IN RISING to say a few words to you as retiring President of The Endocrine Society, it cannot be said that there has not been ample warning of this moment. For two years I have known that only an act of God could avert the necessity of my speaking at this time and of your being a captive audience.

All sorts of notions have passed through my mind for subject matter with which to harangue you. One might philosophize on how to chart the course of this Society of ours, with its wide mixture of disciplines. In this connection the obvious could be cited, that our goal is to bring medicine ever closer to being an exact science while still preserving its art and thus maintaining the friendly and revered position which physicians have enjoyed for so long in our society. One fears sadly that as scientific medicine has flowered, much of our former prestige has already been lost, and we are now looked upon as following a trade rather than a profession. One might also give cogent reasons for wishing to maintain the unity of our Society, urging that there be one journal rather than two, so that the clinician would be almost compelled to read of laboratory doings and the laboratory might continue to receive the full stimulus of the clues to further understanding that nature provides so prolifically in sick persons.

Another possible subject for discourse was a recollection of personalities in the world of endocrine investigation whom I have met along the way. Or an attempt might have been made at a learned discussion of the moral obligations of the medical scientist, to society in general and to the human sick in particular. None of these seemed to strike the right chord; and so I turned to reflect on some of the bizarre, and at times downright silly, wisps of intellectual synthesis which have motivated certain phases of the investigative efforts of our own little group. This tale might be entitled “On Bones, Stones and Concrete”—the last named substance being descriptive perhaps of the author’s brain.

In 1927 Fuller Albright was induced by Read Ellsworth to spend a year at Johns Hopkins. Through the fortunes of war or chance, my fourth year...
medical quarter was spent that fall under the rack of these two tireless workers. As their chosen scut-boy, one was compelled to work late into the night, hovering over bottles of urine and blood, in tasks which then seemed far beyond the call of duty. But there were compensations: contact with their probing minds over many hours resulted in an approach to clinical medicine which has been a lasting joy; and later at the Massachusetts General Hospital, calcium, phosphorus, bones and urine became integral components of my life blood.

Skipping now some years of what I hope was scientific anabolism, a series of happenings occurred that might well justify Ripley’s statement that truth is stranger than fiction. In 1935 a colleague requested consultation on a young man who had developed severe and progressive hypertension immediately after a normal appendix had been removed for abdominal pain. Though we thought the patient did not harbor an adrenal medullary tumor, air injection about the kidneys was believed to show a mass; and consequently both kidney areas were exposed simultaneously, as was the custom in those days. The explorer of the suspected left side was the faster operator and the supposed tumor proved to be mythical. The surgeon operating on the right had nearly completed his exploration when the intern holding a retractor became fatigued and permitted the kidney to slide into the operative wound. A yellowish mass was seen in the kidney and believed to be malignant. The surgeon philosophically carried out a nephrectomy and sighed that the operation had not been entirely in vain after all. To my utter amazement, the patient got better and better; within two weeks the blood pressure had become normal, the heart had compensated, vision improved and indeed the patient’s blood pressure remains quite normal to this day. Had not the radiologists made a wrong diagnosis, the operation not been performed on both sides, the intern not have been up late the night before on some occupation, good or bad, resulting in fatigue, and had the surgeon not been wrong in his diagnosis of malignancy (for it proved to be an infarct which would undoubtedly have been left there), that young man would have long since perished.

This stranger than fiction tale does not end here, however. Some twelve years later, because his usual doctor was out of town, I was asked to see a practitioner of medicine whose story was almost identical to that of the boy’s just told. He had been explored at Johns Hopkins two months before and appendicitis not found. Hypertension, steadily progressive, ensued; and he was now nearly blind and in a state of heart failure. He was told the tale of the boy, and immediately took heart, demanding that his right kidney be removed, for, as he said, “I’m a gone goose if that isn’t what’s the matter.” It took some argument to persuade the urologist to remove the kidney, since the pyelogram was quite normal; but you can imagine our delight to
find the identical lesion present. The practitioner, too, continues to have a
normal blood pressure. On the basis of these 2 patients, Dr. Morgan Ber-
throng investigated the whole problem of renal infarction (these are com-
mon findings at post mortem without hypertension) and conclusively
showed that atrophy was present surrounding the infarcted zones in our 2
patients and not in 100 other patients with infarcts but without hyper-
tension. Thus a boost was provided to the study of hypertension in man
induced by unilateral renal ischemia and its possible cure, a subject which
had fallen into severe disrepute because so few nephrectomies had been
followed by improvement. But perhaps the strangest and most fictional
part of the whole series of incidents was that both surgeons told their
patients that the removed appendices were not diseased — which must be
rare in the annals of modern surgery since our cutting confreres sported
away from the barbers.

