (Fam *Myristicaceae*).

Constituents—It contains about 80% of *d-pinene* and *d-camphene*, 8% of *dipentene*, about 6% of the alcohols *d-borneol, geraniol, d-linalool* and *terpineol*, 4% of *myristicin*, 0.6% of *safrol*, 0.3% of *myristic acid* free and as esters, 0.2% of *eugenol* and *isoeugenol* and traces of the alcohol *terpineol-4*, a citral-like aldehyde and several acids, all present as esters.

Description—Colorless or pale yellow liquid having the characteristic odor and taste of nutmeg; specific gravity (East Indian Oil) 0.880 to 0.910, (West Indian Oil) 0.864 to 0.880.

Solubility—Soluble in an equal amount of alcohol; 1 volume of East Indian Oil in 3 volumes of 90% alcohol; 1 volume of West Indian Oil in 4 volumes of 90% alcohol.

Uses—Primarily as a *flavoring agent*. It is used for this purpose in *Aromatic Ammonia Spirit* (page 1539). The oil also is employed as a *flavor* in foods, certain alcoholic beverages, dentifrices and tobacco; to some extent, it also is used in perfumery. It *formerly* was used as a *carminative* and *local stimulant* to the gastrointestinal tract in a dose of 0.03 mL. In overdoses, it acts as a narcotic poison. *This oil is very difficult to keep and even if slightly terebinthinate is unfit for flavoring purposes.*

Orange Oil

Sweet Orange Oil

The volatile oil obtained by expression from the fresh peel of the ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*). The total aldehyde content, calculated as decanal ($C_{10}H_{20}O$), is 1.2 to 2.5%.

Note—Do not use oil that has a terebinthine odor.

Constituents—Consists of *d-limonene* to the extent of at least 90%; in the remaining 5 to 10% are the odorous constituents, among which, in samples of American origin, are *n-decylic aldehyde, citral, d-linalool, n-nonyl alcohol* and traces of *esters of formic, acetic, caprylic* and *capric* acids.

In addition to most of these compounds, Italian-produced oil contains *d-terpineol, terpinolene, α-terpinene* and *methyl anthranilate*.

Kept under the usual conditions it is very prone to decompose, and rapidly acquires a terebinthine odor.

Description—Intensely yellow orange or deep orange liquid, which possesses the characteristic odor and taste of the outer part of fresh sweet orange peel; specific gravity 0.842 to 0.846.

Solubility—Miscible with dehydrated alcohol and with carbon disulfide; dissolves in an equal volume of glacial acetic acid.

Uses—A *flavoring agent* in elixirs and other preparations.

Orange Flower Oil

Neroli Oil

The volatile oil distilled from the fresh flowers of *Citrus aurantium* Linné (Fam *Rutaceae*).

Constituents—*β-Ocimene, l-α-pinene, l-camphene, dipentene, l-linalool, geraniol, farnesol, d-terpineol, phenylethyl alcohol, nerol, nerolidol, decylic aldehyde, jasmone, methyl anthranilate, indole, acetic esters of the alcohols* present and traces of *esters of benzoic, phenylacetic* and *palmitic acids*.

Description—Pale yellow, slightly fluorescent liquid, which becomes reddish brown on exposure to light and air; distinctive, fragrant odor, similar to that of orange blossoms, and an aromatic, at first sweet, then somewhat bitter, taste; may become turbid or solid at low temperatures; specific gravity 0.863 to 0.880; neutral to litmus paper; an alcoholic solution has a *violet fluorescence*.

Uses—A *flavor* and *perfume*. Several less valuable varieties of the oil are known commercially. These are designated as *Bigarade* (from the fresh flowers of bitter orange, the ordinary neroli oil), *Portugal* (from the fresh flowers of sweet orange) and *Petit-grain* (from the leaves and young shoots of the bitter orange). The finest variety is known as *Petale*.

Orange Flower Water—page 1300.

Sweet Orange Peel Tincture

Preparation—From sweet orange peel, which is the outer rind of the nonartificially colored, fresh, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*), by Process M (page 1543). Macerate 500 g of the sweet orange peel (*Note—Exclude the inner, white portion of the rind*) in 900 mL of alcohol, and complete the preparation with alcohol to make the product measure 1000 mL. Use talc as the filtering medium.

The white portion of the rind must not be used, as the proportion of oil, which is only in the yellow rind, is reduced, and the bitter principle *hesperidin* is introduced.

Alcohol Content—62 to 72%.

Uses—A *flavor*, used in syrups, elixirs and emulsions. This tincture was introduced to provide a delicate orange flavor direct from the fruit instead of depending upon orange oil which so frequently is terebinthinate and unfit for use. The tincture keeps well.

Compound Orange Spirit

Contains, in each 100 mL, 25 to 30 mL of the mixed oils.

Orange Oil	200 mL
Lemon Oil	50 mL
Coriander Oil	20 mL
Anise Oil	5 mL
Alcohol, a sufficient quantity,	
To make	1000 mL

Mix the oils with sufficient alcohol to make the product measure 1000 mL.

Alcohol Content—65 to 70%.

Uses—A *flavor* for elixirs. An alcoholic solution of this kind permits the uniform introduction of small proportions of oils and also preserves orange and lemon oils from rapid oxidation. These two oils should be bought in small quantities by the pharmacist, since the spirit is made most satisfactorily from oils taken from bottles not previously opened. This will insure that delicacy of flavor which should always be characteristic of elixirs.

Orange Syrup

Syrup of Orange Peel

Contains, in each 100 mL, 450 to 550 mg of citric acid ($C_6H_8O_7$).

Sweet Orange Peel Tincture	50 mL
Citric Acid (anhydrous)	5 g
Talc	15 g
Sucrose	820 g
Purified Water, a sufficient quantity,	
To make	1000 mL

Triturate the talc with the tincture and citric acid, and gradually add 400 mL of purified water. Then filter, returning the first portions of the filtrate until it becomes clear, and wash the mortar and filter with enough purified water to make the filtrate measure 450 mL. Dissolve the sucrose in this filtrate by agitation, without heating, and add enough purified water to make the product measure 1000 mL. Mix and strain.

Note—Do not use syrup that has a terebinthine odor or taste or shows other indications of deterioration.

Alcohol Content—2 to 5%.

Uses—A pleasant, acidic vehicle.

Peppermint

American Mint; Lamb Mint; Brandy Mint

Consists of the dried leaf and flowering top of *Mentha piperita* Linné (Fam *Labiatae*).

Uses—The source of green color for *Peppermint Spirit* (page 798). The odor of fresh peppermint is due to the presence of about 2% of a volatile oil, much of which is lost on drying the leaves in air. It is cultivated widely both in the US and France. It formerly was used as a carminative.

Peppermint Oil—The volatile oil distilled with steam from the fresh overground parts of the flowering plant of *Mentha piperita* Linné (Fam *Labiatae*), rectified by distillation and neither partially nor wholly dementholized. It yields not less than 5% of esters, calculated as menthyl acetate [$C_{12}H_{22}O_2$], and not less than 50% of total menthol [$C_{10}H_{20}O$], free and as esters. *Constituents:* This is one of the most important of the group of volatile oils. The chief constituent is *Menthol* (page 765) which occurs in the levorotatory form; its ester, *menthyl acetate*, is present in a much smaller amount. Other compounds which are present include the ketone *menthone, piperitone, α-pinene, l-limonene, phellandrene, cadinene, menthyl isovalerate, isovaleric aldehyde, acetaldehyde, menthofuran, cineol*, an unidentified *lactone* [$C_{10}H_{16}O_2$] and probably *amyl acetate*. Colorless or pale yellow liquid, having a strong,

penetrating odor of peppermint and a pungent taste, followed by a sensation of cold when air is drawn into the mouth; specific gravity 0.896 to 0.908; 1 volume dissolves in 3 volumes of 70% alcohol. *Uses:* A *flavoring agent*, *carminative*, *antiseptic* and *local anesthetic*. It also is used extensively as a *flavor* in candy, chewing gum, etc.

Peppermint Spirit—page 798.

Peppermint Water—page 1300.

Phenylethyl Alcohol

Benzeneethanol; 2-Phenylethanol

Phenethyl alcohol [60-12-8] $C_8H_{10}O$ (122.17); occurs in a number of essential oils such as those of rose, neroli, hyacinth, carnation and others.

Description—Colorless liquid with a *rose*-like odor and a sharp, burning taste; solidifies at −27°; specific gravity 1.017 to 1.020.

Solubility—1 g in 80 mL of water; ≈1 mL of alcohol, chloroform or ether; very soluble in fixed oils, glycerin or propylene glycol; slightly soluble in mineral oil.

Uses—Introduced for use as an antibacterial agent in ophthalmic solutions, but it is of limited effectiveness.

It is used in *flavors*, as a *soap perfume* and in the preparation of synthetic oils of rose and similar flower oils. It is also a valuable perfume fixative.

Pine Needle Oil

Dwarf Pine Oil

The volatile oil distilled with steam from the fresh leaf of *Pinus mugo* Turra and its variety *pumilio* (Huenke) Zenari (Fam *Pinaceae*); contains 3 to 10%, by weight, of esters calculated as $C_{12}H_{20}O_2$ (bornyl acetate).

Constituents—It contains the terpenes *l-α-pinene*, *d-pinene*, *l-phellandrene*, *l-limonene*, *dipentene*, and possibly *sylvestrene*, the ester *bornyl acetate* and several unidentified terpene and sesquiterpene alcohols.

Description—Colorless to yellowish liquid, having a pleasant, aromatic odor and a bitter, pungent taste; specific gravity 0.853 to 0.871 at 25°.

Solubility—Dissolves in 4.5 to 10 volumes of 90% alcohol, often with turbidity.

Uses—Chiefly as a *perfume* and *flavoring agent*. It also is employed as an inhalant in bronchitis.

Raspberry Syrup—page 1302.

