1) Volcanic dust may have been an important cause of climatic fluctuations over the past 400 years. Except for the warm period in the first half of the 1800's (*26*), the computed volcano curve quite closely matches the observations curve (Fig. 1). The correlation coefficients (Table 1, run V) for the entire record are very significant, even with the linear trend removed, and the correlation coefficients for the most recent period, with the best volcano data and actual instrumental observations, are very high. The 5-year average correlation is higher than the correlation between 5-year averages of the two independent sets of observations of Budyko-Asakura (*24*) and Mitchell (*17*).

2) The hypothesis of sunspot-related solar constant changes is not supported. The significant correlation (Table 1, run S) of the entire record with the model result is almost entirely due to the upward linear trend in both series, and is even lower for the most recent period with more reliable data. The computed smoothed sunspot curve (Fig. 1) does not resemble the observations curve in any of its details. Thus the hypothesis of Eddy (*3*) that the Little Ice Age is related to the Maunder sunspot minimum through variations in the solar constant is not supported. This result does not rule out changes in the solar constant as causes of climatic change, but, if there is a relation, these changes must either be related to some yet to be discovered index other than sunspots or to sunspots in some very complex way (*27*).

3) Combining the volcano and sunspot forcings (Table 1, run V + S) (Fig. 1, volcanoes and smoothed sunspots curve) does not improve the volcano results.

4) Carbon dioxide produced by fossil-fuel burning does not seem to have had a significant effect on climatic change as yet. With it the results are slightly better for the entire record and slightly worse for the most recent portion. This conclusion should be qualified because there may be compensating anthropogenic influences such as aerosols (*15*), and the model tends to underemphasize the CO_2 effect as compared to more sophisticated radiation models which treat the stratosphere explicitly (*28*).

5) The random forcing results indicate the amount of natural variability to be expected in the climate without any external forcing. This is certainly an important cause of climatic fluctuations and may explain the difference between the observations and model results from purely external forcing.

6) In judging the above results, one must also bear in mind that both the climate reconstruction and the volcanic dust data are less reliable at the beginning of the record than at the end. Future research should help to clarify the magnitude of this problem and may actually improve the above results.

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References and Notes

1. *Understanding Climate Change* (National Academy of Sciences, Washington, D.C., 1975).
2. H. H. Lamb, in *World Survey of Climatology*, H. Flohn, Ed. (Elsevier, Amsterdam, 1969), vol. 2.
3. J. A. Eddy, *Sci. Am.* **236** (No. 5), 80 (1977); *Climatic Change* **1**, 173 (1977).
4. _____, *Science* **192**, 1189 (1976).
5. This has also been shown by J. M. Mitchell, in *Changes of Climate* (Unesco, Paris, 1963), pp. 161–181.
6. I. I. Borzenkova *et al.*, *Meteorol. Gidrol. No. 7* (1976), p. 27.
7. B. S. Groveman and H. E. Landsberg, *Publication No. 79-182* (Meteorology Program, University of Maryland, College Park, 1979).
8. B. S. Groveman, thesis, University of Maryland (1979); _____ and H. E. Landsberg, *Publication No. 79-181* (Meteorology Program, University of Maryland, College Park, 1979); *Geophys. Res. Lett.* **6**, 767 (1979).
9. R. S. Kraemer, *Bull. Am. Meteorol. Soc.* **59**, 822 (1978).
10. S. H. Schneider and C. Mass, *Science* **190**, 741 (1975).
11. K. Ya. Kondratyev and G. A. Nikolsky, *Q. J. R. Meteorol. Soc.* **96**, 509 (1970).
12. _____, in *Solar-Terrestrial Influences on Weather and Climate* (Ohio State University, Columbus, 1978), pp. 30–31.
13. C. Mass and S. H. Schneider, *J. Atmos. Sci.* **34**, 1995 (1977).
14. A. Robock, thesis, Massachusetts Institute of Technology (1977).
15. _____, *J. Atmos. Sci.* **35**, 1111 (1978).
16. The model is based on that of W. D. Sellers [*J. Appl. Meteorol.* **12**, 241 (1973); *ibid.* **13**, 831 (1974)]. The basic energy balance equation solved in the model for surface air temperature over land and water separately for each 10° latitude band with a 15-day time step is

