Induced Systemic Hypersensitivity: Selye's Theory

The nature of the local mechanism of calcification is one of the most important unsolved problems of biochemistry.

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"Calciphylaxis," a term coined by the author, is a condition of induced systemic hypersensitivity in which tissues respond to various challenging agents with a precipitous, either evanescent or dense, deposit of calcium salts. "Calciphylaxis" denotes the defensive or phylactic response induced by the selective deposition of calcium in a challenged area. The book **Calciphylaxis**, by Hans Selye (University of Chicago Press, Chicago, III., 1962. 583 pp. $25), contains a description of laboratory procedures and the directions for performing experiments to produce calciphylaxis as well as an atlas of colored photographs selected to illustrate some of the most typical calciphylactic responses. If the author's experiments can be repeated and confirmed by other investigators, calciphylaxis will become a new word in the medical dictionary and an instrument for interpreting and investigating physiologic and pathologic processes concerned with the deposition of calcium salt in the body.

Calciphylaxis hypersensitivity depends on: (i) a sensitizing calcifier such as dihydrotachysterol and other vitamin-D compounds or parathyroid extract and (ii) a challenger such as multivalent cation salts, drugs that deplete the granules of mast cells, albumin, and other substances. After the lapse of a critical period between sensitization with the hypercalcemic substance and challenge with the metal ion, calcium salts will be deposited in soft tissue. The site of the deposit depends upon many factors such as the dosage, the timing, the route of administration, and the chemical substance used for the challenger. The challenger can be either direct or indirect, but in any event, even the direct challenger probably acts through chemical responses induced in the immediate environment. In effect, the challenger is a "vital mordant" because it attracts calcium as a chemical substance attracts dyes to a tissue. Challengers do not produce calcification merely by precipitating blood calcium; the timing must coincide with the liberation of some endogenous calcium precipitant under the influence of the sensitizer. The effect is apparently to produce a milky extracellular fluid saturated with calcium phosphate salts or an actual precipitation of calcium phosphate. The process is inhibited by adrenocorticotrophin, glucocorticoids, estrogen, and methyltestosterone, under some conditions. Calciphylaxis resembles the precipitation of calcium phosphate and salts after the injection of substances that are known as direct calcifiers—for example, potassium permanganate.

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Calcinosis Agents-New Emphases

Selye drops the old concepts of dystrophic and metastatic calcification and distinguishes merely between locally induced and systemogenic calcification. There are many metal salts that will trap calcium somewhat as a mordant prepares inanimate tissues for the uptake of dyes. It has long been known that calcium chloride injected into a soft tissue will produce calcification, but Selye is the first to emphasize that this is owing not merely to damage but is a result of a highly specific property of a drug, which is quite independent of the ability to produce inflammation and necrosis or other signs of nonspecific tissue injury. Calcification occurs long after the injected salt is absorbed, and the process is therefore not simply precipitation. Apparently the receptive target tissue itself contains the prerequisites for inducing local calcification. In many instances the tissue produces a fibrous reaction (after an evanescent shower of fine calcium precipitation) that outlasts the presence of histologically demonstrable calcium. Selye describes this as "calcinosclerosis," because he assumes that, after calcium first precipitates in the extracellular fluid, it may be rapidly absorbed and may give rise to inflammation, sclerosis, and finally to hyalinization. Selye produced calcareous tendonitis in rats by sensitizing them with dihydrotachysterol plus either intravenous Thorotrast or Ferrigen. It is implied that clinical conditions associated with extraosseous deposits of calcium could be imitated by a calciphylactic experiment on the rat.

The New Phenomenon

The claim in the discovery of calciphylaxis is that a single oral dose of dihydrotachysterol, too small to produce nonspecific calcification in tissue, consistently sensitizes the animal for typical calciphylactic responses. Presumably there is no increase in the blood calcium and no interference with kidney function or calcium excretion. In the case of a direct calcifier, the injected salt transforms the injection site into a calcium trap; indirect calcifiers produce topical calcification only when the dose given is sufficient to induce an extraordinary degree of systemic sensitization. This state can be seen, after slight mechanical trauma or irritation, in the form of deposits of calcium salts in the skin. One of the most dramatic of these is depilation with prompt calcification of the site from which the hair has been removed. Anions, even phosphates, do not act as challengers. When phosphate produces calcification in a sensitized animal, the salt is an indirect challenger whose action is relayed through other compounds and not through the phosphates.

