

Summer 1982

Of Cabbages and Kings: The Heme Pathway: [Dr. Attallah Kappas]

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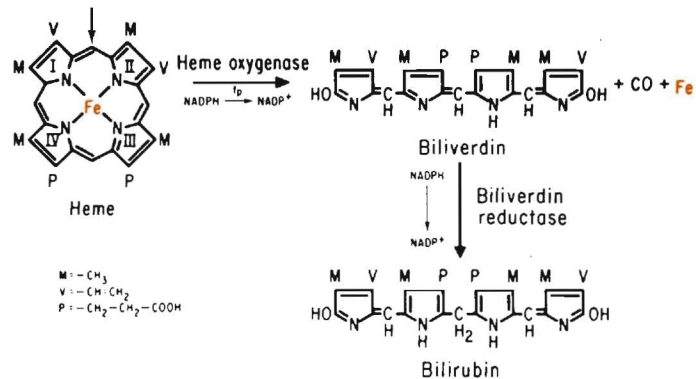


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THE ROCKEFELLER UNIVERSITY RESEARCH PROFILES

SUMMER 1982

Of Cabbages And Kings: The Heme Pathway

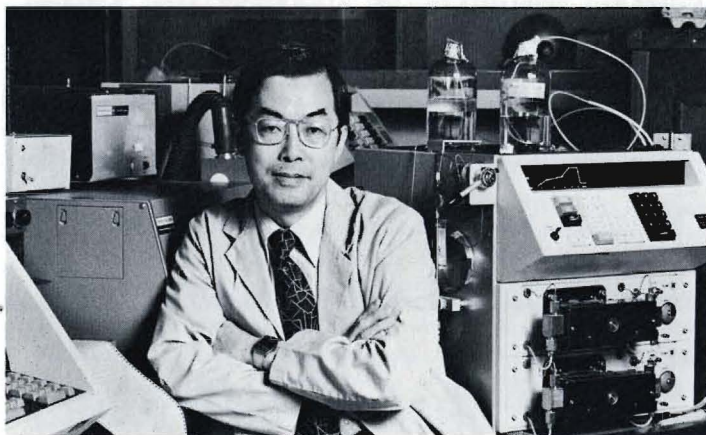
In the office of Professor Attallah Kappas there is a photograph of a smiling, apparently healthy young woman standing with her parents. He keeps that picture "as a kind of talisman." She was one of my first patients when I came to Rockefeller 16 years ago. Not long before the photograph was taken, she had been extremely ill with a severe attack of acute intermittent porphyria, which had eluded proper diagnosis elsewhere."

Dr. Kappas is physician-in-chief of The Rockefeller University Hospital, the clinical research arm of The Rockefeller University. Most of the patients who come to the hospital have, like the girl in the picture, serious chronic diseases; some rare, like acute intermittent porphyria (AIP); some more common, like diabetes, arteriosclerosis, or arthritis. They come for treatment and to participate in laboratory studies through which the hospital's researchers learn more about the underlying biological mechanisms of their disorders.

Dr. Kappas heads the hospital's metabolism-pharmacology laboratory. He and his colleagues study liver diseases, particularly the biochemical and clinical problems that involve the oxygen-binding pigment called heme. They explore the pathways by which heme is synthesized and degraded in the liver, and the role heme plays in cellular metabolism and the bio-



Dr. Kappas in his office and on the ward.

Dr. Sassa

logical transformation of various chemicals. These chemicals may be substances made in the body, such as steroid hormones—Dr. Kappas's original area of research—or those that enter the body from the outside environment in the form of drugs, pollutants, and food components.

Trained as an endocrinologist, Dr. Kappas hadn't expected, before his arrival at Rockefeller, to be one day pondering the genetics of the porphyrias and the biochemistry of heme and cytochromes, studying the pharmacological effects of nutrition, or treating people suffering from lead poisoning. He had wanted to learn more about estrogens and the liver. "But," he explains, "as so often happens in research, you start with a problem that has inherent depth and you find yourself crossing jurisdictions, so to speak, both clinically and scientifically. You move with the problem." Of late, he has moved back to endocrinology—by way of the heme pathway—to what he hopes will result in a new and better treatment for postnatal jaundice, a prevalent and sometimes disabling condition in the newborn.

"THE MOST HONORED CALLING"

The first step that set Attallah Kappas on the road to clinical science, which later in his medical-school years represented for him "the most honored calling," was his parents' "deep

respect for learning." He earned a bachelor's degree at Columbia University and the M.D., in 1950, from the University of Chicago School of Medicine, which 25 years later conferred on him its Distinguished Service Award in Medical Sciences. After a time spent at Sloan-Kettering Institute in New York and the Peter Bent Brigham Hospital in Boston practicing medicine and learning about steroid biochemistry, he returned to the medical faculty of the University of Chicago in 1957. There he initiated a variety of investigations on the pharmacology of steroid hormones in man.

