After the initial 72 hr of treatment, all unmedicated control areas continued to demonstrate the presence of *Pseudomonas*. Of the 15 burns treated with silver sulfadiazine dry foam, one remained infected with the test bacteria. In contrast, seven of the 15 burns remained positive for *Pseudomonas* after treatment with the corresponding medicated ointment. Chi-square computations demonstrated the significance of these data ($p < 0.05 > 0.01$). However, at the conclusion of the *in vivo* crossover study, four burns treated with the medicated dry foam remained infected while five of the areas treated with the medicated ointment remained infected ($p = 0.1$).

In assessing the results of the initial *in vivo* study with those of the subsequent crossover study, several factors must be considered. The 72-hr delay in instituting therapy in the crossover study may have led to an infected environment not readily affected by rates of release from the dosage form. The proliferation of the test bacteria during this initial 72 hr probably resulted in widespread subeschar colonization. This movement of the bacteria into tissues below the burn produced a medium for growth not easily treated with topical agents.

In clinical use, both local and systemic therapy would be indicated to combat the advancing bacteria successfully. Furthermore, surgical excision of the devitalized eschar would be performed as an aid in the elimination of the infecting organism. The presence of eschar provides an excellent medium for bacterial growth and also provides a barrier between the applied drug product and the subeschar colonies, possibly preventing therapeutic contact and effect. Moreover, the protein binding characteristics of silver ion and the sulfonamide may prevent deep percutaneous absorption (3).

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Growth of Calcium Oxalate in Gel Systems

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Abstract □ Methods are described for growing calcium oxalate in silica and gelatin gels under different conditions. The results obtained indicate that, in silica gel, calcium oxalate grows into single individual crystals, twins, and rosettes. Bipyramidal calcium oxalate dihydrate crystals similar to those present in the urine of stone formers were prepared in the silica gel system. The gelatin gel offered a suitably structured substrate on which calcium oxalate monohydrate crystals grow into aggregates. The orientation pattern of calcium oxalate crystals suggests that the growth process is controlled by the stereospecificity of the gelatin medium supporting growth.

Keyphrases □ Calcium oxalate—growth of crystals in silica and gelatin gels, relevance to stone formation □ Crystal growth—calcium oxalate in silica and gelatin gel systems, types of growth □ Silica—substrate for growing calcium oxalate crystals □ Gelatin—substrate for growing calcium oxalate crystals

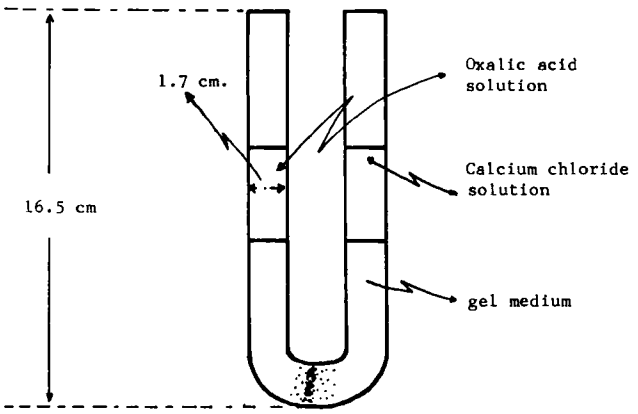

Figure 1—*Dimensions of the U-shaped tubes selected for the gel growth studies.*

Recent reports on the growth of calcium oxalate *in vitro*, either by precipitation from solution or from urine, generated valuable information on growth kinetics and the factors controlling crystal growth (1, 2). Attempts to grow crystal aggregates, similar to natural concretion, have so far met with little success (3, 4). This report describes a method for growing single crystals and artificial concretions of calcium oxalate. It is believed that this *in vitro* experimental model could be of fundamental significance in understanding the complex mechanisms of stone formation.

Studies on the crystallization of poorly soluble salts are often slowed down by the lack of methods for growing single crystals that permit close observations and understanding of the growth process and the factors controlling such phenomena. Interest in the gel medium for crystal growth has been greatly stimulated by the work of Henisch (5). Single crystals of calcium tartrate, tungstate, carbonate, and sulfate were grown using silica gel as the growth medium (6–10). This technique offered new opportunities for the production of useful single crystals and presented new observations in mechanism studies.