$$C\frac{\partial T}{\partial t} = Q(1 - \alpha) - I - \text{div}\,(F)$$

where T is temperature, t is time, C is the thermal inertia, Q is the incoming solar radiation, α is the planetary albedo, I is the outgoing infrared radiation, and F is the horizontal energy transport by atmospheric and oceanic motions. For a discussion of changes made to the model and a detailed description of its performance, see (*14*) and A. Robock, in *Report of the JOC Study Conference on Climate Models: Performance, Intercomparison, and Sensitivity Studies* (World Meteorological Organization, Geneva, in press).
17. J. M. Mitchell, Jr., *Ann. N.Y. Acad. Sci.* **95**, 235 (1961).
18. A. Robock (*Mon. Weather Rev.*, in press) presents the seasonal cycles of snow and sea ice and regression with surface temperature as well as detailed calculations of surface albedo, including the effects of meltwater on the snow and ice albedos.
19. The sensitivity parameter is defined as

$$\beta = S_0\frac{d\overline{T}}{dS}$$

where $\overline{T}$ is the global mean surface temperature, S is the solar constant, and S_0 is its present value. It is discussed extensively in (*10*) and by R. D. Cess [*J. Atmos. Sci.* **33**, 1831 (1976)]. The statement that 200°C is a very reasonable value for β is based on the results of Cess who compared several types of climate models. The actual value of β in the real world is not known but probably lies in the range of 100° to 300°C.
20. H. H. Lamb, *Philos. Trans. R. Soc. London Ser. A* **266**, 425 (1970).
21. J. M. Mitchell, Jr., in *Global Effects of Environmental Pollution*, S. F. Singer, Ed. (Reidel, Dordrecht, 1970), pp. 139–155.
22. W. S. Broecker, *Science* **189**, 460 (1975).
23. T. H. Vonder Haar and A. H. Oort, *J. Phys. Oceanogr.* **3**, 169 (1973).
24. M. I. Budyko and H. Asakura, in (*1*), p. 148.
25. E. R. Cook and G. C. Jacoby, Jr., *Science* **198**, 399 (1977).
26. H. E. Landsberg (personal communication) believes that this portion of the curve may not be representative of the hemispheric average, but it is supported by the available data (*7*). See also H. E. Landsberg, *J. Interdiscip. Hist.*, in press.
27. Robock (*15*) tested several other linear and quadratic sunspot–solar constant relationships, with negative and positive coefficients in the equations, with and without explicitly including the sunspot cycle, and found that none of them resulted in a good climate simulation for the past 100 years. The long-term (400-year) linear trend found in the data and model results may be a solar effect, but it remains to be tested. Another sunspot–solar constant hypothesis that may explain part of the recent climate change has been suggested by D. V. Hoyt, *Climatic Change* **2**, 79 (1979).
28. S. H. Schneider, *J. Atmos. Sci.* **32**, 2060 (1975).
29. H. D. Brunk, *An Introduction to Mathematical Statistics* (Blaisdell, Waltham, Mass., 1965), pp. 220–222.
30. I thank H. Landsberg and C. Mass for their comments on the first draft of this report, S. Schneider for his suggestions as a reviewer, and A. Krol, S. Winslow, and C. Villanti for technical assistance. This research was supported by NASA grant NSG-5209.