Rose Oil

Otto of Rose; Attar of Rose

The volatile oil distilled with steam from the fresh flowers of *Rosa gallica* Linné, *Rosa damascena* Miller, *Rosa alba* Linné, *Rosa centifolia* Linné and varieties of these species (Fam *Rosaceae*).

Constituents—From the quantitative standpoint the chief components are the alcohols *geraniol* [$C_{10}H_{18}O$] and *l-citronellol* [$C_{10}H_{20}O$]. The sesquiterpene alcohols *farnesol* and *nerol* occur to the extent of 1% and 5 to 10%, respectively. Together, the four alcohols constitute 70 to 75% of the oil. *Phenylethyl alcohol*, which comprises 1% of the oil, is an important odoriferous constituent. Other compounds present are *linalool*, *eugenol*, *nonyl aldehyde*, traces of *citral* and two solid hydrocarbons of the paraffin series.

Description—A colorless or yellow liquid, which has the characteristic odor and taste of rose; at 25°, a viscous liquid; on gradual cooling it changes to a translucent, crystalline mass, which may be liquefied easily by warming; specific gravity 0.848 to 0.863 at 30° compared with water at 15°; 1 pt. mixes with 1 mL of chloroform without turbidity; on the addition of 20 mL of 90% alcohol to this solution, the resulting liquid is neutral or acid to moistened litmus paper and deposits a crystalline residue within 5 min on standing at 20°.

Uses—Principally as a *perfume*. It is recognized officially for its use as an ingredient in *Rose Water Ointment* and cosmetics.

Stronger Rose Water

Triple Rose Water

A saturated solution of the odoriferous principles of the flowers of *Rosa centifolia* Linné (Fam *Rosaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

Note—When diluted with an equal volume of purified water, it may be supplied when *Rose Water* is required.

Description—Nearly colorless and clear liquid which possesses the pleasant odor and taste of fresh rose blossoms; must be free from empyreuma, mustiness and fungal growths.

Uses—An ingredient in *Rose Water Ointment*. It sometimes is prepared extemporaneously from concentrates or from rose oil, but such water is not official and rarely compares favorably with the fresh distillate from rose petals.

Saccharin

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide; Glusidе; *o*-Benzosulfimide
Saxin (*Burroughs Wellcome*); Sweeta (*Squibb*)

1,2-Benzisothiazolin-3-one 1,1-dioxide [81-07-2] $C_7H_5NO_3S$ (183.18).

Preparation—Toluene is reacted with chlorosulfonic acid to form *o*-toluenesulfonyl chloride, which is converted to the sulfonamide with ammonia. The methyl group then is oxidized with dichromate yielding *o*-sulfamoylbenzoic acid which, when heated, forms the cyclic imide.

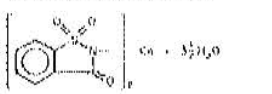
Description—White crystals or a white crystalline powder; odorless or has a faint aromatic odor; in dilute solution it is intensely sweet; solutions are acid to litmus; melts between 226 to 230°.

Solubility—1 g in 290 mL of water, 31 mL of alcohol or 25 mL of boiling water; slightly soluble in chloroform or ether; readily dissolved by dilute solution of ammonia, solutions of alkali hydroxides or solutions of alkali carbonates with the evolution of CO_2.

Uses—A sweetening agent in *Aromatic Cascara Sagrada Fluidextract* and highly alcoholic preparations. It is an intensely sweet substance. A 60-mg portion is equivalent in sweetening power to approximately 30 g of sucrose. It is used as a *sweetening agent* in vehicles, canned foods, beverages and in diets for diabetics to replace the sucrose. The relative sweetening power of saccharin is increased by dilution.

Saccharin Calcium

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide, calcium salt, hydrate (2:7)
Calcium *o*-Benzosulfimide



1,2-Benzisothiazolin-3-one 1,1-dioxide calcium salt hydrate (2:7) [6381-91-5] $C_{14}H_{18}CaN_2O_{16}S_2 \cdot 3\frac{1}{2}H_2O$ (467.48); *anhydrous* [6485-34-3] (404.43).

Preparation—Saccharin is reacted with a semimolar quantity of calcium hydroxide in aqueous medium and the resulting solution is concentrated to crystallization.

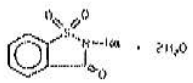
Description—White crystals or a white, crystalline powder; odorless or has a faint aromatic odor; and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose.

Solubility—1 g in 2.6 mL of water or 4.7 mL of alcohol.

Uses and Dose—See *Saccharin*.

Saccharin Sodium

1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide, sodium salt, dihydrate; Soluble Saccharin, Soluble Glusidе, Sodium o-Benzosulfimide



1,2-Benzisothiazolin-3-one 1,1-dioxide sodium salt dihydrate [6155-57-3] $C_7H_4NNaO_3S.2H_2O$ (241.19); *anhydrous* [128-44-9] (205.16).

Preparation—Saccharin is dissolved in an equimolar quantity of aqueous sodium hydroxide and the solution is concentrated to crystallization.

Description—White crystals or a white crystalline powder; odorless or has a faint aromatic odor and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose; when in powdered form it usually contains about ⅛ the theoretical amount of water of hydration due to efflorescence.

Solubility—1 g in 1.5 mL of water or 50 mL of alcohol.

Uses—Same as *Saccharin* but has the advantage of being more soluble in neutral aqueous solutions.

Application—15 to 60 mg as necessary.

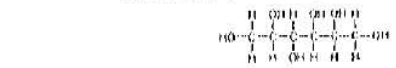
Dosage Form—Tablets: 15, 30 and 60 mg.

Sarsaparilla Syrup, Compound—RPS-13, page 445.

Shorry Wine—page RPS-15, page 1240.

Sorbitol

Sionin; Sorbit; D-Sorbitol; D-Glucitol Sorbo (*Atlas*)



D-Glucitol [50-70-4] $C_6H_{14}O_6$ (182.17); it may contain small amounts of other polyhydric alcohols.

Preparation—Commercially by reduction (hydrogenation) of certain sugars, such as glucose.

Description—White, hygroscopic powder, granules or flakes, having a sweet taste; the usual form melts about 96°.

Solubility—1 g in about 0.45 mL of water; slightly soluble in alcohol, methanol or acetic acid.

Uses—An *osmotic diuretic* given intravenously in 50% (*w/v*) solution to diminish edema, lower cerebrospinal pressure or reduce intraocular pressure in glaucoma. It also is used as a laxative, sweetener, humectant, plasticizer and, in 70% (*w/w*) solution, as a vehicle.

Dose—50 to 100 mL of a 50% solution; *laxative, oral*, 30 to 50 g.

Sorbitol Solution is a water solution containing, in each 100 g, 69–71 g of total solids consisting essentially of D-sorbitol and a small amount of mannitol and other isomeric polyhydric alcohols. The content of D-sorbitol [$C_6H_8(OH)_6$] in each 100 g is not less than 64 g. *Description:* Clear, colorless, syrupy liquid, having a sweet taste and no characteristic odor; neutral to litmus; specific gravity not less than 1.285; refractive index at 20° 1.455 to 1.465. *Uses:* It is not to be injected. It has been used as a replacement for propylene glycol and glycerin.

Spearmint

Spearmint Leaves; Spearmint Herb; Mint

The dried leaf and flowering top of *Mentha spicata* Linné (*Mentha viridis* Linné) (Common Spearmint) or of *Mentha cardiaca* Gerard ex Baker (Scotch Spearmint) (Fam *Labiatae*).

Fresh spearmint is used in preparing mint sauce and also the well-known mint julep. The volatile oil is the only constituent of importance in this plant; the yield is from ½ to 1%.

Uses—A flavoring agent.

Spearmint Oil is the volatile oil distilled with steam from the fresh over-ground parts of the flowering plant of *Mentha spicata* or of *Mentha cardiaca;* contains not less than 55%, by volume, of $C_{10}H_{14}O$ (carvone = 150.22). The chief odoriferous constituent is the ketone *l-carvone*. American oil also contains *dihydrocarveol acetate* [$CH_3COOC_{10}H_{17}$], *l-limonene* [$C_{10}H_{16}$], a small amount of *phellandrene* [$C_{10}H_{16}$] and traces of *esters of valeric* and *caproic acids*. Colorless, yellow or greenish yellow liquid, having the characteristic odor and taste of spearmint; specific gravity 0.917 to 0.934; soluble in 1 volume of 80% alcohol, but upon further dilution may become turbid. *Uses:* Primarily as a flavoring agent. It also has been used as a *carminative* in doses of 0.1 mL.

Sucrose

α-D-Glucopyranoside, β-D-fructofuranosyl-, Sugar; Cane Sugar; Beet Sugar

Sucrose [57-50-1] $C_{12}H_{22}O_{11}$ (342.30); a sugar obtained from *Saccharum officinarum* Linné (Fam *Gramineae*), *Beta vulgaris* Linné (Fam *Chenopodiaceae*), and other sources. It contains no added substances.

For the structural formula, see page 382.

Preparation—Commercially from the sugar cane, beet root and sorghum. Originally, sugar cane was the only source, but at present the root of *Beta vulgaris* is used largely in Europe, and to an increasing degree in this country, for making sucrose.

The sugar cane is crushed and the juice amounting to about 80% is expressed with roller mills. The juice after "defecation" with lime and removal of excess of lime by carbonic acid gas, is run into vacuum pans for concentration and the saccharine juice is evaporated in this until it begins to crystallize. After the crystallization is complete, the warm mixture of crystals and syrup is run into centrifuge, in which the crystals of raw sugar are drained and dried. The syrup resulting as a by-product from raw sugar is known as *molasses*. Raw beet sugar is made by a similar process, but is more troublesome to purify than that made from sugar cane.

The refined sugar from either raw cane or beet sugar is prepared by dissolving the raw sugar in water, clarifying, filtering and, finally, decolorizing the solution by passing it through bone-black filters. The water-white solution finally is evaporated under reduced pressure to the crystallizing point and then forced to crystallize in small granules which are collected and drained in a centrifuge.