The growing pattern of crystals is dependent on the structure of the gel and the nature of the additives present in the gel medium. For very poorly soluble salts, the growth rate is essentially a diffusion process and the chemical reaction is not the rate-de-

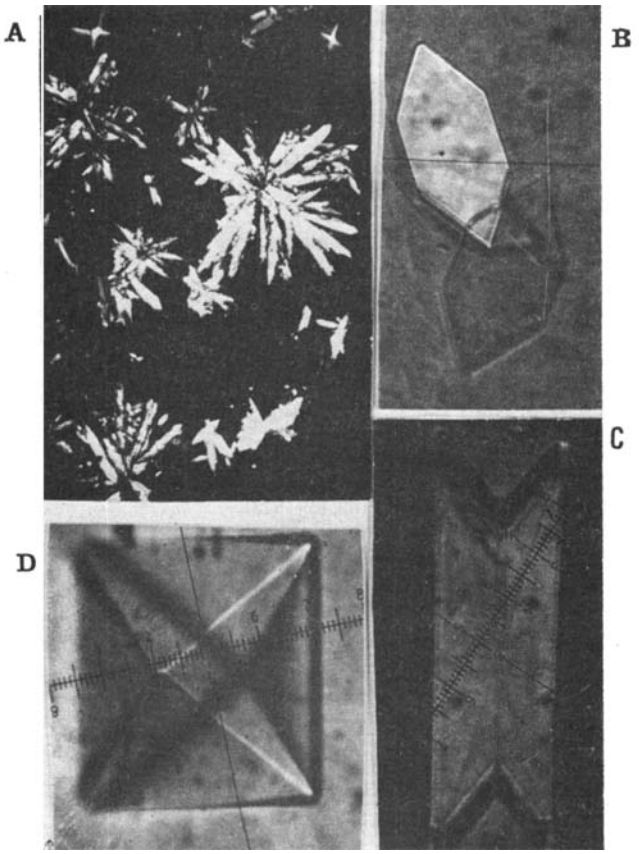

Figure 2—*Calcium oxalate crystals grown in silica gel. Key: A, calcium oxalate monohydrate (whewellite) grown as rosettes (×125); B, calcium oxalate monohydrate flat plate-like crystals (×500) grown using sodium oxatate as the source of oxalic ion instead of oxalic acid; C, twin production of whewellite (×500)—the incidence of this growth imperfection was higher when 60 ppm of magnesium was incorporated in the gel; and D, bipyramidal calcium oxalate dihydrate (weddelite) (×500) obtained when 100 ppm of pyrophosphate was added to the medium.*

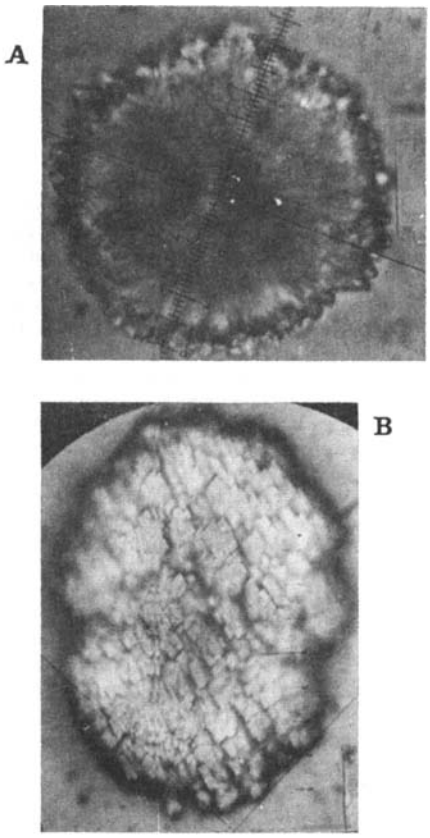

Figure 3—*Calcium oxalate crystals grown in gelatin gel. Key: A, calcium oxalate concretion (×500); and B, surface profile of the calcium oxalate crystallites in the concretions (×500).*

termining step (5). The gel acts as a support for the crystal and leads to its growth without exerting major forces upon it. The structure of the gel controls the whole process of diffusion and growth rate. The gel composition can play a role in orientation and build up of the crystalline material. Moreover, the presence of additives (any foreign substance other than the reacting species) can completely modify the crystal morphology.

In this study, calcium oxalate was selected because it represents the nucleus of two-thirds of the stones formed in the urinary tract (11) and the field of calcium oxalate crystallization is less well documented than is the crystallization of other calcium salts. From the foregoing, it is seen that the growing pattern (habit, size, quantity, and aggregation) is dependent on the structure of the gel and on the nature of the additives present in the gel medium.

EXPERIMENTAL

Two types of gels were studied: silica and gelatin. Silica was chosen because of its high inertia, and gelatin was studied because of its protein content and its structural analogy with collagen. The concentration chosen in each case to produce the gel was a compromise between the facts that a low concentration of gel will be too weak, allowing the ions to diffuse too rapidly and thus leading to numerous nuclei, and that a high concentration of gel will give poor crystals due to the very small pore size, thus interfering with the freely growing crystals.

In the case of the silica gel medium, a 10% solution of sodium metasilicate (reagent grade) was acidified to pH 6.2 with 3 *M* acetic acid. The solution was immediately poured into U-shaped tubes (Fig. 1) and stored in the dark for 24 hr to allow gelling. When additives were used to modify growth, they were incorporated in the gel medium before setting.

