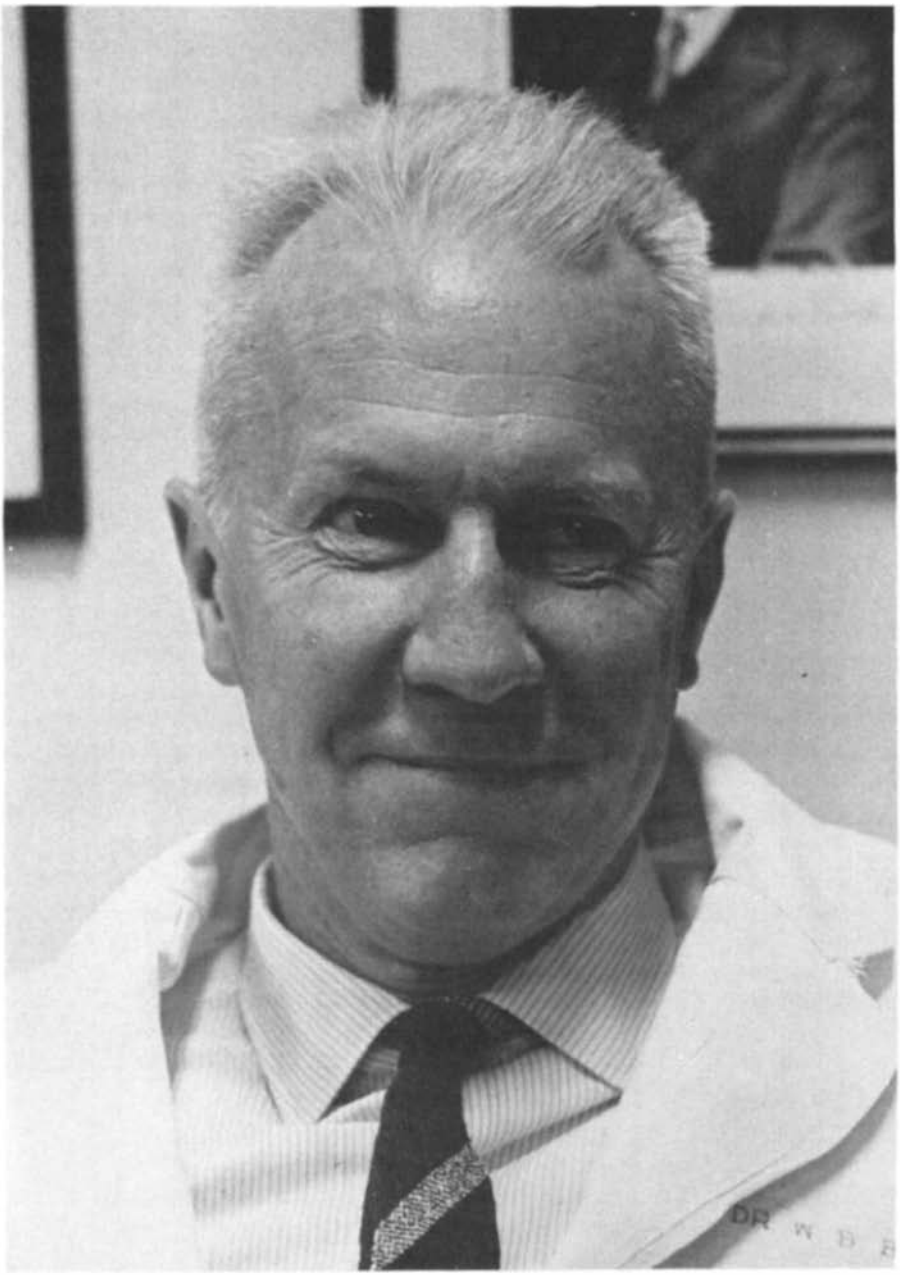

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PERSONAL REFLECTIONS ON CLINICAL INVESTIGATIONS

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Introduction

I was fortunate to participate in one of the explosive phases of clinical nutrition more than 40 years ago, just before World War II began. At that time water-soluble vitamin B was becoming the vitamin-B complex, budding off many separate new vitamins. These were being discovered by students of animal nutrition and biochemistry, and by those interested in the nutritional growth requirements of such lowly organisms as bacteria, yeasts, and fungi.

As an undergraduate medical student at the University of Virginia, I saw pellagra. We were told about malnutrition and Goldberger's work. I saw one pellagra patient on the Osler Service at Johns Hopkins in 1935–1936. The next year, when I went to the Thorndike Laboratory, Soma Weiss and Robert Wilkins were in the midst of their exciting studies demonstrating that vitamin B_1, thiamin, quieted the alarming and precarious hyperdynamic state of the circulation in beri-beri, then so prevalent among the alcoholic gentry who crowded into the Boston City Hospital.