In the mid-1960s, he began thinking about the effects on the liver of estrogens, the female sex hormones. As he wrote at the time: "It is well known that the liver plays a central role in the transformation and biological inactivation of estrogens. The possibility that, in this metabolic interaction, estrogens might themselves act directly on the liver or alter its functional integrity in ways which might have clinical expression is less widely recognized."

Although little was known then about the porphyric diseases, of which AIP is the most common hereditary form in this country, there were strong indications—the prevalence of attacks in women, its onset after puberty, and its exacerbation during menstruation and pregnancy—that hormones were involved in its pathogenesis.

Sam Granick, a plant physiologist and biochemist who, until his death in 1977, spent more than 30 years at The Rockefeller University studying chlorophyll and other biological pigments, was then beginning to work with cultured liver cells on problems concerning the regulation of porphyrin production.

"Dr. Granick had the methodology that I needed to investigate steroid influences on the liver," says Dr. Kappas. "So I decided to take what I thought would be a year's sabbatical from the University of Chicago to go to New York and work with him." He arrived at Dr. Granick's laboratory in 1966 as a guest investigator under a Guggenheim Fellowship.

The word porphyria derives from porphyrin, the generic name for tetrapyrrole pigments, which include chlorophyll in plants, and heme, perhaps the most important human pig-

ment. A porphyrin is a four-ring-shaped structure. When it has an atom of iron at the center, as is usual in higher organisms, a porphyrin becomes a heme, which binds oxygen. Heme combines with the protein globin to make hemoglobin, which transports oxygen in the blood. It also combines with other proteins, for example in liver cells, to form cytochromes that, among other functions, catalyze the oxidative metabolism of chemical substances in the body. Without this oxidation process, many chemicals would act on body organs ceaselessly, with toxic consequences.

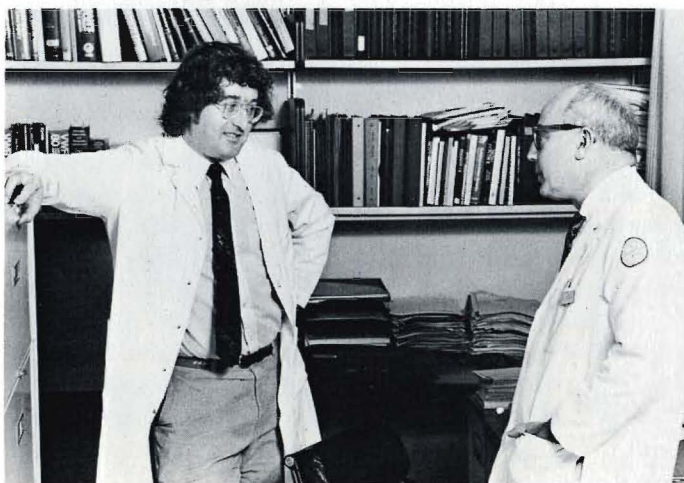
The heme pathway is a complicated, multi-enzymatic sequence. In AIP, the synthesis of heme is interrupted early in the process when misinformation from an abnormal gene causes a malfunction in an essential enzyme. As the name implies, AIP is characterized by attacks that come and go. The symptoms can include excruciating abdominal pain, neurological derangements including paralysis, and psychosis. "Mad" King George III of England is believed by some to have had a form of porphyria.

As the work of Dr. Kappas and others has made clear, attacks of AIP are triggered by factors in either the external or internal environment. Shortly after his arrival at Rockefeller, he and Dr. Granick demonstrated conclusively that natural steroids are among the triggers; as it turns out, not estrogens but progesterone, another female hormone. So are certain foods and drugs. Curiously, however, not everyone with the miscreant gene shows clinical signs of AIP. For example, the father of the girl in the photograph also has the genetic trait, but has never had the disease. His sex may be an influencing factor. Yet there are women who also carry the AIP gene and are equally exposed to environmental triggers but never fall prey to attacks. What began for Dr. Kappas as "curiosity about an endocrinological question involving an uncommon group of genetic disorders" led to broader questions about heme biology.