Description—Colorless or white crystals, crystalline masses or blocks, or a white, crystalline powder; odorless; sweet taste; stable in air; solutions neutral to litmus; melts with decomposition from 160 to 185°; specific gravity of about 1.57; specific rotation at 20° not less than +65.9°; unlike the other official sugars (dextrose, fructose and lactose), it does not reduce Fehling's solution even in hot solutions; also differs from those sugars in that it is darkened and charred by sulfuric acid in the cold; fermentable and, in dilute aqueous solutions, it ferments into alcohol and eventually acetic acid.

Sucrose is hydrolyzed by dilute mineral acids, slowly in the cold, and rapidly on heating into one molecule each of dextrose or levulose. This process is known technically as "inversion" and the product is referred to as "invert sugar;" the term inversion being derived from the change, through the hydrolysis, in the optical rotation from dextro of the sucrose to levo of the hydrolyzed product. The enzyme *invertase* also hydrolyzes sucrose.

Solubility—1 g in 0.5 mL of water, 170 mL of alcohol or in slightly more than 0.2 mL of boiling water; insoluble in chloroform or ether.

Uses—Principally as a pharmaceutical necessity for making syrups and lozenges. It gives viscosity and consistency to fluids.

Intravenous administration of hypertonic solutions has been employed chiefly to initiate *osmotic diuresis*. Such a procedure is not completely safe and renal tubular damage may result, particularly in patients with existing renal pathology. Safer and more effective diuretics are available.

Compressible Sugar

Sucrose that may contain some starch, malto-dextrin or invert sugar; contains 95.0 to 98.0% of sucrose.

Description—White, crystalline, odorless powder; sweet taste; stable in air.

Solubility—The sucrose portion is very soluble in water.

Uses—A *pharmaceutic aid* as a *tableting excipient* and *sweetening agent*. See also *Sucrose*.

Confectioner's Sugar

Sucrose ground together with corn starch to a fine powder; contains 95.0 to 97.0% of sucrose.

Description—Fine, white, odorless powder; sweet taste; stable in air; specific rotation not less than +62.6°.

Solubility—The sucrose portion is soluble in cold water; this is entirely soluble in boiling water.

Uses—A *pharmaceutic aid* as a *tableting excipient* and *sweetening agent*. See also *Sucrose*.

Syrup—page 1302.

Tolu Balsam

Tolu

A balsam obtained from *Myroxylon balsamum* (Linné) Harms (Fam *Leguminosae*).

Constituents—Up to 80% *resin*, about 7% *volatile oil*, 12 to 15% free *cinnamic acid*, 2 to 8% benzoic acid and 0.05% *vanillin*. The volatile oil is composed chiefly of *benzyl benzoate* and *benzyl cinnamate*, *ethyl benzoate*, *ethyl cinnamate*, a terpene called *tolene* (possibly identical with *phellandrene*) and the sesquiterpene alcohol *farnesol* also have been reported to be present.

Description—Brown or yellowish brown, plastic solid; transparent in thin layers and brittle when old, dried or exposed to cold temperatures; pleasant, aromatic odor resembling that of vanilla and a mild, aromatic taste.

Solubility—Nearly insoluble in water or in solvent hexane; soluble in alcohol, chloroform or ether, sometimes with slight residue or turbidity.

Uses—A *vehicle*, *flavoring agent* and stimulating *expectorant* as a syrup. It is also an ingredient of *Compound Benzoin Tincture* (page 760).

Tolu Balsam Syrup [Syrup of Tolu; Tolu Syrup]—*Preparation:* Add tolu balsam tincture (60 mL, all at once) to magnesium carbonate (10 g) and sucrose (100 g) in a mortar, and mix intimately. Gradually add purified water (430 mL) with trituration, and filter. Dissolve the remainder of sucrose (760 g) in the clear filtrate with gentle heating, strain the syrup while warm and add purified water (qs) through the strainer to make the product measure 1000 mL. Mix thoroughly. *Note:* May be made also in the following manner: Place the remaining sucrose (760 g) in a suitable percolator, the neck of which nearly is filled with loosely packed cotton, moistened after packing with a few drops of water. Pour the filtrate, obtained as directed in the formula above, upon the sucrose, and regulate the outflow to a steady drip of percolate. When all of the liquid has run through, return portions of the percolate, if necessary, to dissolve all of the sucrose. Then pass enough purified water through the cotton to make the product measure 1000 mL. Mix thoroughly. *Alcohol Content:* 3 to 5%. *Uses:* Chiefly for its agreeable *flavor* in cough syrups. *Dose:* 10 mL.

Tolu Balsam Tincture [Tolu Tincture]—*Preparation:* With tolu balsam (200 g), prepare a tincture by Process M (page 1543), using alcohol as the menstruum. *Alcohol Content:* 77 to 83%. *Uses:* A balsamic preparation employed as an addition to expectorant mixtures; also used in the preparation of *Tolu Balsam Syrup*. *Dose:* 2 mL.

Vanilla

Vanilla Bean

The cured, full-grown, unripe fruit of *Vanilla planifolia* Andrews, often known in commerce as Mexican or Bourbon Vanilla, or of *Vanilla tahitensis* J W Moore, known in commerce as Tahiti Vanilla (Fam *Orchidaceae*); yields not less than 12% of anhydrous extractive soluble in diluted alcohol.

Constituents—Contains a trace of a volatile oil, fixed oil, 4% resin, sugar, *vanillic acid* and about 2.5% *vanillin* (see below). The highest grade of vanilla comes from Madagascar; considerable quantities of the drug also are produced in Mexico.

Uses—A flavor.

Note—Do not use if it has become brittle.

Vanilla Tincture [Extract of Vanilla]—*Preparation:* Add water (200 mL) to comminuted vanilla (cut into small pieces, 100 g) in a suitable covered container, and macerate during 12 hr, preferably in a warm place. Add alcohol (200 mL) to the mixture of vanilla and water, mix well and macerate about 3 days. Transfer the mixture to a percolator containing sucrose (in coarse granules, 200 g), and drain; then pack the drug firmly, and percolate slowly, using diluted alcohol (qs) as the menstruum. If the percolator is packed with an evenly distributed mixture of the comminuted vanilla, sucrose and clean, dry sand, the increased surface area permits more efficient percolation. This tincture is unusual in that it is the only official one in which sucrose is specified as an ingredient. *Alcohol Content:* 38 to 42%. *Uses:* A *flavoring agent*. See *Flavors*, page 1290.

Vanillin

Benzaldehyde, 4-hydroxy-3-methoxy-,

4-Hydroxy-3-methoxybenzaldehyde [121-33-5] $C_8H_8O_3$ (152.15).

Preparation—From vanilla, which contains 2 to 3%. It also is found in many other substances, including tissues of certain plants, crude beet sugar, asparagus and even asafetida. Commercially, it is made synthetically. While chemically identical with the product obtained from the "vanilla bean," "flavoring preparations" made from it never equal in flavor the preparation in which vanilla alone is used because vanilla contains other odorous products. It is synthesized by oxidation processes from either coniferin or eugenol, by treating guaiacol with chloroform in the presence of an alkali, and by other methods.

Description—Fine, white to slightly yellow crystals, usually needle-like having an odor and taste suggestive of vanilla; affected by light; solutions are acid to litmus; melts from 81 to 83°.

Solubility—1 g in about 100 mL of water, about 20 mL of glycerin or 20 mL of water at 80°; freely soluble in alcohol, chloroform, ether or solutions of the fixed alkali hydroxides.

Incompatibilities—Combines with *glycerin*, forming a compound which is almost insoluble in alcohol. It is decomposed by *alkalies* and is oxidized slowly by the *air*.

Uses—Only as a *flavor*. Solutions of it sometimes are sold as a synthetic substitute for vanilla for flavoring foods but it is inferior in flavor to the real vanilla extract.

Water—page 1300.

Water, Purified—page 1301.

Wild Cherry Syrup—page 1302.

Other Flavoring Agents

Anise NF IX [Anise Seed; European Aniseed; Sweet Cumin]—The dried ripe fruit of *Pimpinella anisum* Linné. It contains about 1.75% of volatile oil. *Uses:* A flavor and carminative.

Ceylon Cinnamon—The dried inner bark of the shoots of coppiced trees of *Cinnamomum zeylanicum* Nees (Fam *Lauraceae*); contains, in each 100 g, not less than 0.5 mL volatile oil. *Uses:* A *carminative* and *flavor*.

Clove—The dried flower-bud of *Eugenia caryophyllus* (Sprengel) Bullock et Harrison (Fam *Myrtaceae*). It contains, in each 100 g, not less than 16 mL of clove oil. *Uses:* An *aromatic* in doses of 0.25 g and as a condiment in foods.

Coriander—The dried ripe fruit of *Coriandrum sativum* Linné (Fam *Umbelliferae*); yields not less than 0.25 mL volatile coriander oil/100 g. *Uses:* Seldom used alone, but sometimes is combined with other agents, chiefly as a *flavor*. It also is used as a condiment and flavor in cooking.

Eucalyptol [Cineol; Cajeputol; Cal $H_{18}O$ (154.26)]—Obtained from eucalyptus oil and from other sources. Colorless liquid, having a characteristic, aromatic, distinctly camphoraceous odor and a pungent, cooling, spicy taste. 1 volume is soluble in 5 volumes of 60% alcohol; miscible with alcohol, chloroform, ether, glacial acetic acid or fixed or volatile oils; insoluble in water. *Uses:* Primarily as a *flavoring agent*. Locally it is employed for its *antiseptic* effect in inflammations of the nose and throat and in certain skin diseases. It sometimes is used by inhalation in bronchitis.

Fennel [Fennel Seed]—The dried ripe fruit of cultivated varieties of *Foeniculum vulgare* Miller (Fam *Umbelliferae*); contains 4 to 6% of an oxygenated volatile oil and 10% of a fixed oil. *Uses:* A *flavor* and *carminative*.