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Chlorpromazine and Its Metabolites Alter Polymerization and Gelation of Actin

Abstract. *Hepatic hydroxylated metabolites of chlorpromazine (10^{-5}M to 10^{-4}M), a frequently used phenothiazine tranquilizer, produce solid gel formation with filamentous actin, but the less toxic chlorpromazine sulfoxide metabolite does not. At higher concentrations (5×10^{-4}M) chlorpromazine inhibits actin polymerization. These dose-response relationships parallel the drug's hepatic toxicity in vivo and suggest that interactions between chlorpromazine or chlorpromazine metabolites and actin could be an underlying mechanism of cell injury.*

Chlorpromazine (CPZ), commonly used as a phenothiazine tranquilizer, is an amphiphilic cationic detergent (*1*) that has multiple effects on membrane structure and function (*2*). Whether the therapeutic or untoward effects of CPZ are related to these effects is not known, but the drug produces abnormalities of the liver in many patients and infrequently causes cholestatic jaundice (*3*), probably by altering the properties of hepatocyte membranes. For example, CPZ diminishes bile secretion in the dog (*4*), rhesus monkey (*5*), and isolated perfused rat

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liver (*6*); in experiments with rat liver both in vitro and in vivo, the plasma membrane enzymes Na^+- and K^+-dependent adenosine triphosphatase (Na^+,K^+-ATPase) (*7, 8*) and Mg^{2+}-dependent ATPase (*6, 8*) are inhibited and there is morphologic evidence of cytoplasmic vacuolation and myeloid body formation (*9*).

Many of these toxic effects of CPZ might be related to binding of the drug or its hepatic metabolites to phospholipid within the membrane, particularly to phosphatidyl serine on the inner half of the bilayer, as suggested previously (*10*). But cytoplasmic vacuolization and surface membrane blebbing is also seen with agents that alter the function of microfilaments (*11*), and these otherwise nonspecific morphologic findings suggest that impairment of the cytoskeleton might be a primary drug effect. We now find that CPZ and several of its metabolites which are formed by hepatic metabolism are capable of modifying the ability of actin, the protein constituent of microfilaments, to polymerize and undergo gel formation, two fundamental properties of actin which influence its functional role in the cell (*12*).

Actin was prepared from rabbit skeletal muscle by a modification (*13*) of the method of Spudich and Watt (*14*). This more plentiful source of actin was used since we have previously shown that rat liver actin is reasonably similar to rabbit muscle actin with respect to properties of polymerization and activation of myosin ATPase activity (*15*). The polymerization of actin to its filamentous form (F-actin) in the presence of 2 m*M* Mg^{2+} and 0.5 m*M* ATP was assayed by viscometry at 25°C in a free-fall Ostwald viscometer (*16*). Though such a system is non-Newtonian, in control experiments, we observed highly reproducible and linear increases in specific viscosity with increasing concentrations of actin (0.2 to 1.0 mg/ml). As shown in Fig. 1, when CPZ (5×10^{-4} *M*) was incubated with actin under polymerizing conditions, we observed a decrease in the specific viscosity of actin compared to controls, whereas CPZ sulfoxide, a metabolite of CPZ that is considerably less hepatotoxic both in vitro (*8, 17*) and in vivo (*17*) consistently produced a much smaller reduction in actin viscosity. In contrast, when we examined dihydroxy metabolites of CPZ (3,7-dihydroxy-CPZ and 3,8-dihydroxy-CPZ) we observed a marked increase above control viscosity at actin concentrations giving specific viscosity values greater than 0.6 (Fig. 2). Indeed, as the concentration of actin was increased and approached 1 mg/ml the more viscous actin solutions formed a solid gel in the presence of the dihydroxy metabolites of CPZ but not with CPZ sulfoxide.

Further studies (Table 1) showed that ring hydroxylations of CPZ (3,7; 3,8; and 3,7,8) potentiate the molecule's ability to change the actin solution into a firm gel. This gelation of F-actin presumably occurs because of cross-linking, a process that prevents the F-actin from being able to activate Mg^{2+}-dependent myosin ATPase and result in contraction. Naturally occurring gelation factors have been described in extracts from several divergent sources including acanthamoeba (*18, 19*), sea urchin eggs (*20*), macrophages (*21*), and rat liver (*22*), and have been purified in some instances. These proteins cause a gel to form when incubated with rabbit muscle F-actin (2