Again passing over some years, it became required of me to deliver the
Guiteras Lecture before the American Urological Association, owing to the
kindness of that Association’s then President, my old tennis partner, Dr. J.
A. C. Colston. His assigned topic was “The Etiology of Kidney Stones,” a
subject then beginning to be discussed by their group, rather than mechani-
cal methods for removal of stones, which had been their concern for cen-
turies.

It was a pretty dilemma, and a way out of it seemed to be to stress cer-
tain analogies between the behavior of skeletal tissues when they calcify
and the probable mechanisms of calculus formation. The more one probed
into these matters, the more convincing became the parallelism between
cartilage calcification, especially, and calcific stone formation. I say car-
tilage in particular because here we believe that the crystal deposition takes
place freely exposed to extracellular water, in distinction to bone where
osteoid is almost certainly protected by a membrane with a chemical
gradient — be this membrane an anatomic or physico-chemical partition.
My colleagues Rubin and Levine had showed that all forms of biologic
calcification in man have organic matrices with very similar histochemical
properties, in that they are metachromatic to toluidine blue and react
positively with the Hotchkiss stain. For seventy-five years histologists had
told us that one never sees mineral resorption from the skeleton without
coincident disappearance of its matrix or osteoid; and, in that Guiteras
Lecture, the hypothesis was advanced that enzymatically dissolved skele-
tal matrix traversed the blood, appeared in the urine and provided the
potential matrix for renal calculi. One is far from sure now that this thesis
may not be correct in principle.

The next steps stemmed from observations first made by Robison and
extensively followed up by the Hopkins pediatric group, including How-
land, Kramer, Park, Wilkins and many others. These consisted essentially of three basic facts:

1. That cartilage in a growing animal will be rachitic, i.e., uncalcified, if there is significant lowering of either calcium or phosphorus concentration (or both) in that animal's serum.

2. That healing of the rickets will occur in vivo if the Ca×P “product” is elevated by any means—even including starvation—which raises the serum phosphorus level by way of the protoplasmic breakdown.

3. That the rachitic cartilage will calcify in vitro if placed in solutions having concentrations of calcium and phosphorus similar to those required for in vivo crystal deposition. In simple solutions the reliability of this calcification in vitro is very great to those experienced in the technique of the procedure.

A fourth piece of information was the observation of Jackson and Park, amply substantiated by Follis and others, that a high proportion of patients with chronic renal insufficiency had histologic rickets, despite concentrations of calcium and phosphorus in their sera far too high for rickets to develop in other circumstances.

Yendt and his colleagues followed this up by finding that sera of uremic patients, or its ultrafiltrate, would often fail to calcify rachitic cartilage in vitro, despite extraordinarily high Ca×P products. Additions of urea, magnesium and potassium to normal “calcifying” sera in quantities compatible with life, did not prevent in vitro calcification; and we pondered on what it was about uremic sera that either acted as a matrix blocker, as a crystal poison, or kept calcium and phosphorus in such a state that their proclivity to crystallize in the matrix was lost. Did something normally emerge from serum into urine with these same properties and, if so, was it what keeps all of us from having a continuous rain of urinary calculi? It had long been a puzzle, and still is, as to how such fabulously high concentrations of calcium and phosphorus can remain in urine without precipitation.

It was this series of musing which led to a request of Dr. William Thomas that he see what would happen to rachitic cartilage if placed overnight in sterile urine which had been brought to pH 7.4 and specific gravity 1.011. Dr. Thomas’s reluctance to follow such a silly pursuit may be imagined; disenchantment with an idea could not have been more eloquently exhibited by an army mule. But to his and my amazement, not only did the urine fail to calcify the cartilage but actually appeared to demineralize that portion already calcified to some extent and the bone as well. When this happened over and over again, he turned to the urine of stone formers; and, using exactly the same technique, found that, in the first 8 urines tried, all of these vigorously calcified the cartilage. It should be stated here and now that there is not absolute invariability to these tests, i.e., there are occa-
persons who pass urine which calcifies cartilage who have never had a urinary symptom; and sometimes a person with a resident calcific calculus will have a non-calcifying urine. Having been reared in an atmosphere where much emphasis was placed on sin and the devil, for brevity's sake we classified urines which calcify as "evil," and those which do not as "good."