Ginger NF [Zingiber]—The dried rhizome of *Zingiber officinale* Roscoe (Fam *Zingiberaceae*), known in commerce as Jamaica Ginger, African Ginger and Cochin Ginger. The outer cortical layers often are removed either partially or completely. *Constituents:* A pungent substance, *zingerol*; volatile oil (Jamaica Ginger, about 1%; African Ginger, 2 to 3%), containing the terpenes *d*-*camphene* and *β*-*phellandrene* and the sesquiterpene *zingiberene*; *citral cineol* and *borneol*. *Uses:* A *flavoring agent*. It formerly was employed in a dose of 600 mg as an intestinal stimulant and carminative in colic and in diarrhea.

Ginger Oleoresin—Yields 18 to 35 mL of volatile ginger oil/100 g of oleoresin. *Preparation:* Extract the oleoresin from ginger, in moderately coarse powder, by percolation, using either acetone, alcohol or ether as the menstruum.

Glycyrrhiza Extract [Licorice Root Extract; Licorice]—An extract prepared from the rhizome and roots of species of *Glycyrrhiza* Tournefort ex Linné (Fam *Leguminosae*). *Description:* Brown powder or in flattened, cylindrical rolls or in masses; the rolls or masses have a glossy

black color externally, and a brittle, sharp, smooth, conchoidal fracture; the extract has a characteristic and sweet taste which is not more than very slightly acrid. *Uses:* A *flavoring agent.*

Lavender [Lavandula]—The flowers of *Lavandula spica* (*Lavandula officinalis* or *Lavandula vera*); contains a volatile oil with the principal constituent *l*-linalyl acetate. *Uses:* A *perfume.*

Lemon Peel USP XV, BP [Fresh Lemon Peel]—The outer yellow rind of the fresh ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*); contains a volatile oil and hesperidin. *Uses:* A *flavor.*

Lemon Tincture USP XVIII [Lemon Peel Tincture]—*Preparation:* From lemon peel, which is the outer yellow rind of the fresh, ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), by *Process M* (page 1543), 500 g of the peel being macerated in 900 mL alcohol and the preparation being completed with alcohol to make the product measure 1000 mL. Use talc as the filtering medium. The white portion of the rind must not be used, as the proportion of oil, which is found only in the yellow rind, is reduced and the bitter principle, hesperidin, introduced. *Alcohol Content:* 62 to 72%. *Uses:* A flavor, its fineness of flavor being assured as it comes from the fresh fruit, and being an alcoholic solution it is more stable than the oil.

Myrcia Oil [Bay Oil; Oil of Bay]—The volatile oil distilled from leaves of *Pimenta racemosa* (Miller) J W Moore (Fam *Myrtaceae*); contains the phenolic compounds eugenol and chavicol. *Uses:* In the preparation of bay rum as a *perfume.*

Orange Oil, Bitter—The volatile oil obtained by expression from the fresh peel of the fruit of *Citrus aurantium* Linné (Fam *Rutaceae*); contains primarily *d*-limonene. Pale yellow liquid with a characteristic, aromatic odor of the Seville orange; if it has a terebinthinate odor, it should not be dispensed; refractive index 1.4725 to 1.4755 at 20°. It differs little from *Orange Oil* (page 1296) except for the botanical source. Miscible with anhydrous alcohol and with about 4 volumes alcohol. *Uses:* A *flavor.*

Orange Peel, Bitter [Bitter Orange; Curacao Orange Peel; Bigarade Orange]—The dried rind of the unripe but fully grown fruit of *Citrus aurantium* Linné (Fam *Rutaceae*). *Constituents:* The inner part of the peel from the bitter orange contains a volatile oil and the glycoside *hesperidin* ($C_{28}H_{34}O_{15}$). This, upon hydrolysis in the presence of H_2SO_4, yields *hesperetin* ($C_{16}H_{14}O_6$), *rhamnose* ($C_6H_{12}O_5$), and D-glucose ($C_6H_{12}O_6$). *Uses:* A *flavoring agent.* It has been used as a bitter.

Orange Peel, Sweet USP XV—The fresh, outer rind of the non-artificially colored, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*); the white, inner portion of the rind is to be excluded. Contains a volatile oil but no hesperidin, since the glycoside occurs in the white portion of the rind. *Uses:* A *flavor.*

Orris [Orris Root; Iris; Florentine Orris]—The peeled and dried rhizome of *Iris germanica* Linné, including its variety *florentina* Dykes (*Iris florentina* Linné), or of *Iris pallida* Lamarck (Fam *Iridaceae*); contains about 0.1 to 0.2% of a volatile oil (orris butter), myristic acid and the ketone irone; irone provides the fragrant odor of orris. *Uses:* A *perfume.*

Pimenta Oil [Pimento Oil; Allspice Oil]—The volatile oil distilled from the fruit of *Pimenta officinalis* Lindley (Fam *Myrtaceae*). *Uses:* A *carminative* and *stimulant* and also as a *condiment* in foods.

Rosemary Oil—The volatile oil distilled with steam from the fresh flowering tops of *Rosmarinus officinalis* Linné (Fam *Labiatae*); yields not less than 1.5% of esters calculated as bornyl acetate ($C_{12}H_{20}O_2$), and not less than 8% of total borneol ($C_{10}H_{18}O$), free and as esters. *Constituents:* The amount of esters, calculated as bornyl acetate, and of total borneol, respectively, varies somewhat with its geographic source. Cineol is present to the extent of about 19–25%, depending on the source. The terpenes *d*- and *l*-α-*pinene*, *dipentene* and *camphene*, and the ketone *camphor* also occur in this oil. *Description:* Colorless or pale yellow liquid, having the characteristic odor of rosemary, and a warm, camphoraceous taste; specific gravity 0.894 to 0.912. Soluble in 1 volume of 90% alcohol, by volume, but upon further dilution may become turbid. *Uses:* A *flavor* and *perfume*, chiefly, in rubefacient liniments such as *Camphor and Soap Liniment.*

Sassafras—The dried bark of the root of *Sassafras albidum* (Nuttall) Nees (Fam *Lauraceae*). *Uses:* Principally because of its high content of volatile oil which serves to disguise the taste of disagreeable substances. An infusion (*sassafras tea*) formerly was used extensively as a home remedy, particularly in the southern states.

Sassafras Oil—The volatile oil distilled with steam from *Sassafras. Uses:* A *flavor* by confectioners, particularly in hard candies. Either the oil or safrol is used as a *preservative* in mucilage and library paste, being far superior to methyl salicylate for this purpose. Since the oil is *antiseptic*, it sometimes is employed in conjunction with other agents for local application in diseases of the nose and throat; safrol also is used in this way.

Wild Cherry [Wild Black Cherry Bark]—The carefully dried stem bark of *Prunus serotina* Ehrhart (Fam *Rosaceae*), free of borke and preferably having been collected in autumn. *Constituents:* A glucoside of *d*-*mandelonitrile* ($C_6H_5CHOH.CN$) known as *prunasin* (page 385), the enzyme *emulsin*, tannin, a bitter principle, starch, resin, etc. In the BP and the English literature this drug has been termed "Virginian Prune"—a literal but incorrect translation of the older botanical name, *Prunus virginiana. Uses:* A *flavoring agent*, especially in cough preparations. It is an ingredient in *Wild Cherry Syrup.* As with bitter almond, contact with water, in the presence of emulsin, results in the production of benzaldehyde and HCN. All preparations of wild cherry should be made without heat in order to avoid destruction of the enzyme which is responsible for the production of the free active principles.

Diluting Agents

Diluting agents (vehicles or carriers) are indifferent substances which are used as solvents for active medicinals. They are of primary importance for diluting and flavoring drugs which are intended for oral administration, but a few such agents are designed specifically for diluting parenteral injections. The latter group is considered separately.

The expert selection of diluting agents has been an important factor in popularizing the "specialties" of manufacturing pharmacists. Since a large selection of diluting agents is available in a choice of colors and flavors, the prescriber has an opportunity to make his own prescriptions more acceptable to the patient. The best diluting agent is usually the best solvent for the drug. Water-soluble substances, for example, should be flavored and diluted with an aqueous agent and alcohol-soluble drugs with an alcoholic vehicle. Thus, the diluting agents presented herein are divided into three groups on the basis of their physical properties: aqueous, hydroalcoholic and alcoholic.

Aqueous Diluting Agents

Aqueous diluting agents include aromatic waters, syrups and mucilages. Aromatic waters are used as diluting agents for water-soluble substances and salts, but cannot mask the taste of very disagreeable drugs. Some of the more common flavored aqueous agents and the official forms of water are listed below.

Orange Flower Water

Stronger Orange Flower Water; Triple Orange Flower Water

A saturated solution of the odoriferous principles of the flowers of *Citrus aurantium* Linné (Fam. *Rutaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

Description—Should be nearly colorless, clear or only faintly opalescent; the odor should be that of the orange blossoms; it must be free from empyreuma, mustiness and fungoid growths.

Uses—A *vehicle flavor* and *perfume* in syrups, elixirs and solutions.

Peppermint Water

A clear, saturated solution of peppermint oil in purified water, prepared by one of the processes described under *Aromatic Waters* (page 1522).

Uses—A *carminative* and *flavored vehicle.*

Dose—15 mL.

Tolu Balsam Syrup—page 1296.

Water

Water [7732-18-5] H_2O (18.02).

Drinking water, which is subject to EPA regulations with respect to drinking water, and which is delivered by the municipal or other local public system or drawn from a private well or reservoir, is the starting material for all forms of water covered by Pharmacopeial monographs.

Drinking water may be used in the preparation of USP drug substances (eg, in the extraction of certain vegetable drugs and in the manufacture of a few preparations used externally) but not in the preparation of dosage forms, or in the preparation of reagents or test solutions. It is no longer the subject of a separate monograph (in the USP), inasmuch as the cited standards vary from one community to another and generally are beyond the control of private parties or corporations.

Purified Water

Water obtained by distillation, ion-exchange treatment, reverse osmosis or any other suitable process; contains no added substances.

