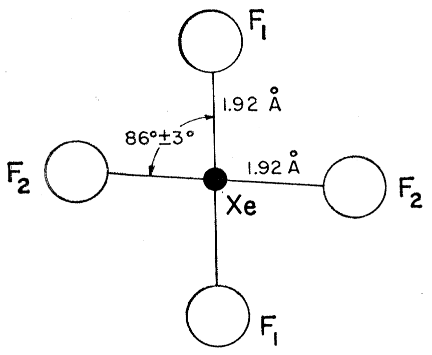

Fig. 1. The structure of the XeF_4 molecule in the solid.

terial was sublimed into a quartz tube and purified by alternate heating, cooling, and pumping. Crystals suitable for x-ray photography were grown directly in the sealed-off quartz tube by providing a thermal gradient along the tube. There was no evidence of decomposition of the crystals during the x-ray photography.

Xenon tetrafluoride crystallizes in the monoclinic system with cell constants $a = 5.03$ Å, $b = 5.90$ Å, $c = 5.75$ Å (all $\pm$ 0.03 Å), $\beta = 100° \pm 1°$. On the basis of the observed extinctions ($h0l$, $h + l$ odd; $0k0$, k odd) the space group is probably $C^5_{2h} - P2_1/n$. From elementary packing considerations (van der Waals radius of $F = 1.35$ Å) it is evident that only two molecules of XeF_4 can be accommodated in this unit cell of volume 168 Å^3. The calculated density is 4.10 g/cm^3.

Data suitable for structure analysis were collected at room temperature with MoKα radiation from a plate-like crystal of dimensions 1 by 1 by 0.3 mm. The precession method was used to record the three nets $h, h - l + n, l$ with $n = 0,2,4$. For each net the normal to the 1- by 1-mm face of the crystal was at a constant angle to the x-ray beam, and thus all intensities on a given net should be equally affected by absorption. Since separate scale factors were used for the three nets, absorption errors should be small in spite of the high linear absorption coefficient of 104 cm^{-1}. The intensities from these photographs correlate well with intensities of the $h, h + l, l$ net obtained from a second, much smaller crystal. The intensities of 268 independent reflections were estimated visually, corrected for Lorentz and polarization effects, and converted to structure amplitudes.

As there are only two molecules in the unit cell, Xe may be placed at the origin and at the body-centered position. After a least-squares refinement of scale factors and the Xe thermal parameter, a three-dimensional difference Fourier, with coefficients $(F_{obs} - F_{Xe})$ for those reflections for which $(h + k + l)$ is even, was calculated. This difference Fourier necessarily has extra symmetry, and two structures equally compatible with the x-ray data can be derived from it. Least-squares refinements of these structures led to the following x-,y-,z-parameters for the two independent fluorine atoms; F^1, -0.225, ± 0.027, -0.306; F_2, 0.242, 0.165, -0.162 (all approximately $\pm$ 0.008).

The thermal parameter of Xe is 1.3 $\pm$ 0.1 Å^2, that of the two fluorines is 3.5 $\pm$ 1.0 Å^2. The conventional crystallographic R factor for these parameters is 0.11 against that of 0.16 based on Xe alone. In order to resolve the ambiguity in the sign of y (F_1), structure factors calculated for both signs were compared with structure amplitudes for the nine reflections observed on the $h, h - l + l, l$ net. Since only the fluorine atoms contribute to these structure amplitudes, even this limited comparison enables us to conclude that y (F_1) $= -0.027$.

The molecule has symmetry D_{4h} within the limits of error of this study, although such symmetry is not required by the space group. The angle F_1-Xe-F_2 is 86 $\pm$ 3° and the two independent distances Xe to F do not differ significantly and have an average value of 1.92 $\pm$ 0.03 Å (Fig. 1). The shortest intermolecular F...F contact is 2.95 Å. This and all other intermolecular distances are reasonable; the molecule fills space well, providing further confirmation of the formula XeF_4. Since all of the intermolecular F...F contacts in this structure exceed slightly the expected van der Waals contact of 2.7 Å it is not surprising that a second phase of XeF_4, with a density some 10 percent higher than that of the present structure, exists (*2*). The structure of this denser phase is at present unknown.

Although a neutron diffraction study would enable us to refine the structure further, the geometry of the molecule is well defined in the present x-ray study, and we plan no further work on the structure (*3*).