In 1937 I went to work in Marion Blankenhorn's Department of Medicine in Cincinnati. It was an exciting place to be. Gene Stead, Gene Ferris, Johnson McGuire, Leon Schiff, Lee Foshay, and others there were stimulating young investigators and teachers. Tom Spies had done excellent clinical studies on pellagra at the Lakeside Hospital in Cleveland and the Cincinnati General Hospital. Near the end of my year as a senior medical resident an

[1]William B. Bean, medical scholar—physician, clinical investigator, editor, teacher, writer, and medical philosopher—was intimately involved in clinical nutrition research during the exciting era of discoveries of the 1930s–1950s. His reflections on clinical research in and knowledge of nutrition during that period of more direct, relatively uncomplicated, less restrictive investigations provide much wisdom for consideration by investigative-minded physicians today.

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opportunity arose to work as a Fellow in nutrition. I had no special competence in the field of human nutrition but had helped Soma Weiss and Bob Wilkins in some of their clinical experiments. A good friend of Blankenhorn, Dr. James McLester of Birmingham, Alabama, still skeptical of the ideas introduced by Goldberger, welcomed Tom Spies to Birmingham to see if he could get the same good results in treating desperately ill pellagrins there that he had obtained in Ohio. The mobility of the staff, which shifted to Birmingham for the spring and summer months and then returned to Cincinnati for the fall and winter months, was remarkable. Richard and Sue Vilter and I had the main clinical and laboratory responsibilities. In the considerable outpouring of papers from the nutrition clinic, Spies's name led all the rest. Charles Aring, Cincinnati neurologist, essayist, and scholar, made prominent contributions to the thiamin and beri-beri studies. Many physicians, biochemists, nurses, dentists, and others from various medical schools in the country were eager participants. In addition to A. B. Chinn and Blankenhorn, the following co-workers are listed alphabetically: W. F. Ashe, A. E. Axelrod, W. Beckh, C. E. Bills, Hugh Butt, C. Cogswell, Clark Cooper, Zola K. Cooper, G. Delfs, R. Eakin, Conrad Elvehjem, Joe P. Evans, E. Gross, Morton Hamburger, Harold E. Himwich, M. P. Hudson, T. H. Jukes, Walter F. Lever, J. B. McLester, A. W. Mann, V. Minnick, Carl V. Moore, Robert A. Moore, Gordon R. Morey, Milton Rosenbaum, J. M. Ruegsegger, E. E. Snell, S. R. Stanbury, R. E. Stone, E. P. Swain, Emory D. Warner, R. J. Williams. After I had left Carl Vilter and Wally Frommeyer were important contributors.

A Note on the History of Pellagra

Three recently published books (25a, 27a, 40a) afford detailed accounts of the history of pellagra. These and the earlier compilation of selected reprints of Joseph Goldberger and an evaluation of his classical studies of the disease, ***Goldberger on Pellagra*** by Milton Terris (62a), make it redundant to detail here an account of the evolution of understanding of this fascinating deficiency syndrome. Rather, I recall here but a few especially poignant personal recollections pertinent to my own early involvement with clinical evidence concerning pellagra.

For more than two hundred years the nature of pellagra had been a subject of great debate and confusion (32). Many drugs had been tested on severely ill pellagrins brought into a hospital, put to bed, and given fluids and good nursing care. For a brief time many experienced clinical improvement. Spies had shown that this might occur even while they were eating a pellagra-producing diet or given nothing but salt solution and dextrose. Such a program, however, could not be continued long or the patients would suddenly get sicker and might die if the elements missing from the diet were not restored in ample quantities.

Perhaps the first controlled study in human nutrition after Lind's observation on scurvy was Cerri's study of pellagra carried out in Milan, Italy in 1795 and 1796 (32). Cerri was convinced that a diet made up largely of corn and corn products somehow explained the very high incidence of pellagra among the country folk. He selected ten of them, who for two years moved to town and ate the diet common to those in the city. On this regimen no signs of pellagra developed, while in the peasant controls in the country the incidence remained high. The following year the subjects were allowed to revert to their polenta (corn meal) diet, and pellagra returned as usual. One, however, was so much impressed that he got work in the city and never had pellagra again. These observations have been largely neglected by those who have written on pellagra.