CYTOCHROME P-450

The protein cytochrome P-450 is a central component of the

enzyme system involving the heme pathway. Some substances speed its action; some, like metals, inhibit it. Dr. Kappas and his colleagues have been studying the effects of many substances on the P-450 system in tissue culture, experimental animals, and both normal and sick people. The Rockefeller Hospital is a center for the study of environmental pollutants, particularly lead, trace elements, and other metals. Lead poisoning is a frequent and often undetected problem that can be extremely serious, especially in children who are more prone than adults to permanent damage of the bone marrow, brain, or kidneys. According to a recent report from the National Center for Health Statistics, four percent of American preschoolers have excessive levels of lead in their blood. A few years ago, Shigeru Sassa, a member of Dr. Kappas's group, developed a fast, easy, precise, and inexpensive test for lead poisoning that is far more sensitive than previous ones and is now in wide use. Dr. Sassa, who started at Rockefeller as a graduate fellow with Dr. Granick, also developed an assay for the detection of AIP in the fetus. In Dr. Kappas's view, "Dr. Sassa's enzymological assays and innovative techniques for quantitative study of heme processes in cells and tissues have been crucial to the work of this and other laboratories studying heme biology."



Dr. Anderson, right, with Assistant for Research Li-Lan Tsai. Chick embryos are injected with drugs to see the effects on porphyrin and heme synthesis in the liver.

Dr. Drummond and Dr. Kappas



Dr. Kappas in front of The Rockefeller University Hospital.

The P-450 system can be the site of competitive interplay between chemicals; an important aspect of the laboratory's work has been to help elucidate these interactions, especially as they diminish the therapeutic efficacy or increase the potential toxicity of medicinal drugs. Drug metabolism can be affected by other drugs, cigarette smoke, alcohol, and ordinary foods.

"At the risk of taking the romance out of gourmet dining," says Dr. Kappas, "it is useful to remember that foods comprise many chemicals that significantly influence drug metabolism in the liver." Studies by members of the laboratory, including several by Drs. Kappas and Karl E. Anderson in association with Dr. Allan H. Conney from Hoffmann-LaRoche, have yielded some astonishing findings on nutritional influences. For example, certain vegetables, such as cabbages and brussels sprouts, dramatically accelerate drug metabolism; charcoal-broiled steak can speed it by as much as 950 percent in the intestine and liver. Corroboration has come from research elsewhere on drug-nutrient interactions.

"I think there are important inferences to be drawn from such observations if we are going to reduce the high incidence of drug toxicity," Dr. Kappas says. "It seems obvious, to give an extreme example, that a postoperative patient who has been receiving nothing but glucose feedings intravenously for a week is going to respond very differently to a drug than the patient eating three solid meals a day."

The rate-limiting enzyme in heme breakdown is heme oxygenase. This enzyme activity increases markedly after birth, resulting in an excessive production of bilirubin, the yellow bile pigment that is a product of the breakdown of heme. The disposal mechanism for bilirubin in the liver is not mature in the newborn. In many infants, this incompetence has pathological consequences that can lead to brain damage or death. Neonatal jaundice—hyberbilirubinemia—is caused by an excess of bilirubin accumulating in the blood. Dr. Kappas and Dr. George Drummond, a laboratory member from Scotland, are applying what has been learned about the way heme oxygenase is regulated by inhibitory metals and metalloporphyrins to the development of a potential new treatment for neonatal jaundice.

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"All current therapies," Dr. Kappas states, "are directed at getting rid of the bilirubin after it has been formed. Our approach is to try to block bilirubin production before it starts. The metalloporphyrin we're working with at present has tin instead of iron in the ring structure and it can block almost completely the binding of heme to heme oxygenase, thus preventing bile pigment formation."

Although the treatment is still undergoing animal trials, the Food and Drug Administration has approved initial studies in adult humans. These studies look extremely promising and have aroused considerable interest in pediatric circles. The project especially pleases Dr. Kappas because it represents a direct path from the lab to the bedside—every clinical researcher's hope—and because it relates to endocrinology, to the first question about hormones, gestation, and liver function that captured his interest 20 years ago.

NO LONGER A GUEST

Dr. Kappas was appointed a professor in 1971 and physician-in-chief in 1974. In his role as hospital administrator, he has overseen much-needed renovations of patient and laboratory facilities, brought in new laboratory groups, and introduced a program of postdoctoral training for a new generation of physician-scientists. Last year he was named Sherman Fairchild Professor under a major new gift from the Sherman Fairchild Foundation to support clinical research at the hospital.

The young woman in the photograph still has porphyria, but her condition is now under control. She has never again had an attack as severe as that first one. The work of researchers like Dr. Kappas and his colleagues has helped to assure that she and others like her will not, as AIP victims did in the past, die from unnecessary surgery or inappropriate drugs.

As for Dr. Kappas: "I planned to stay at Rockefeller just long enough to work out one laboratory problem and its medical implications. I'm still here and I'm still working on them."