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3. Research performed under the auspices of the U.S. Atomic Energy Commission. The molecular structure described above was initially found by refinement in a body-centered space group, and disorder in the stacking of the molecules had to be postulated in order to obtain agreement with the data. We are indebted to S. Siegel of Argonne National Laboratory for generously pointing out an error in our space group determination; the error arose because our data were initially collected in such a way that no reflections for which $(h + k + l)$ is odd were observed. We are indebted to D. R. Mackenzie and R. H. J. Wiswall for the preparation of the sample.

7 December 1962

Tertiary Lake Deposits in Western Coterminous United States

Strata deposited by long-vanished lakes in the western coterminous United States have been subjects of interest since the middle of the 19th century. They are the repositories of large numbers of fossils which range in size from remains of one-celled plants to bones of dinosaurs. In some, the details of minute insects and the vein structure of leaves are most delicately and perfectly preserved.

The lake deposits provide important clues to the paleogeography of the continent, to past climates, and to the development of modern landforms and climates. The lake deposits of Tertiary age provide virtually the only commercial sources of borate minerals and of trona and are important contributors of many other saline minerals to the economy. Locally, the lacustrine deposits yield petroleum and natural gas. In many areas they are the sources of clay used in the ceramic industry, of diatomite, and of sand and gravel used in construction. The interlayering of lacustrine and fluvial deposits furnishes the physical framework for artesian water supplies in many western basins. For these and other reasons, the distribution of lacustrine deposits is of immediate and lasting interest to many people.

The accompanying map (Fig. 1) shows the reported occurrence of lake-deposited materials in 11 of the western states in Paleocene and Eocene time (red overprint) and in Oligocene, Miocene, and Pliocene time (black), respectively. An earlier map (*1*) showed the distribution of lakes of Pleistocene age in the same region.