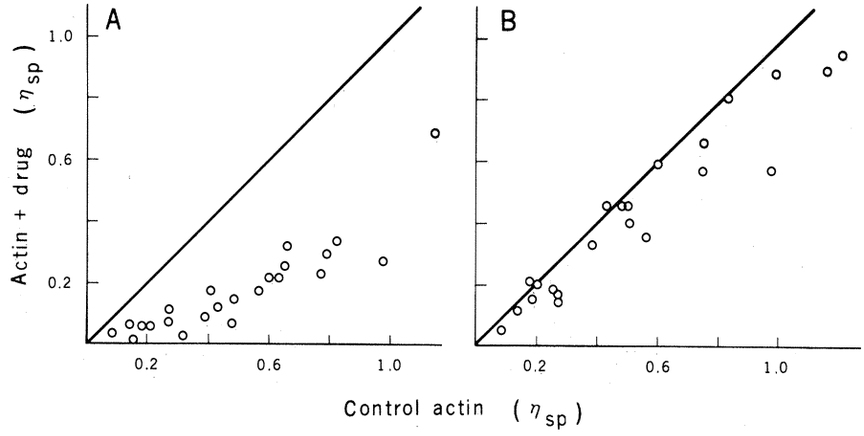

Fig. 1. The specific viscosity of actin alone plotted against the specific viscosity of the same actin concentration in the presence of (A) CPZ (5×10^{-4} *M*) and (B) CPZ sulfoxide (5×10^{-4} *M*). Relative viscosities, η_r, were determined as the ratio of the flow time of samples to that of buffer; specific viscosity, η_{sp}, equals $\eta_r - 1$. Actin concentrations of 0.2 to 1.0 mg/ml were incubated in polymerizing buffer consisting of 3 m*M* imidazole, 0.5 m*M* ATP, 2 m*M* $MgCl_2$, 0.75 m*M* mercaptoethanol, 0.01 percent NaN_3, *p*H 7.5 at 25°C as used by Gordon *et al.* (*16*), and viscosity was measured in 0.5-ml Cannon-Manning semimicro viscometers (sizes 75 and 100) after > 2 hours when the monomeric and polymerized actin were at equilibrium. In (A) the actin viscosity was always reduced by the presence of CPZ; in (B) the CPZ sulfoxide had a much less marked effect.

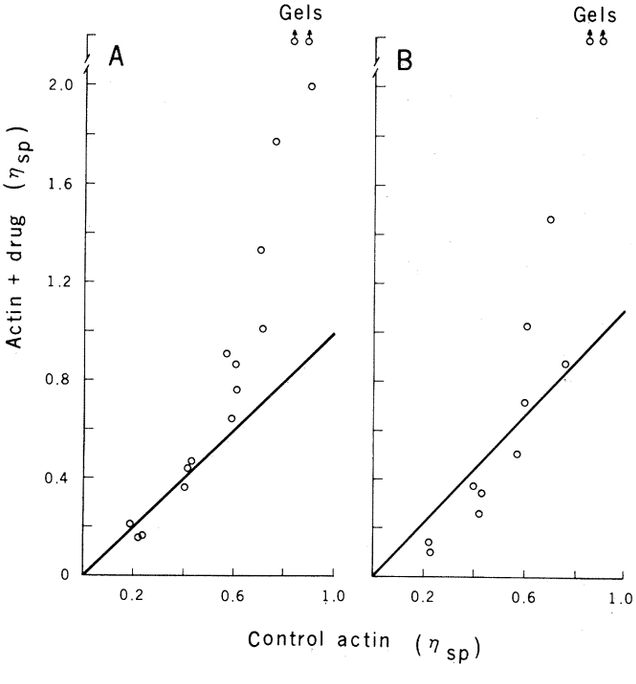

Fig. 2. The viscosity of actin is plotted against the viscosity of the same concentrations of actin in the presence of (A) 3,7-dihydroxy-CPZ (5×10^{-4} *M*) and (B) 3,8-dihydroxy-CPZ. Methods were the same as in Fig. 1. When concentrations of the control actin increased to values that produced a specific viscosity of about 0.6 or above, there was a marked increase in specific viscosity in the presence of either drug. Neither drug had any effect on viscosity in buffer alone. These findings suggest that cross-linkage begins to occur above a critical concentration of F-actin. Viscosities could not be measured when the highest concentrations of actin were incubated with drug because of the formation of solid gel.