Caution—Do not use this in preparations intended for parenteral administration. For such purposes, use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection, page 1304.

Preparation—From water complying with EPA regulations with respect to drinking water. A former official process for water, when prepared by distillation, is given below. The pharmacist who is preparing sterile solutions, and must have freshly distilled water of exceptionally high grade, not only free from all bacterial or other microscopic growths but also free from the products of metabolic processes resulting from the growth of such organisms in the water, advantageously may follow this plan. The metabolic products commonly are spoken of as pyrogens and usually consist of complex organic compounds which cause febrile reactions if present in the solvent for parenteral medicinal substances.

Distillation Process

Water	1000 Vol
To make	750 Vol

Distil the water from a suitable apparatus provided with a block-tin or glass condenser. Collect the first 100 volumes and reject this portion. Then collect 750 volumes and keep the distilled water in glass-stoppered bottles, which have been rinsed with steam or very hot distilled water immediately before being filled. The first 100 volumes are discarded to eliminate foreign volatile substances found in ordinary water and only 750 volumes are collected, since the residue in the still contains concentrated dissolved solids.

Description—Colorless, clear liquid, without odor or taste.

Uses—A *pharmaceutic aid* (vehicle and solvent). It must be used in compounding dosage forms for internal (oral) administration as well as sterile pharmaceuticals applied externally, such as collyria and dermatological preparations, but these must be sterilized before use.

Whenever water is called for in official tests and assays, this must be used.

Syrups Used as Diluting Agents

Syrups are useful as diluting agents for water-soluble drugs and act both as solvents and flavoring agents. The flavored syrups usually consist of simple syrup (85% sucrose in water) containing appropriate flavoring substances. *Glycyrrhiza Syrup* is an excellent vehicle for saline substances because of its colloidal properties, sweet flavor and lingering taste of licorice. *Acacia Syrup* is valuable in disguising the taste of urea. Fruit syrups are especially effective for masking sour tastes. *Aromatic Eriodictyon Syrup* is the diluting agent of choice for masking the bitter taste of alkaloids. *Cocoa Syrup* and *Cherry Syrup* are good general flavoring agents.

Acacia Syrup

Acacia, granular or powdered	100 g
Sodium Benzoate	1 g
Vanilla Tincture	5 mL
Sucrose	800 g
Purified Water, a sufficient quantity.	
To make	1000 mL

Mix the acacia, sodium benzoate and sucrose; then add 425 mL of purified water, and mix well. Heat the mixture on a steam bath until solution is completed. When cool, remove the scum, add the vanilla tincture and sufficient purified water to make the product measure 1000 mL, and strain, if necessary.

Uses—A *flavored vehicle* and *demulcent*.

Cherry Syrup

Syrupus Cerasi

Cherry Juice	475 mL
Sucrose	800 g
Alcohol	20 mL
Purified Water, a sufficient quantity.	
To make	1000 mL

Dissolve the sucrose in cherry juice by heating on a steam bath, cool and remove the foam and floating solids. Add the alcohol and sufficient purified water to make 1000 mL, and mix.

Alcohol Content—1 to 2%.

Uses—A pleasantly *flavored vehicle* which is particularly useful in masking the taste of saline and sour drugs.

Cocoa Syrup

Cacao Syrup; Chocolate-flavored Syrup; Chocolate Syrup

Cocoa	180 g
Sucrose	600 g
Liquid Glucose	180 g
Glycerin	50 mL
Sodium Chloride	2 g
Vanillin	0.2 g
Sodium Benzoate	1 g
Purified Water, a sufficient quantity,	
To make	1000 mL

Mix the sucrose and the cocoa, and to this mixture gradually add a solution of the liquid glucose, glycerin, sodium chloride, vanillin and sodium benzoate in 325 mL of hot purified water. Bring the entire mixture to a boil, and maintain at boiling temperature for 3 min. Allow to cool to room temperature and add sufficient purified water to make the product measure 1000 mL.

Note—Cocoa containing not more than 12% nonvolatile, ether-soluble extractive ("fat") yields a syrup having a minimum tendency to separate. "Breakfast cocoa" contains over 22% "fat."

Uses—A pleasantly *flavored vehicle*.

Aromatic Eriodictyon Syrup

Aromatic Yerba Santa Syrup; Syrupus Corrigens

Eriodictyon Fluidextract	32 mL
Potassium Hydroxide Solution (1 in 20)	25 mL
Compound Cardamom Tincture	05 mL
Lemon Oil	0.5 mL
Clove Oil	1 mL
Alcohol	32 mL
Sucrose	800 g
Magnesium Carbonate	5 g
Purified Water, a sufficient quantity.	
To make	1000 mL

Dissolve the oils in the alcohol, add the fluidextract and the tincture, then the potassium hydroxide solution and 325 mL of purified water. Add the magnesium carbonate, shake the mixture, allow it to stand overnight, filter and add sufficient purified water through the filter to make the liquid measure 500 mL. Pour this filtrate upon the sucrose contained in a bottle, dissolve by placing the bottle in hot water and agitating the contents frequently. Cool the solution and add sufficient purified water to make the product measure 1000 mL.

Alcohol Content—6 to 8%.

Incompatibilities—Alkaline in reaction due to the potassium hydroxide used in its manufacture. *Acids* are neutralized with usually a

concurrent precipitation of the resins of the syrup. The tannin which it contains introduces the incompatibilities of that substance.

Uses—A pleasantly *flavored vehicle*, especially adapted to the administration of bitter substances like quinine.

Syrup

Simple Syrup

Sucrose	850 g
Purified Water, a sufficient quantity,	
To make	1000 mL

May be prepared by using boiling water or, preferably, without heat, by the following process:

Place the sucrose in a suitable percolator the neck of which is nearly filled with loosely packed cotton moistened, after packing, with a few drops of water. Pour carefully about 460 mL of purified water upon the sucrose, and regulate the outflow to a steady drip of percolate. Return the percolate, if necessary, until all of the sucrose has dissolved. Then wash the inside of the percolator and the cotton with sufficient purified water to bring the volume of the percolate to 1000 mL, and mix.

Specific Gravity—Not less than 1.30.

Uses—A *sweet vehicle*, sweetening agent and as the basis for many flavored and medicated syrups.

Other Syrups Used As Diluting Agents

Citric Acid Syrup USP XVIII [Syrup of Lemon]—*Preparation:* Dissolve citric acid (hydrous, 10 g) in purified water (10 mL), and mix the solution with syrup (950 mL). Add lemon tincture (10 mL), and enough syrup to make the product measure 1000 mL, and mix. *Note: Do not dispense it if it has a terebinthine odor or taste or shows other indications of deterioration. Alcohol Content:* Less than 1%. *Incompatibilities:* Reactions characteristic of the acid which it contains; hence, it is not a suitable vehicle for alkaline ingredients such as phenobarbital sodium from which it precipitates phenobarbital. *Uses:* Solely as a *pleasant vehicle*, the formula making it possible to prepare extemporaneously and quickly a syrup having the flavor of lemon.

Glycyrrhiza Syrup USP XVIII [Licorice Syrup]—*Preparation:* Add fennel oil (0.05 mL) and anise oil (0.5 mL) to glycyrrhiza fluidextract (250 mL) and agitate until mixed. Then add syrup (qs) to make the product measure 1000 mL, and mix. *Alcohol Content:* 5 to 6%. *Incompatibilities:* The characteristic flavor is destroyed by acids due to a precipitation of the glycyrrhizin. *Uses:* A *flavored vehicle*, especially adapted to the administration of bitter or nauseous substances.

Hydriodic Acid Syrup—Contains, in each 100 mL 1.3 to 1.5 g HI (127.91). *Preparation:* Mix diluted hydriodic acid (140 mL) with purified water (550 mL), and dissolve dextrose (450 g) in this mixture by agitation. Add purified water (qs) to make the product measure 1000 mL, and filter. *Caution: It must not be dispensed if it contains free iodine, as evidenced by a red coloration. Description:* Transparent, colorless, or not more than pale straw-colored, syrupy liquid; odorless and has a sweet, acidulous taste; specific gravity about 1.18; hydriodic acid is decomposed easily in simple aqueous solution (unless protected by hypophosphorous acid) free iodine being liberated, and if taken internally, when in this condition, it is irritating to the alimentary tract. The dextrose used in this syrup should be of the highest grade obtainable. *Incompatibilities:* The reactions of the *acids* (page 1523) as well as those of the water-soluble iodide salts. Oxidizing agents liberate iodine; alkaloids may be precipitated. *Uses:* Traditionally as a *vehicle for expectorant* drugs. Its therapeutic properties are those of the iodides. *Dose: Usual*, 5 mL.

Raspberry Syrup USP XVIII—*Preparation:* Dissolve sucrose (800 g) in raspberry juice (475 mL) by heating on a steam bath, cool and remove the foam and floating solids. Add alcohol (20 mL) and purified water (qs) to make 1000 mL, and mix. *Alcohol Content:* 1 to 2%. *Incompatibilities:* Raspberry juice is prepared to contain not less than 1.5% citric acid; the syrup, therefore, has reactions characteristic of this acid, notably its incompatibility with alkaline substances. *Uses:* A pleasantly *flavored vehicle* used to disguise the salty or sour taste of saline medicaments.

Wild Cherry Syrup USP XVIII—*Preparation:* Pack wild cherry (in coarse powder, 150 g), previously moistened with water (100 mL), in a cylindrical percolator, and add water (qs) to leave a layer of it above the powder. Macerate for 1 hr, then proceed with rapid percolation, using added water, until 400 mL of percolate is collected. Filter the percolate, if necessary, add sucrose (675 g) and dissolve it by agitation, then add glycerin (150 mL), alcohol (20 mL) and water (qs) to make the product measure 1000 mL. Strain if necessary. *It may be made also in the following manner:* The sucrose may be dissolved by placing it in a second percolator as directed for preparing *Syrup*, and allowing the percolate from the wild cherry to flow through it and into a graduated vessel containing the glycerin and alcohol until the total volume measures 1000 mL. *Note:* Heat is avoided, lest the enzyme emulsin be inactivated. If this should happen, the preparation would contain no free HCN, upon which its action as a sedative for coughs mainly depends. For a discussion of the chemistry involved, see *Wild Cherry* (page 1300). *Alcohol Content:* 1 to 2%. *Uses:* Chiefly as a *flavored vehicle* for cough syrups.