Figure 1 suggests that in earlier

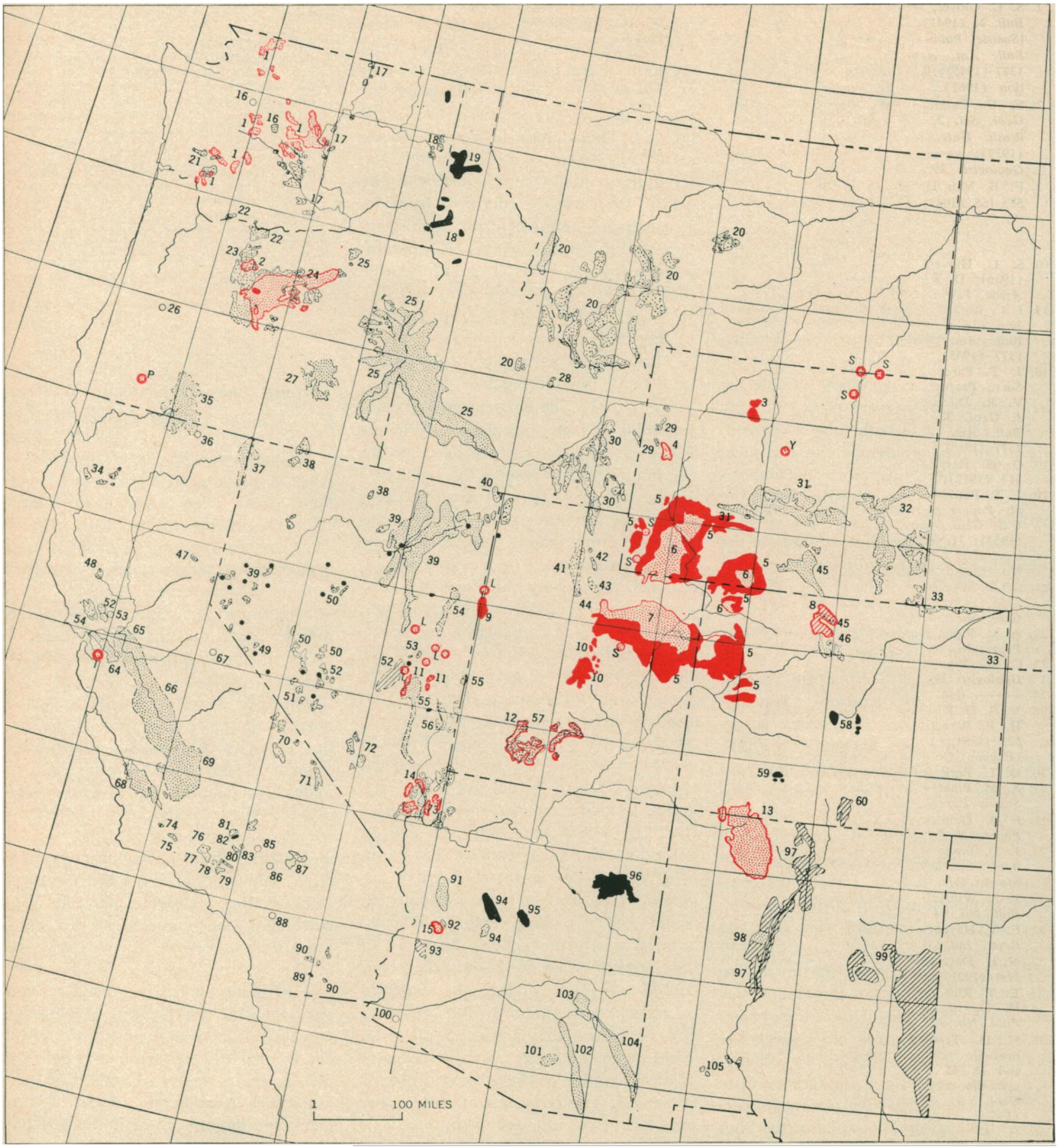

Fig. 1. Map of western coterminous United States, showing the distribution of reported lake deposits of Paleocene or Eocene age (in red) and Oligocene, Miocene, or Pliocene age (in black). (Solid pattern) Formation consisting wholly or largely of lacustrine material; (dot pattern) formation containing lacustrine deposits; (line pattern) formation that may contain lacustrine deposits. *L*, Lacustrine limestone locality (Eocene) [F. B. Van Houten, *Bull. Am. Assoc. Petrol. Geologists* **40**, 2801 (1956)]; *P*, tuffaceous deposits (Eocene) of small lakes in Oregon [D. L. Peck, oral communication (1961)]; *S*, lacustrine ostracod occurrence (Paleocene or Eocene) [F. M. Swain, *J. Paleontol.* **23**, 172 (1949)]; *T*, lacustrine equivalent of Martinez Formation (Paleocene) [N. L. Taliaferro, *Calif. Div. Mines Bull.* **154** (1951)]; *Y*, lacustrine mollusk locality (Eocene) [T. C. Yen, *J. Paleontol.* **20**, 495 (1946)]. (Open circles) Reported lake deposits not mapped, or too small to show at scale used; (solid circles) freshwater diatomite occurrence (Oligocene or Miocene) [F. B. Van Houten, *Bull. Am. Assoc. Petrol. Geologists* **40**, 2801 (1956)]. The numbers are keyed to references, as shown on the facing page.

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Tertiary time much of the western part of the continent was organized into large units that permitted formation of extensive bodies of lake water. The latter part of the Tertiary saw development of a more rugged and diversified topography analogous to that now in existence. Comparison of Fig. 1 with the map showing Pleistocene lakes (*1*) indicates that many of the basins occupied by lakes in Pliocene time were also the sites of Pleistocene lakes. Thus, in many places throughout the West, the landscapes we know today have been in existence for more than a million years in something approaching their present form.

The distribution of lake deposits shown in Fig. 1 is taken from reports in the literature. The sources of information are given on page 109 and keyed by numbers to the map.

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16 October 1962

Metabolic Deficiencies in Protozoa Induced by Thalidomide

Abstract. *Thalidomide inhibits growth of some protozoa. This inhibition was counteracted by nicotinic acid, nicotinamide, nicotinamide adenine dinucleotide, and vitamin* K_1. *The mechanism of toxicity may be an interference of cellular oxidation. A protozoan test system is useful for studying the potential "side actions" of drugs in higher animals and man.*

How thalidomide induces congenital malformations is unknown. Since similar teratogenic effects have been produced in animals by metabolic interferences (*1, 2*), it seemed appropriate to find out whether thalidomide acts as an antimetabolite. The development of peripheral neuritis (*3*) and congenital malformations (*4, 5*) that followed its use has focused attention on the need for additional methods to screen drugs for potential toxicity. For this purpose, a protozoan test system which disclosed the metabolic deficiencies induced by primidone (*6*), thyroactive compounds (*7*), and triparanol (*8*) was used.