Iron salts have long been suspected of being calcifying agents. Iron deposits are seen in tissues during the initial stages of calcium deposition. This form of iron is in the organic substance and

remains even after decalcification. When an iron salt is used to produce calciphylaxis, the Prussian blue-positive iron material disappears from the target area as the calcium enters. Certain challengers act by liberating mast cell granules. These granules contain a substance which attracts calcium, especially in the presence of phosphate and iron. When there is a latent period of calciphylaxis, it apparently depends upon the time necessary to liberate enough calcium from the skeleton for transposition to the challenged sites. It is noted that the critical period is not the time allowed for the development of hypercalcemia but that allowed for the development of the endogenous adjuvants, the state of the mast cell system (whether charged or discharged), the intensity of stress produced by evocative agents, the absorption and excretion of the pathogenic compounds, and the activity of the endocrine system. The resistance to calciphylaxis does not lie in the local process but in the general metabolic changes that attend sensitization and challenge. In this respect there is an important difference between the indirect and direct calcifiers. The theory of calciphylaxis leads to the idea of the existence of a special stromal depot system. In a review of over 1000 articles from the literature on calcifying syndromes, Selye recalls DiMattei's concept of *pharmacothésaurismoses*, the idea that many drugs are stored in the connective tissues of man; this is one way that nature removes poisonous substances from the extracellular fluid and prevents harm to the intracellular chemical system. No measurements were made of serum or tissue calcium, inorganic phosphate, carbonate, citrate, or alkaline phosphatase.

Speculation and Stimulation

This is strictly qualitative work that is unsupported by quantitative data (although the book occupies some 500 pages), a somewhat surprising event in biological science today. The first five chapters (317 pages), are a description of experiments on 50,000 rats. Chapters 6 and 7 (more than 200 pages) deal with clinical implications and speculations. The clinical section is a catalog of disorders associated with soft tissue calcification in man; the farfetched suggestions about treatment, which are included in the section, are sure to detract from the important experimental work. Investigators who repeat Selye's laboratory work will raise this question about the major premise of calciphylaxis: Is it an allergic or hypersensitive state (a manifestation of altered responsiveness dependent upon a sensitizer and a challenging agent) or is it better defined by some other concept? The amount of the hypercalcemic substances, 1.0 milligram of dihydrotachysterol (DHT) and 2.5 grams of albumin, is very large when injected into a 100-gram rat. The book presents no data on the blood volume or serum chemistry to measure the degree of systemic injury and hypercalcemia. It is well known that DHT mobilizes calcium from bone. Some standard experiments must be carried out to support the contention that DHT, apart from its effects on the blood calcium, is a sensitizer.

Large doses of toxic substances may produce anergy, the reverse of calciphylaxis. The old view that metastatic calcification is a chemical reaction to injury (total necrosis being dissolution of the calcifiable structure) is not disproven, and it may even be supported by Seyle's work.

The concept of calciphylaxis, or calcium defense, against a challenging agent is open to question. Why not "calcioffensus," "calciinterment," or "calciinhumatus" of injured or devitalized tissue? In any case, the nature of the local mechanism of calcification is one of the most important unsolved problems of biochemistry. However we choose to interpret Selye's theory, his experiments exhibit a new and startling laboratory phenomenon. This important book is bound to generate a new group of investigators and to stimulate new kinds of experiments on calcium metabolism by workers in all fields of biology and medicine.

Scott's Standard Methods

Standard Methods of Chemical Analysis. vol. 1, *The Elements*. N. Howell Furman, Ed. Van Nostrand, Princeton, N.J., ed. 6, 1962. xix + 1401 pp. Illus. $25.

The value of Scott's *Standard Methods* as a reference source for practical analytical work has been known for half a century. The fifth edition, which appeared in 1939, was the first edited by Howell Furman, who is well known for his contributions to analytical chemistry. The appearance of the sixth edition, which is also edited by Furman, is consequently of considerable interest. Scott's name has been removed from the title page, but many chemists will probably continue to refer to the work by that name.

The objective of *Standard Methods* has been to collect analytical procedures, which are accepted generally as satisfactory and which can be readily applied to certain specified types of samples; this objective has long dictated the organization of the work and the nature of the material included; for example, a minimum amount of background or theoretical material, or critical review of other available methods, has been given. The characteristics of the earlier editions have been maintained in this edition, which will contain three types of chapters: (i) those dealing with a single element, (ii) those dealing with a single "class" of substances, such as plastics or gases, and (iii) those dealing with a single "type" of analytical method, such as microanalysis or ion exchange. While this division makes for certain arbitrariness in the assignment of material, it has apparently served well in the past, and there is reason to believe that, even though this approach may need revision in the future, it will suffice, more or less adequately, for the present.

Volume 1 covers the determination of the elements, chapter by chapter in alphabetical order, with a minimum number of groupings—for example, alkali metals and tantalum and niobium. Volumes 2 and 3, which are scheduled to appear at yearly intervals, will cover classes of material and physical and instrumental methods, respectively.

As an editor, I realize the difficulties of assembling a volume of 53 chapters written by 37 different contributors and of maintaining a comparable level of treatment. Consequently, the large differences in the various chapters, with respect to comprehensiveness of scope and quality and adequacy of treatment, were not unexpected. Some chapters show little indication of any development in the analytical chemistry of the elements concerned during the 20 odd years since publication of the fifth edition; other chapters are complete revisions. Thus, while many chapters fulfill their function as sources of true and tried methods (a characteristic of the Scott set), other chapters are inadequate in that they fail to take account of