Mucilages Used as Diluting Agents

Mucilages are also suitable as diluting agents for water-soluble substances, and are especially useful in stabilizing suspensions and emulsions.

The following mucilage used for this purpose is described under *Emulsifying and Suspending Agents*, page 1304.

Acacia Mucilage—page 1304.

Hydroalcoholic Diluting Agents

Hydroalcoholic diluting agents are suitable for drugs soluble in either water or diluted alcohol. The most important agents in this group are the elixirs. These solutions contain approximately 25% alcohol. *Medicated* elixirs which have therapeutic activity in their own right are not included in this section. Listed below are the common, nonmedicated elixirs which are used purely as diluting agents or solvents for drugs.

Aromatic Elixir

Simple Elixir

Orange Oil	2.4 mL
Lemon Oil	0.6 mL
Coriander Oil	0.24 mL
Anise Oil	0.06 mL
Syrup	375 mL
Talc	30 g
Alcohol,	
Purified Water, each, a sufficient quantity,	
To make	1000 mL

Dissolve the oils in alcohol to make 250 mL. To this solution add the syrup in several portions, agitating vigorously after each addition, and afterwards add, in the same manner, the required quantity of purified water. Mix the talc with the liquid, and filter through a filter wetted with diluted alcohol, returning the filtrate until a clear liquid is obtained.

Alcohol Content—21 to 23%.

Uses—A pleasantly *flavored vehicle*, employed in the preparation of many other elixirs. The chief objection to its extensive use is the high alcohol content (about 22%) which at times may counteract the effect of other medicines.

Cardamom Spirit, Compound—RPS-15, page 1236.

Other Hydroalcoholic Diluting Agents

Glycyrrhiza Elixir [Elixir Adjuvans; Licorice Elixir]—*Preparation:* Mix glycyrrhiza fluidextract (125 mL) and aromatic elixir (875 mL) and filter. *Alcohol Content:* 24 to 23%. *Uses:* A *flavored vehicle.*

Flavored Alcoholic Solutions

Flavored alcoholic solutions, of high alcoholic concentration, are useful as flavors to be added in small quantities to syrups or elixirs. The alcohol content of these solutions is approximately 50%. There are two types of flavored alcoholic solutions: tinctures and spirits. Only nonmedicated tinctures and spirits are used as flavoring agents.

Compound Cardamom Tincture

Cardamom Seed, in moderately coarse powder	20 g
Cinnamon, in fine powder	25 g
Caraway, in moderately coarse powder	12 g
To make	1000 mL

Prepare a tincture by Process M (page 1543), macerating the mixed powders in 750 mL of a mixture of 50 mL of glycerin and 950 mL of diluted alcohol and completing the preparation by using first the remainder of the mixture of alcohol and glycerin prepared as directed above, and then diluted alcohol.

Note—Compound cardamom tincture may be colored with one or more colors (page 1288).

Alcohol Content—43 to 47%.

Uses—A useful vehicle because of its pleasant *flavor* and color.

Lemon Tincture—page 1300.

Myrcia Spirit, Compound—RPS-13, page 452.

Orange Spirit, Compound—page 1296.

Orange Peel, Sweet, Tincture—page 1296.

Peppermint Spirit—page 798.

Diluting Agents for Injections

Injections are liquid preparations, usually solutions or suspensions of drugs, intended to be injected through the skin into the body. Diluting agents used for these preparations may be aqueous or nonaqueous and must meet the requirements for sterility and also of the pyrogen test. Aqueous diluting agents include such preparations as *Sterile Water for Injection* and various sterile, aqueous solutions of electrolytes and/or dextrose. Nonaqueous diluting agents are generally fatty oils of vegetable origin, fatty esters and polyols such as propylene glycol and polyethylene glycol. These agents are used to dissolve or dilute oil-soluble substances and to suspend water-soluble substances when it is desired to decrease the rate of absorption and, hence, prolong the duration of action of the drug substances. Preparations of this type are given intramuscularly. See *Parenteral Preparations*, page 1545.

Corn Oil

Maize Oil

The refined fixed oil obtained from the embryo of *Zea mays* Linné (Fam *Gramineae*).

Preparation—Expressed from the Indian corn embryos or germs separated from the grain in starch manufacture.

Description—Clear, light yellow, oily liquid with a faint characteristic odor and taste; specific gravity 0.914 to 0.921.

Solubility—Slightly soluble in alcohol; miscible with ether, chloroform, benzene or solvent hexane.

Uses—Main official use is as a *solvent* and *vehicle for injections*. It is used as an edible oil substitute for solid fats in the management of hypercholesterolemia. Other uses include making soaps and for burning. It is a semidrying oil and therefore unsuitable for lubricating or mixing paint.

Cottonseed Oil

Cotton Seed Oil; Cotton Oil

The refined fixed oil obtained from the seed of cultivated plants of various varieties of *Gossypium hirsutum* Linné or of other species of *Gossypium* (Fam *Malvaceae*).

Preparation—Cotton seeds contain about 15% oil. The testae of the seeds are first separated, and the kernels are subjected to high pressure in hydraulic presses. The crude oil thus has a bright red to blackish red color. It requires purification before it is suitable for medicinal or food purposes.

Description—Pale yellow, oily liquid with a bland taste; odorless or nearly so; particles of solid fat may separate below 10°; solidifies at about 0° to −5°; specific gravity 0.915 to 0.921.

Solubility—Slightly soluble in alcohol; miscible with ether, chloroform, solvent hexane or carbon disulfide.

Uses—Official as a *solvent* and *vehicle for injections*. It is sometimes taken orally as a mild cathartic in the dose of 30 mL or more. Taken internally, digestible oils retard gastric secretion and motility and increase the caloric intake. It also is used in the manufacture of soaps, oleomargarine, lard substitutes, glycerin, lubricants and cosmetics.

Ethyl Oleate

(*Z*)-9-Octadecenoic acid, ethyl ester

Ethyl oleate [111-62-6] $C_{20}H_{38}O_2$ (310.52).

Preparation—Among other ways, by reacting ethanol with oleoyl chloride in the presence of a suitable dehydrochlorinating agent.

Description—Mobile, practically colorless liquid, having an agreeable taste; specific gravity 0.868 to 0.874; acid value not greater than 0.5; iodine value 75 to 85; sterilized by heating at 150° for 1 hr; properties similar to those of almond and arachis oils, but is less viscous and more rapidly absorbed by the tissues; boils about 207°.

Solubility—Does not dissolve in water; miscible with vegetable oils, mineral oil, alcohol or most organic solvents.

Uses—A *vehicle* for certain intramuscular injectable preparations.

Peanut Oil

Arachis Oil; Groundnut Oil; Nut Oil; Earth-Nut Oil

The refined fixed oil obtained from the seed kernels of one or more of the cultivated varieties of *Arachis hypogaea* Linné (Fam *Leguminosae*).

Description—Colorless or pale yellow, oily liquid, with a characteristic nutty odor and a bland taste; specific gravity 0.912 to 0.920.

Solubility—Very slightly soluble in alcohol; miscible with ether, chloroform or carbon disulfide.

Uses—A *solvent* in preparing oil solutions for injection (page 1549). It also is used for making liniments, ointments, plasters and soaps, as a substitute for olive oil.

Sesame Oil

Teel Oil; Benne Oil; Gingili Oil

The refined fixed oil obtained from the seed of one or more cultivated varieties of *Sesamum indicum* Linné (Fam *Pedaliaceae*).

Description—Pale yellow, almost odorless, oily liquid with a bland taste; specific gravity 0.916 to 0.921.

Solubility—Slightly soluble in alcohol; miscible with ether, chloroform, solvent hexane or carbon disulfide.

Uses—A *solvent* and *vehicle* in official injections. It is used much like olive oil both medicinally and for food. It does not readily turn rancid. It also is used in the manufacture of cosmetics, iodized oil, liniments, ointments and oleomargarine.

Water for Injection

Water purified by distillation or by reverse osmosis. It contains no added substance.

Caution—It is intended for use as a solvent for the preparation of parenteral solutions. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render it sterile and thereafter protect it from microbial contamination.

Description—Clear, colorless, odorless liquid.

Uses—*Pharmaceutic aid* (vehicle and solvent).

Bacteriostatic Water for Injection

Sterile water for injection containing one or more suitable antimicrobial agents.

Note—Use it with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.

Uses—*Sterile vehicle* for parenteral preparations.

Sterile Water for Injection

Water for Parenterals

Water for injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Description—Clear, colorless, odorless, liquid.

Uses—For the preparation of *all aqueous parenteral solutions*, including those used in *animal assays*. See page 1547 for a detailed discussion.

Sterile Water for Irrigation

Water for injection that has been sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Description—Clear, colorless, odorless liquid.

Uses—An *irrigating solution*.

Emulsifying and Suspending Agents

An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid that is immiscible with the first liquid. Emulsions are formed and stabilized with the help of emulsifying agents, which are surfactants and/or viscosity-producing agents. A suspension is defined as a preparation containing finely divided insoluble material suspended in a liquid medium. The presence of a suspending agent is required to overcome agglomeration of the dispersed particles and to increase the viscosity of the medium so that the particles settle more slowly. Emulsifying and suspending agents are used extensively in the formulation of elegant pharmaceutical preparations for oral, parenteral and external use. For the theoretical and practical aspects of emulsions the interested reader is referred to pages 300 and 1605. More detailed information on the use of suspending agents is given on page 1538.

Acacia

Gum Arabic

The dried gummy exudate from the stems and branches of *Acacia senegal* (Linné) Willdenow or of other related African species of *Acacia* (Fam *Leguminosae*).