Table 1. The effect of a series of concentrations of CPZ and five of its metabolites on gelation. When F-actin forms a solid gel, it remains suspended at the bottom of the test tube when the tube is inverted. 3,7-Dihydroxy-CPZ ($5 \times 10^{-5}M$) and 3,8-dihydroxy-CPZ ($5 \times 10^{-5}M$) produced gelation (+) at lower concentrations than did CPZ ($10^{-4}M$). However, 3,7,8-trihydroxy-CPZ was the most potent metabolite and produced solid gels at $10^{-5}M$. The CPZ sulfoxide had no effect at any of these concentrations. Gelation of F-actin therefore appears to be favored by multiple ring hydroxylations of CPZ. Each tube (10 by 75 mm) contained F-actin (final concentration 2 mg/ml) in a 400-μl system including 5 mM $MgCl_2$, 5 mM imidazole, pH 7.0, 0.5 mM ATP, 0.034M sucrose, 0.1 mM EGTA, 0.1 mM dithiothreitol as described by Maruta and Korn (*19*). Tubes were incubated at 30°C in a water bath and inverted at 15-minute intervals to detect solid gel formation. Gels began to form within 15 minutes in the presence of di- and trihydroxy metabolites of CPZ.

Compound	Concentration (M)			
	10^{-6}	10^{-5}	5×10^{-5}	10^{-4}
Chlorpromazine hydrochloride	−	−	−	+*
7,8-Dihydroxy-CPZ	−	−	+	+
3,7-Dihydroxy-CPZ	−	−	+	+
3,8-Dihydroxy-CPZ	−	−	+	+
3,7,8-Trihydroxy-CPZ	−	+	+	+
Chlorpromazine sulfoxide	−	−	−	−

*Although gelation was always seen with di- and trihydroxy metabolites of CPZ in the concentrations indicated, it was a less predictable occurrence with CPZ and when it occurred was only seen at the $10^{-4}M$ concentration.

mg/ml) which also inhibits the ability of F-actin to activate myosin Mg^{2+}-ATPase (*19*). The ability of hydroxylated CPZ metabolites to function as synthetic gelation factors as described here could account for some of the drug's known membrane effects. For example, low CPZ concentrations ($5 \times 10^{-5}M$) prevent whereas high concentrations ($5 \times 10^{-4}M$) accelerate leakage of cellular enzymes from Chang cells (*23*), and low concentrations of CPZ can protect cell organelles such as lysosomes from hypoxic damage (*24*) whereas higher concentrations destroy lysosomal membranes (*25*). The protective effects of CPZ or its metabolites might be mediated by transformation of the submembranous cytoplasm from a sol to a gel at low concentrations, whereas cell injury would occur at the higher drug concentrations where depolymerization of actin would prevent the assembly of microfilaments and thus destabilize the cytoskeleton. Gelation would also be favored where higher actin concentrations were found in submembranous regions, particularly at the biliary pole of the cell (*26*).

Our results indicate that CPZ and its metabolites profoundly alter the polymerization and gelation of F-actin at concentrations that inhibit bile secretion in vivo (*5*, *6*) and membrane enzyme function in vitro (*6*–*8*). They thus suggest that microfilament dysfunction could be a final common pathway by which CPZ might mediate its multiple membrane effects. Although our studies do not exclude an effect on other cytoskeletal elements, classic microfilament antagonists, such as cytochalasin B, like CPZ also inhibit the activity of the plasma membrane proteins Mg^{2+}-ATPase (*27*) and Na^+,K^+-ATPase (*28*), and result in cytoplasmic vacuolization (*29*) and surface membrane blebbing of hepatocytes (*12*), presumably by a primary disturbance of the microfilaments or their membrane attachments.