In the case of the gelatin (purified calfskin gelatin[1]), 55 g was dissolved in 1 liter of double-distilled water by gentle heating for 1 hr at 50°. The solution was partially cooled, and the pH was adjusted to 6.2 with tromethamine. To prevent mold growth during the incubation time, 1 ml of formaldehyde (37%) was added. Slow diffusion of the reacting ions was achieved by carefully placing 10 ml of 0.5 *M* calcium chloride on the gel surface on one side of the U-tube and 10 ml of 0.5 *M* oxalic acid on the gel surface on the other side.

The silica gel tubes were incubated at 37° and the gelatin tubes were incubated at 25° (to avoid liquefaction of the gel). After 6 days the calcium oxalate crystals were harvested and examined in polarized light under the microscope and by IR spectroscopy. The results were reproducible under each tested condition.

RESULTS AND DISCUSSION

Figure 2 shows calcium oxalate crystals grown in silica gel. In these experiments, when small concentrations (10 ppm) of magnesium, pyrophosphate, chlorophyll, and methylene blue were included as additives in silica gels, they slowed down the growth of calcium oxalate. On the other hand, the presence of pyrophosphate

[1] Eastman Kodak.

(100 ppm) favored the formation of the more energetic calcium oxalate dihydrate, apparently by lowering the energy needed for the formation of this form. It was found that calcium oxalate dihydrate formed in the presence of pyrophosphate is identical to the bipyramidal octahedral calcium oxalate dihydrate crystals obtained from the urine of chronic stone formers (12). The results obtained in silica gel are important for two reasons:

1. They emphasize the importance of environmental conditions on crystal morphology and growth rate of calcium oxalate crystals.
2. They show that it is possible to grow a single crystal of calcium oxalate dihydrate identical to those encountered *in vivo*.

In the gelatin gel system described, calcium oxalate grew in a completely different manner. Figure 3 shows the concretion found in the gelatin gel after 6 days and a surface profile illustrating the organization and orientation of the calcium oxalate crystallites in these aggregates. In this system (unlike silica gel), gelatin offered a suitably structured substrate on which calcium oxalate crystals nucleated and developed such an oriented pattern. The presence or absence of pyrophosphate or magnesium ions in the gel did not influence either the pattern of growth or the proportion of the calcium oxalate aggregates formed. This growth phenomenon indicates that the gelatin matrix and its protein moiety were capable of controlling the nucleation, growth, and orientation of calcium oxalate crystals.

Like silica gel, gelatin gel provided a favorable growth supporting medium on which the slowly diffusing calcium and oxalate ions nucleated; but by virtue of the stereospecificity of its nucleating sites, calcium oxalate crystals developed in the gelatin into such a degree of organization. The obtained results add experimental evidence for the important role of protein-structured substrate in dictating growth and specific orientation in the formation of calcium oxalate concretions. They also support Gebhardt's (13) assumption that epitaxial nucleation of stone components on suitably structured substrate (*e.g.*, collagen fibers) is the primary factor in stone formation.

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Synthesis of (4-Quinolinoamino)aminoalkyltetrahydronaphthalene Derivatives for Possible Antimalarial Activity

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Abstract □ (4-Quinolinoamino)aminoalkyltetrahydronaphthalene derivatives were synthesized in an attempt to introduce new agents with antimalarial activity.

Keyphrases □ (4-Quinolinoamino)aminoalkyltetrahydronaphthalene derivatives—synthesized and screened for antimalarial activity □ 4-Aminoquinoline compounds—synthesized and screened for antimalarial activity □ Antimalarial activity—(4-quinolinoamino)aminoalkyltetrahydronaphthalene derivatives

Compounds of the 4-aminoquinoline type still play a major role in the treatment of malaria. The development of resistance by some strains to most of the present antimalarials gave the initiative for several trials of new chemotherapeutic agents that may overcome this problem. In tropical countries where malaria eradication activities are still lacking, the provision of effective chemoprophylaxis and treatment represents a major problem.

DISCUSSION

In previous articles (1, 2), the synthesis and biological activity of a new compound 4-(7-chloro-4-quinolylamino)-2-diethylaminomethyl-5,6,7,8-tetrahydro-1-naphthol (I) were described. Structurally, the compound is related to 4-aminoquinoline and bears a substituted tetrahydronaphthalene (tetralin) system as a side chain. The rationale for including the tetralin system is that it may undergo metabolic transformation to a naphthoquinone type of structure.

Derivatives of this type have shown considerable antimalarial activity. They appear to act by inhibiting the respiration of plasmodia (3). New compounds that would structurally include both the nitrogen heterocycle and a naphthoquinone structure might be useful as antimalarials, since the resistance of the parasite to one should not imply resistance to the other because both act through different mechanisms.

Biological studies based on the response to the product by *Plasmodium berghei* in mice revealed that oral doses of I at 5–100 mg/kg are curative. In addition, the agent proved to give complete protection against later exposure to massive infection by the parasite through subcutaneous application (2), thus providing effective chemoprophylaxis beside chemotherapeutic activity.