Constituents—Principally calcium, magnesium and potassium salts of the polysaccharide *arabic acid*, which on acid hydrolysis yields L-arabinose, L-rhamnose, D-galactose and an aldobionic acid containing D-glucuronic acid and D-galactose.

Description—*Acacia:* Spheroidal tears up to 32 mm in diameter or angular fragments of white to yellowish white color; translucent or somewhat opaque; very brittle; almost odorless; produces a mucilaginous sensation on the tongue. *Flake Acacia:* White to yellowish white, thin flakes. *Powdered Acacia:* White to yellowish white, angular microscopic fragments. *Granular Acacia:* White to pale yellowish white, fine granules. *Spray-dried Acacia:* White to off-white compacted microscopic fragments or whole spheres.

Solubility—Insoluble in alcohol, but almost completely soluble in twice its weight of water at room temperature; the resulting solution flows readily and is acid to litmus.

Incompatibilities—*Alcohol or alcoholic solutions* precipitate acacia as a stringy mass when the alcohol amounts to more than about 35% of the total volume. Solution is effected by dilution with water. The mucilage is destroyed through precipitation of the acacia by *heavy metals*. *Borax* also causes a precipitation which is prevented by glycerin. It contains calcium and, therefore, possesses the incompatibilities of this ion.

It contains a *peroxidase* which acts as an oxidizing agent and produces colored derivatives of *aminopyrine, antipyrine, cresol, guaiacol, phenol, tannin, thymol, vanillin* and other substances. Among the alkaloids affected are *atropine, apomorphine, cocaine, homatropine, hyoscyamine, morphine, physostigmine* and *scopolamine*. A partial destruction of the alkaloid occurs in the reaction. Heating the solution of acacia for a few minutes at 100° destroys the peroxidase and the color reactions are avoided.

Uses—Extensively as a *suspending agent* for insoluble substances in water (page 1538), in the preparation of emulsions (pages 298 and 1534) and for making pills and troches (page 1664).

It is used for its *demulcent* action in inflammations of the throat or stomach.

Its solutions should not be used as a substitute for serum protein in the treatment of *shock* and as a *diuretic* in hypoproteinemic edema, since it produces serious syndromes that may result in death.

Acacia Mucilage [Mucilage of Gum Arabic]—*Preparation:* Place acacia (in small fragments, 350 g) in a graduated bottle having a wide mouth and a capacity not greatly exceeding 1000 mL, wash the drug with cold purified water, allow it to drain and add enough warm purified water, in which benzoic acid (2 g) has been dissolved, to make the product measure 1000 mL. After stoppering, lay the bottle on its side, rotate it occasionally, and when the acacia has dissolved strain the mucilage. *It also may be prepared as follows:* dissolve benzoic acid (2 g) in purified water (400 mL) with the aid of heat, and add the solution to powdered or granular acacia (350 g), in a mortar, triturating until the acacia is dissolved. Then add sufficient purified water to make the product measure 1000 mL, and strain if necessary. This second method is primarily for extemporaneous preparation. *Uses:* A *demulcent* and a *suspending agent*. It also has been employed as an *excipient* in making pills and troches, and as an *emulsifying agent* for cod liver oil and other substances. *Caution—It must be free from mold or any other indication of decomposition.*

Agar

Agar-Agar; Vegetable Gelatin; Gelose; Chinese or Japanese Gelatin

The dried, hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* (Linné) Gaillon (Fam *Gelidiaceae*), *Gracilaria confervoides* (Linné) Greville (Fam *Sphaerococcaceae*) and related red algae (Class *Rhodophyceae*).

Constituents—Chiefly of the calcium salt of a galactan mono-(acid sulfate).

Description—Usually in bundles of thin, membranous, agglutinated strips or in cut, flaked, or granulated forms; may be weak yellowish orange, yellowish gray to pale yellow or colorless; tough when damp, brittle when dry; odorless or with a slight odor; produces a mucilaginous sensation on the tongue. Also supplied as a white to yellowish white or pale-yellow powder.

Solubility—Insoluble in cold water; soluble in boiling water.

Incompatibilities—Like other gums, it is dehydrated and precipitated from solution by *alcohol*. *Tannic acid* causes precipitation; *electrolytes* cause partial dehydration and decrease in viscosity of sols.

Uses—A relatively ineffective bulk-producing laxative used in a variety of proprietary cathartics. In mineral oil emulsions it acts as a stabilizer. The usual dose is 4 to 16 g once or twice a day.

It also is used in culture media for bacteriological work and in the manufacture of ice cream, confectionaries, etc.

Alginic Acid

Alginic acid [9005-32-7] (average equivalent weight 200); a hydrophilic colloidal carbohydrate extracted with dilute alkali from various species of brown seaweeds (*Phaeophyceae*).

Preparation—Precipitates when an aqueous solution of *Sodium Alginate* is treated with mineral acid.

Description—White to yellowish white, fibrous powder; odorless or practically odorless, and tasteless; pH (3 in 100 dispersion in water) 1.5 to 3.5; pK_a (0.1*N* NaCl, 20°) 3.42.

Solubility—Insoluble in water or organic solvents; soluble in alkaline solutions.

Uses—A *pharmaceutic aid* (tablet binder and emulsifying agent). It is used as a sizing agent in the paper and textile industries.

Sodium Alginate

Alginic acid, sodium salt; Algin; Manucol; Norgine, Kelgin (*Kelco*)

Sodium alginate [9005-38-3] (average equivalent weight 220); the purified carbohydrate product extracted from brown seaweeds by the use of dilute alkali. It consists chiefly of the sodium salt of alginic acid, a polyuronic acid composed of beta-D-mannuronic acid residues linked so that the carboxyl group of each unit is free while the aldehyde group is shielded by a glycosidic linkage.

Description—Nearly odorless and tasteless, coarse or fine powder, yellowish white in color.

Solubility—Dissolves in water, forming a viscous, colloidal solution; insoluble in alcohol or in hydroalcoholic solutions in which the alcohol content is greater than about 30% by weight; insoluble in chloroform, ether or acids, when the pH of the solution becomes lower than about 3.

Uses—A *thickening* and *emulsifying agent*. This property makes it useful in a variety of areas. For example, it is used to impart smoothness and body to ice cream and to prevent formation of ice particles.

Bentonite

Wilkinite; Soap Clay; Mineral Soap

Bentonite [1302-78-9]; a native, colloidal, hydrated aluminum silicate.

Occurrence—Bentonite is found in the Midwest of the US and Canada. Originally called *Taylorite* after its discoverer in Wyoming, its name was changed to bentonite after its discovery in the Fort Benton formation of the Upper Cretaceous of Wyoming.

Description—Very fine, odorless powder with a slightly earthy taste, free from grit; the powder is nearly white, but may be a pale buff or cream-colored.

The US Geological Survey has defined bentonite as "a transported stratified clay formed by the alteration of volcanic ash shortly after deposition." Chemically, it is $Al_2O_3.4SiO_2.H_2O$ plus other minerals as impurities. It consists of colloidal crystalline plates, of less than microscopic dimensions in thickness, and of colloidal dimensions in breadth. This fact accounts for the extreme swelling that occurs when it is placed in water, since the water penetrates between an infinite number of plates. A good specimen swells 12 to 14 times its volume.

Solubility—Insoluble in water or acids, but it has the property of adsorbing large quantities of water, swelling to approximately 12 times its original volume, and forming highly viscous thixotropic suspensions or *gels*. This property makes it highly useful in pharmacy. Its gel-forming property is augmented by the addition of small amounts of alkaline substances, such as magnesium oxide. It does not swell in organic solvents.

Incompatibilities—*Acids* and *acid salts* decrease its water-absorbing power and thus cause a breakdown of the magma. Suspensions are most stable at a pH above 7.

Uses—A *protective colloid* for the *stabilization of suspensions*. It also has been used as an emulsifier for oil and as a base for plasters, ointments and similar preparations.

Bentonite Magma—*Preparation:* Sprinkle bentonite (50 g), in portions, on hot purified water (800 g), allowing each portion to become thoroughly wetted without stirring. Allow it to stand with occasional stirring for 24 hr. Stir until a uniform magma is obtained, add purified water to make 1000 g, and mix. The magma may be prepared also by mechanical means such as by use of a blender, as follows: Place purified water (about 500 g) in the blender, and while the machine is running, add bentonite (50 g). Add purified water to make up to about 1000 g or up to the operating capacity of the blender. Blend the mixture for 5 to 10 min, add purified water to make 1000 g, and mix. *Uses:* A *suspending agent* for insoluble medicaments.

Carbomer

Carboxypolymethylene

A synthetic high-molecular-weight cross-linked polymer of acrylic acid; contains 56 to 68% of carboxylic acid (—COOH) groups. The viscosity of a neutralized preparation (2.5 g/500 mL water) is 30,000 to 40,000 centipoises.

Description—White, fluffy powder with a slight characteristic odor; hygroscopic; pH (1 in 100 dispersion) about 3; specific gravity about 1.41.

Solubility (neutralized with alkali hydroxides or amines)—Dissolves in water, alcohol and glycerin.

Uses—A *thickening, suspending, dispersing* and *emulsifying agent* for pharmaceuticals, cosmetics, waxes, paints and other industrial products.

Carrageenan

Carrageenan [9000-07-1].

Preparation—The hydrocolloid extracted with water or aqueous alkali from certain red seaweeds of the class *Rhodophyceae*, and separated from the solution by precipitation with alcohol (methanol, ethanol or isopropanol) or by drum-roll drying or freezing.

Constituents—It is a variable mixture of potassium, sodium, calcium, magnesium and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers, the hexoses being alternately linked α-1,3 and β-1,4 in the polymer. The three main types of copolymers present are *kappa*-carrageenan, *iota*-carrageenan and *lambda*-carrageenan, which differ in the composition and manner of linkage of monomeric units and the degree of sulfation (the ester sulfate content for carrageenans varies from 18 to 40%). *Kappa*-carrageenan and *iota*-carrageenan are the gelling fractions; *lambda*-carrageenan is the nongelling fraction. The gelling fractions may be separated from the nongelling fraction by addition of potassium chloride to an aqueous solution of carrageenan. Carrageenan separated by drum-roll drying may contain mono- and diglycerides or up to 5% of polysorbate 80 used as roll-stripping agents.