The minimal effect of CPZ sulfoxide on actin polymerization and its lack of gelation properties emphasizes both the specificity of the effect and the potential importance of hepatic metabolism in activation and deactivation of the more toxic metabolites of CPZ (*30*). Hepatic microsomal fractions from rat and man rapidly hydroxylate CPZ in the 7 position (*31*), but 3-hydroxylation (*32*) is slow in human and rat liver (*33*), and 8-hydroxylation is a minor pathway (*34*). All of these compounds are apparently metabolized to sulfoxides. Enhancement of 3- or 8-hydroxylation or diminished sulfoxidation would result in the accumulation of more toxic metabolites and could provide an explanation for the apparent unpredictable "idiosyncratic" development of cholestatic jaundice following CPZ therapy.

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References and Notes

1. A. T. Florence, *Adv. Colloid Interface Sci.* **2**, 115 (1968).
2. B. Deuticke, *Biochim. Biophys. Acta* **163**, 494 (1968); P. Seeman, *Pharmacol. Rev.* **24**, 583 (1972); M. P. Sheetz and S. J. Singer. *Proc. Natl. Acad. Sci. U.S.A.* **71**, 4457 (1974); M. P. Sheetz, R. G. Painter, S. J. Singer, *J. Cell Biol.* **70**, 193 (1976); E. B. Keeffe, *Gastroenterology* **76**, 1286 (Abstr.) (1979).
3. J. K. DeVore, C. Daughtery, E. M. Schneider, *Gastroenterology* **31**, 391 (1956); R. Dickes, V. Schenker, L. Deutsch, *N. Engl. J. Med.* **256**, 1 (1957); L. G. Bartholomew *et al.*, *Gastroenterology* **34**, 1096 (1958); V. Perez, F. Shaffner, H. Popper, *Prog. Liver Dis.* **4**, 597 (1972); K. G. Ishak and N. S. Irey, *Arch. Pathol.* **93**, 283 (1972).
4. P. L. Stefko and G. Zbinden, *Am. J. Gastroenterol.* **39**, 410 (1963).
5. E. Ros, D. M. Small, M. C. Carey, *Eur. J. Clin. Invest.* **9**, 29 (1979).
6. J. Kendler, S. Bowry, L. B. Seef, H. S. Zimmerman, *Biochem. Pharmacol.* **20**, 2439 (1971); N. Tavoloni, J. S. Reed, J. L. Boyer, *J. Lab. Clin. Med.* **94**, 726 (1979).
7. J. D. Judah and K. Ahmed, *J. Cell. Comp. Physiol.* **64**, 355 (1964); J. L. Boyer and M. Root, *Clin. Res.* **24**, 281A (Abstr.) (1976).
8. A. M. Samuels and M. C. Carey, *Gastroenterology* **74**, 1183 (1978).
9. Z. Hruban, N. Tavoloni, J. S. Reed, J. L. Boyer, *Virchows Arch. B* **26**, 289 (1978).
10. M. C. Carey, P. C. Hirom, D. M. Small, *Biochem. J.* **153**, 519 (1976).
11. E. Weiss, I. Sterz, M. Frimmer, R. Kroker, *Beitr. Pathol.* **150**, 345 (1973); M. Frimmer and E. Petzinger, in *Membrane Alterations as Basis of Liver Injury*, H. Popper, L. Bianchi, W. Reutter, Eds. (MTP Press, Lancaster, England, 1977), pp. 293–299; M. Prentki, C. Chaponnier, B. Jeanrenaud, G. Gabbiani, *J. Cell Biol.* **81**, 592 (1979).
12. M. Clarke and J. A. Spudich, *Annu. Rev. Biochem.* **46**, 797 (1977); E. D. Korn, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 588 (1978).