Thalidomide, in appropriate concentrations, inhibited growth of the photosynthetic flagellates *Euglena gracilis, Ochromonas malhamensis,* and *Ochromonas danica,* and the ciliate *Tetrahymena pyriformis* and was therefore judged toxic for these organisms. Methods for growing these protozoa have been described (*9*). An aqueous solution of thalidomide [α-*N*(phthalimido)glutarimide] was prepared by dissolving the drug with dilute KOH and then immediately neutralizing with dilute HCl so that the concentration was 100 mg/ml. Further dilutions were made with distilled water. All organisms were grown in chemically defined media. Thalidomide was added to the media in concentrations which inhibited protozoan growth (Table 1). Media were sterilized by autoclaving at 118° to 121°C, 16 pounds per square inch, for 30 minutes. Metabolites that were not heat resistant, such as tryptophan intermediates, nicotinamide adenine dinucleotide (NAD), and vitamin K_1 (menadione) were sterilized by passage through ultra-fine fritted glass filters and added aseptically in appropriate dilution with distilled water. The toxic effects of thalidomide were not altered by autoclaving. Growth of *Lactobacillus leichmannii, L. casei, L. arabinosus, Pediococcus cerevisiae, Escherichia coli* I, and *E. coli* 113-3, was not inhibited by thalidomide; therefore, only results obtained with protozoa are given here.

Growth was inhibited by thalidomide at concentrations of 2.0 mg/ml for *Ochromonas danica,* 3.0 mg/ml for *Euglena gracilis* and *Tetrahymena pyriformis,* and 6.0 mg/ml for *Ochromonas malhamensis* (Table 1.). This toxicity was not altered by purines or pyrimidines (adenine, adenosine, guanine, guanosine, uracil, uridine, cytosine, cytidine, thymine, thymidine, xanthine, xanthosine, inosine), or amino acids (alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tyrosine, valine), or a metals mixture (Fe, Zn, Mn, Cu, Mo, Co, V, I, Se), alone or in combinations.

A vitamin mixture containing thiamine, nicotinic acid, pantothenate, pyridoxamine, riboflavin, choline, inositol, thymine, orotic acid, *p*-aminobenzoic acid, vitamin B_{12}, biotin, thioctic acid, and folic acid reversed the toxicity of thalidomide for all organisms. Nicotinic acid proved to be the active agent. None of the other vitamins diminished the toxicity, nor was any synergistic with nicotinic acid. Nicotinamide or NAD could be substituted for nicotinic acid with similar effect.

Table 1. Inhibition of the toxicity of thalidomide toward protozoa by nicotinic acid, NAD, and menadione. Growth of the organisms was measured with a Welch Densichron photometer equipped with a red-sensitive probe and is expressed in optical density units (O.D.); an O.D. of 1.0 corresponds to 0.5 to 0.55 g (dry weight) of organisms per liter.

Thalidomide (mg/ml)	Inhibitory agent (mg/ml)				
	None	Nicotinic acid		NAD 0.1	Menadione 0.0001
		0.001	0.01		
		Euglena gracilis			
0	2.7	2.7	2.7	2.6	2.6
1	0.7	1.4	2.5	1.7	1.8
2	0.3	1.3	2.4	1.2	1.2
3	0	0.9	1.8	1.0	0.9
		Ochromonas danica			
0	1.9	1.9	1.9	1.9	1.9
1	0.9	1.6	1.7	1.6	0
2	0	1.3	1.3	1.4	0
3	0	1.1	1.3	0.9	0
		Ochromonas malhamensis			
0	2.2	2.2	2.2	2.2	2.2
2	1.8	1.8	1.8	1.8	1.8
4	1.0	1.3	1.5	1.6	0.8
6	0	0.6	0.8	0.7	0
		Tetrahymena pyriformis			
0	0.5	1.2	1.2	1.2	0.5
3	0	0.9	1.0	0.9	0.2
6	0	0.8	0.9	0.8	0.2
9	0	0.6	0.7	0.7	0.1

Because tryptophan is a precursor of nicotinic acid, metabolites along the pathway of synthesis to nicotinic acid were tested. 5-Hydroxytryptamine, kynurenic acid, xanthurenic acid and quinolinic acid partly inhibited the toxicity of thalidomide for *O. malhamensis*; quinolinic acid slightly inhibited the toxicity of thalidomide for *O. danica,* and none of these compounds inhibited the toxicity of thalidomide for *E. gracilis* or *T. pyriformis.*

Since NAD inhibited the toxicity of thalidomide, vitamin K_1 (menadione) was also tested for this behavior because it, too, participates in metabolic oxidations (*10*). Menadione inhibited the toxicity of thalidomide for *E. gracilis* and *T. pyriformis* but not for *O. malhamensis* and *O. danica.*

The nicotinic acid antagonist, 6-aminonicotinamide, behaved like thalidomide toward *E. gracilis* and *O. malhamensis* and, as expected, its action was overcome by nicotinic acid. *T. pyriformis* and *O. danica* were not inhibited by 6-aminonicotinamide at concentrations up to 1.0 mg/ml.

Thalidomide may possibly act at the point where nicotinic acid is synthesized