Description—Yellow-brown to white, coarse to fine powder; odorless; tasteless, producing a mucilaginous sensation on the tongue.

Solubility—All carrageenans hydrate rapidly in cold water, but only *lambda*-carrageenan and sodium carrageenans dissolve completely. Gelling carrageenans require heating to about 80° for complete solution where potassium and calcium ions are present.

Uses—In the pharmaceutical and food industries as an emulsifying, suspending and gelling agent.

Carboxymethylcellulose Sodium

Carbose D; Carboxymethocel S; CMC; Cellulose Gum (*Hercules*)

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]; contains 6.5–9.5% of sodium (Na), calculated on the dried basis. It is available in several viscosity types: low, medium, high and extra high.

Description—White to cream-colored powder or granules; the powder is hygroscopic; pH (1 in 100 aqueous solution) about 7.5.

Solubility—Easily dispersed in water to form colloidal solutions; insoluble in alcohol, ether or most other organic solvents.

Uses—*Pharmaceutic aid* (suspending agent, tablet excipient or viscosity-increasing agent). In tablet form it is used as a hydrophilic colloid laxative.

Dose—*Usual, adult, laxative,* 1.5 g 3 or 4 times a day.

Dosage Form: Tablets: 500 mg.

Powdered Cellulose

Cellulose [9004-34-6] $(C_6H_{10}O_5)_n$; purified, mechanically disintegrated cellulose prepared by processing alpha cellulose obtained as a pulp from fibrous plant materials.

Description—White, odorless substance, consisting of fibrous particles, which may be compressed into self-binding tablets which disintegrate rapidly in water; exists in various grades, exhibiting degrees of fineness ranging from a free-flowing dense powder to a coarse, fluffy, nonflowing material; pH (supernatant liquid of a 10 g/90 mL aqueous suspension after 1 hr) 5 to 7.5.

Solubility—Insoluble in water, dilute acids or nearly all organic solvents; slightly soluble in NaOH solution (1 in 20).

Uses—*Pharmaceutic aid* (tablet diluent, adsorbent or suspending agent).

Cetyl Alcohol—page 1312.

Cholesterol

Cholest-5-en-3-ol, (3β)-, Cholesterin

Cholest-5-en-3β-ol [57-88-5] $C_{27}H_{46}O$ (386.66).

For the structural formula, see page 389.

A steroid alcohol widely distributed in the animal organism. In addition to cholesterol and its esters, several closely related steroid alcohols occur in the yolk of eggs, the brain, milk, fish oils, wool fat

(10 to 20%), etc. These closely resemble it in properties. One of the methods of commercial production involves extraction of it from the unsaponifiable matter in the spinal cord of cattle, using petroleum benzin. Wool fat also is used as a source.

Description—White or faintly yellow, almost odorless pearly leaflets or granules; usually acquires a yellow to pale tan color on prolonged exposure to light or to elevated temperatures; melts 147 to 150°.

Solubility—Insoluble in water; 1 g slowly dissolves in 100 mL of alcohol or about 50 mL of dehydrated alcohol; soluble in acetone, hot alcohol, chloroform, dioxane, ether, ethyl acetate, solvent hexane or vegetable oils.

Uses—To enhance incorporation and emulsification of medicinal products in oils or fats. It is a *pharmaceutical necessity* for *Hydrophilic Petrolatum*, in which it enhances water-absorbing capacity. See Chapter 19.

Dioctyl Sodium Sulfosuccinate (Docusate Sodium)—page 789.

Gelatin

White Gelatin

A product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissues and bones of animals. Gelatin derived from an acid-treated precursor is known as Type A and exhibits an isoelectric point between pH 7 and 9, while gelatin derived from an alkali-treated precursor is known as Type B and exhibits an isoelectric point between pH 4.7 and 5.2.

Gelatin for use in the manufacture of capsules in which to dispense medicines, or for the coating of tablets, may be colored with a certified color, may contain not more than 0.15% of sulfur dioxide, may contain a suitable concentration of sodium lauryl sulfate and suitable antimicrobial agents, and may have any suitable gel strength that is designated by Bloom Gelometer number.

Regarding the special gelatin for use in the preparation of emulsions, see *Emulsions* (page 1534).

Description—Sheets, flakes or shreds, or a coarse to fine powder; faintly yellow or amber in color, the color varying in depth according to the particle size; slight, characteristic bouillon-like odor; stable in air when dry, but is subject to microbial decomposition when moist or in solution.

Solubility—Insoluble in cold water, but swells and softens when immersed in it, gradually absorbing from 5 to 10 times its own weight of water; soluble in hot water, acetic acid or hot mixtures of glycerin and water; insoluble in alcohol, chloroform, ether or fixed and volatile oils.

Uses—In pharmacy, to coat pills and form capsules, and as a vehicle for suppositories. It also is recommended as an emulsifying agent. See under *Emulsions* in Chapters 19 and 83, also *Suppositories* (page 1669), and *Absorbable Gelatin Sponge* (page 816). It also has been used as an adjuvant protein food in malnutrition.

Glyceryl Monostearate—page 1312.

Hydroxyethyl Cellulose

Cellulose, 2-hydroxyethyl ether; Cellosize (*Union Carbide*); Natrosol (*Hercules*)

Cellulose hydroxyethyl ether [9004-62-0].

Preparation—Cellulose is treated with NaOH and then reacted with ethylene oxide.

Description—White, odorless, tasteless, free-flowing powder; softens at about 137°; refractive index (2% solution) about 1.336; pH about 7; solutions are nonionic.

Solubility—Dissolves readily in cold or hot water to give clear, smooth, viscous solutions; partially soluble in acetic acid; insoluble in most organic solvents.

Uses—Resembles carboxymethylcellulose sodium in that it is a cellulose ether, but differs in being nonionic and, hence, its solutions are unaffected by cations. It is used pharmaceutically as a thickener, protective colloid, binder, stabilizer and suspending agent in emulsions, jellies and ointments, lotions, ophthalmic solutions, suppositories and tablets.

Hydroxypropyl Cellulose

Cellulose, 2-hydroxypropyl ether; Klucel (*Hercules*)

Cellulose hydroxypropyl ether [9004-64-2].

Preparation—After treating with NaOH, cellulose is reacted with propylene oxide at elevated temperature and pressure.

Description—Off-white, odorless, tasteless powder; softens at 130°; burns out completely about 475° in N_2 or O_2; refractive index (2% solution) about 1.337; pH (aqueous solution) 5 to 8.5; solutions are nonionic.

Solubility—Soluble in water below 40° (insoluble above 45°); soluble in many polar organic solvents.

Uses—A broad combination of properties useful in a variety of industries. It is used pharmaceutically as a binder, granulation agent and film-coater in the manufacture of tablets; an alcohol-soluble thickener and suspending agent for elixirs and lotions and a stabilizer for emulsions.

Hydroxypropyl Methylcellulose

Cellulose, 2-hydroxypropyl methyl ether

Cellulose hydroxypropyl methyl ether [9004-65-3], available in grades containing 16.5 to 30.0% of methoxy and 4.0 to 32.0% of hydroxypropoxy groups, and thus in viscosity and thermal gelation temperatures of solutions of specified concentration.

Preparation—The appropriate grade of methylcellulose (see below) is treated with NaOH and reacted with propylene oxide at elevated temperature and pressure and for a reaction time sufficient to produce the desired degree of attachment of methyl and hydroxypropyl groups by ether linkages to the anhydroglucose rings of cellulose.

Description—White to slightly off-white, fibrous or granular, free-flowing powder.

Solubility—Swells in water and produces a clear to opalescent, viscous colloidal mixture; undergoes reversible transformation from sol to gel on heating and cooling, respectively. Insoluble in anhydrous alcohol, ether or chloroform.

Uses—A protective colloid that is useful as a dispersing and thickening agent, and in ophthalmic solutions to provide the demulcent action and viscous properties essential for contact-lens use and in "artificial-tear" formulations. See *Hydroxypropyl Methylcellulose Ophthalmic Solution* (page 760).

Lanolin, Anhydrous—page 1311.

Methylcellulose

Cellulose, methyl ether; Methocel (Dow); Cellothyl (*Warner Chilcott*); Hydrolose (*Upjohn*); Synecolose (*Blue Line*)

Cellulose methyl ether [9004-67-5]; a methyl ether of cellulose containing 27.5 to 31.5% of methoxy groups.

Preparation—By the reaction of methyl chloride or of dimethyl sulfate on cellulose dissolved in sodium hydroxide. The cellulose methyl ether so formed is coagulated by adding methanol or other suitable agent and centrifuged. Since cellulose has 3 hydroxyl groups/glucose residue, several methylcelluloses can be made varying, among other properties, in solubility and viscosity. Types useful for pharmaceutical application contain from 1 to 2 methoxy radicals/glucose residue.

Description—White, fibrous powder or granules; aqueous suspensions neutral to litmus; stable to alkalies and dilute acids.

Solubility—Insoluble in ether, alcohol or chloroform; soluble in glacial acetic acid and in a mixture of equal parts of alcohol and chloroform; swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in hot water and saturated salt solutions; salts of minerals acids and particularly of polybasic acids, phenols and tannins coagulate its solutions, but this can be prevented by the addition of alcohol or of glycol diacetate.

Uses—A synthetic substitute for natural gums that has both pharmaceutic and therapeutic applications. Pharmaceutically, it is used as a *dispersing, thickening, emulsifying, sizing* and *coating agent*. It is an ingredient of many nose drops, eye preparations, burn medications, cosmetics, tooth pastes, liquid dentifrices, hair fixatives, creams and lotions. It functions as a protective colloid for