13. E. Eisenberg and W. W. Kielley, *J. Biol. Chem.* **249**, 4742 (1974).
14. J. A. Spudich and S. Watt, *ibid.* **246**, 4866 (1971).
15. D. J. Gordon, J. L. Boyer, E. D. Korn, *ibid.* **252**, 8300 (1977).
16. D. J. Gordon, Y-Z. Yang, E. D. Korn, *ibid.* **251**, 7474 (1976).
17. C. O. Abernathy, L. Lukacs, H. J. Zimmerman, *Proc. Soc. Exp. Biol. Med.* **155**, 474 (1977); N. Tavoloni, B. Nemchausky, J. Reed, J. L. Boyer, *Gastroenterology* **75**, 990 (Abstr.) (1978).
18. T. D. Pollard, *J. Cell Biol.* **68**, 599 (1976).
19. H. Maruta and E. D. Korn, *J. Biol. Chem.* **252**, 399 (1977).
20. R. E. Kane, *J. Cell Biol.* **71**, 704 (1976).
21. T. P. Stossel and J. H. Hartwig, *ibid.* **68**, 602 (1976).
22. E. Elias and J. L. Boyer, *Clin. Res.* **27**, 265 (Abstr.) (1979).
23. C. A. Dujovne and H. J. Zimmerman, *Proc. Soc. Exp. Biol. Med.* **131**, 583 (1969); H. J. Zimmerman and J. Kendler, *ibid.* **135**, 201 (1970).
24. K. R. Chien, J. Abrams, G. Pfau, J. L. Farber, *Am. J. Pathol.* **88**, 539 (1977).
25. C. deDuve, in *Symposium on the Interaction of Drugs and Subcellular Components in Animal Cells*, P. N. Campbell, Ed. (Churchill, London, 1968), pp. 155–169; P. S. Guth, O. Z. Sellinger, J. Amaro, L. Elmer, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **22**, 626 (1963); P. S. Guth, J. Amaro, O. Z. Sellinger, L. Elmer, *Biochem. Pharmacol.* **14**, 769 (1965); L. J. Ignarro, *J. Pharmacol. Exp. Ther.* **182**, 179 (1972); P. Jacques, R. S. Ennis, C. deDuve, *J. Cell Biol.* **23**, 45 (Abstr.) (1964); H. Koenig and A. Jubril, *Biochim. Biophys. Acta* **65**, 543 (1962); H. Koenig; *J. Histochem. Cytochem.* **13**, 20 (1965); C. S. Popov, *Biochem. Pharmacol.* **18**, 1778 (1969).
26. S. W. French and P. L. Davies, *Gastroenterology* **68**, 765 (1975).
27. M. J. Phillips, M. Oda, J. Yousef, M. M. Fisher, K. N. Jeejeebhoy, K. Funatsu, in *Membrane Alterations as Basis of Liver Injury*, H. Popper, L. Bianchi, W. Reutter, Eds. (MTP Press, Lancaster, England, 1977), pp. 343–352; M. Oda and M. J. Phillips, *Lab. Invest.* **37**, 350 (1977).
28. R. E. Barnett and J. Palazzetto, *Ann. N.Y. Acad. Sci.* **242**, 69 (1974); C. J. Bos and P. Emmelot, *Chem. Biol. Interact.* **8**, 349 (1974).
29. M. J. Phillips, M. Oda, E. Mak, M. M. Fisher, K. N. Jeejeebhoy, *Gastroenterology* **69**, 48 (1975).
30. J. L. Boyer, *ibid.* **74**, 1331 (1978).
31. H. Goldenberg and V. Fishman, *Biochem. Biophys. Res. Commun.* **14**, 404 (1964).
32. V. Fishman and H. Goldenberg, *J. Pharmacol. Exp. Ther.* **150**, 122 (1965).
33. P. F. Coccia and W. W. Westerfeld, *ibid.* **157**, 446 (1967).
34. P. Turano, W. J. Turner, A. A. Manian, *J. Chromatogr.* **75**, 277 (1973); J. K. Suzuki, A. Zirnis, A. A. Manian, *J. Heterocycl. Chem.* **13**, 1067 (1976).
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