Amusing information has been derived from our somewhat muddled attempts to play with these urines and to change them from good to evil and vice versa. It has been found that dialysis does not alter the good or evil propensity, *i.e.*, the dialysate, when restored by evaporation to its original specific gravity, remains good if the original urine was good, and evil, if that had been the urine's previous bent. *Thus far,* only one reasonably practical fact has emerged—a diametric opposite of what might have been anticipated. If one feeds to a recurrent stone-former a considerable quantity of added phosphorus, stone formation will almost invariably cease. This has been shown by a series of patients, some of whom have gone now for three years without new calculus formation; and the average number of stones passed or removed in the first 17 patients of this series was 11 per patient per year over the previous five-year period. Exceedingly painstaking studies by Dr. Purisch on 2 of these patients while on the Metabolism Ward, with urines partitioned throughout the twenty-four hours, have shown that the cartilage tells us that their urines are thoroughly evil on a low phosphorus diet, fairly evil on ordinary phosphorus diets and quite good on high phosphorus diets. Yet, addition of equivalent amounts of phosphorus to the urine of these persons after its passage, though it forms no precipitate, will not induce reversion from the evil to the good state.

We may turn now to the most bizarre aspect of our delvings into the origin and prevention of renal calculi. The fact that stones can grow and solidify in the stream of a fluid current, reminded one of the great discovery of Portland—the combination of materials which form concrete and permit its hardening even under sea water. Portland's finding made possible the jetties and breakwaters for her rugged coasts, without which England could hardly have become mistress of the seas. Cement, of course, has no organic matrix; and heat is required and furnished chemically in the hydration process of its crystal growth. However, perhaps a site on the kidney stone's matrix provides a nidus for crystal initiation, and crystal growth up to a point proceeds in similar fashion to that of concrete. At least, a clue to what prevents concrete from setting, might furnish a means of attack for calculus prevention. To our astonishment it was found that physicists know little or nothing about the actual basic mechanism of concrete hardening. It was of considerable interest also to learn that urine has long been known to inhibit the setting of concrete. We decided, therefore, to see if concrete could distinguish for us a good from an evil urine; and preliminary investi-
gations in this regard were carried out by Russell Morris, Jr., a 12-year-old investigative collaborator, in his cellar during spare time from his school work. When it appeared from young Morris’s little blocks of concrete that good and evil urine might indeed reflect a difference in the quality of the product, more elaborate methods of testing were sought. We were fortunate in enlisting the aid of Dr. P. Kenerick Maher, physical chemist, and in charge of the basic cement research of W. R. Grace & Company. Dr. Maher was given 10 small sealed frozen tubes of each of 3 urines, one good, one naturally evil, and the third made evil by chemical manipulation in the laboratory. Using x-ray diffraction of whole pure cement as it was setting, Dr. Maher found distinct and uniform differences between good and bad urines. He then took a single component of the four which go into the purest cement (they will all harden individually with water but won’t make nearly as good cement)—namely, tricalcium aluminate, the most important of the components in speeding up cement setting and in the hydration of which a fourth calcium molecule and one of water are accepted. Preliminary patterns with this material again showed a consistent, readily distinguishable difference between the good and evil urines; and most interesting, the curve for water lay right in between the curve for good urine and that for bad. So, weirdly, it may turn out that we will be using cement as a guide to tell us who will and who will not likely have a kidney stone, or whether we are helping or hurting a patient with a given kind of treatment. How crazy can you get in the pursuit of clinical investigation?

For me this has been a most exciting year and I hope one of growth spurt for the Society in its late adolescence. To cap the climax, nothing could have given me more pleasure than to be presiding when the Society’s most coveted award was presented to Lawson Wilkins, close friend and fellow traveler along endocrine pathways. The association with him at our Wednesday afternoon sessions for twenty-five years has provided me undoubtedly my best instruction and happiest scientific moments.

I should be remiss if, before closing, I did not express to you my deeply felt appreciation for the honor and privilege of being your President. But I am humbly aware that such encomiums from scientific and academic societies, though bestowed upon an individual, are often in reality an expression of approbation to the colleagues, Fellows and students who have been his co-workers. With warm sentiment my gratitude goes out to those who, through the years, have really done my work, guided my hands and constantly educated me with youthful ideas and elegant criticism. To them and it is a pleasure to see not a few in this audience—from the bottom of my heart I say thank you.

It is now time to turn over the reins of this organization to an old friend and fellow worker in these vineyards, a man of vigor, originality and integrity—Ted Astwood. The Society will be in good hands.