A good example of the pre-Goldberger confusion is found in a 1912 book entitled *Report of the Pellagra Commission of the State of Illinois* (40). It describes the distressing outbreak of pellagra in Illinois mental hospitals from 1909–1911. Of the 258 patients with pellagra in Peoria, 128 died. In Kankakee, with fewer patients, 40% died, and about a third died at the Elgin State Hospital [subsequently the site of a long series of remarkable studies by Horwitt et al, in which deficiencies of niacin, thiamine, riboflavin, or tocopherol were induced by feeding diets deficient in the nutrients. These studies were made in collaboration between the Food and Nutrition Board of the National Research Council and the Elgin State Hospital over a 23-year period (33a)]. At that time all the Commission could think of were infections. Study of fecal bacteria occupied 105 pages of the special report, which then proceeded to complement fixation tests, cutaneous tests with corn extracts in pellagrins, and a learned discourse on black flies and buffalo gnats, including beautiful drawings of the various larval phases of the Simulium in Illinois. An essay on the protozoan infections was followed by dietary studies from the hospital concerned only with the food as issued, not the food as eaten. A corn-free diet was compared with a mainly-corn diet without definite conclusions. The experiment is a good example of how not to do a study comparing one food with another. In the summary the authors wrote that "the lack of definite information regarding the food requirements and metabolism in the class of subjects experimented upon has made it difficult to interpret the results obtained in these studies." A rather wistful comment added that "the experimental work here reported is in itself brief and is not extensive enough to allow any broad interpretation."

Joseph Goldberger Solves the Problem

The spectacular prevalence of pellagra in the Southern states seemed related to poverty. Of course, infection was known to follow poverty fairly closely. In 1914, Joseph Goldberger of the US Public Health Service, the old Marine Hospital Service, was sent to Georgia to see if the peculiar epidemiology of

pellagra indicated an infection. The seasonal peak of pellagra occurred in the late spring and early summer, some two or three months before the peak intensity of sunshine and heat. In cotton towns the disease clustered among the homes of workers who lived in poor quarters, often along the banks of streams or rivers subjected to flooding, and largely without plumbing. Goldberger's work in solving certain epidemics of insect-borne skin disorders made him a logical person to find some kind of infecting organism. In the South, Goldberger was under the triple jeopardy of being a Yankee, a Federal Government worker, and a Jew. His assignment seemed to add Northern insult to Southern injury, though eventually some southerners accepted the surprising results of his heroic experiments.

Goldberger not only tormented himself as an experimental subject, he also used his wife as a subject in hair-raising ingestions or injections of horrible samples of the effluvia of very ill victims of pellagra. While this ranks high as an example of heroic autoexperimentation and of a wife's devotion, it failed to reveal any infecting organism. Indeed, Goldberger was well aware of the fact that nurses, attendants, and physicians almost never got pellagra in asylums, hospitals, or prisons. Thus having found no infection, he turned to study of diet. After he learned what the people who developed pellagra customarily ate, he obtained convict volunteers as subjects, promised them early reprieve, and fed them the same food as customarily eaten by those developing pellagra. After many months the prisoners developed pellagra, which cleared up on a good diet. Goldberger found, in particular, that inexpensive brewer's yeast was a good biological food for treatment or prevention. He suspected that an amino acid deficiency, particularly that of tryptophane, was important—a suggestion made by Sandwith as early as 1913 (29–31, 41a).

Nicotinic Acid: The New Era

In 1937, Elvehjem, Woolley, and their associates (27) found that canine black tongue, which Goldberger had identified as a good experimental model of human pellagra, was relieved dramatically by nicotinic acid. It was most interesting to see the spectacular and sometimes astonishing efforts to establish priority of publication in nailing nicotinic acid to the clinical mast. In New Orleans, Durham, Augusta, Birmingham, and Cincinnati there was a great scurrying around to find out what nicotinic acid might do for sick pellagrins.

The name nicotinic acid for this derivative of nicotine was rather frightening (48–52), and the term niacin was coined to avoid any implication of a toxic material. A dramatic and alarming, but fortunately innocuous, event occurred when Spies and his associates each took a quantity of nicotinic acid by mouth. Soon, to their astonishment, they developed a blotchy erythema of the face and upper body. Some experienced a pounding head-

ache and a little nausea. No doubt anxiety was a part of the reaction, which fortunately soon passed without damage.

Later on I studied whether nicotinic acid and related compounds that did not produce flushing were effective in the prevention and treatment of pellagra. Several, indeed, had this property. In order to study the great variety of compounds to determine what specifically caused the flushing, it was necessary to measure skin temperature in fasting subjects. Since many compounds had to be prepared and were available in small quantities, the tests involved the intravenous injection of 20 mg of the experimental compounds, each of which I had previously tested on myself. Subjects lay flat on their backs, lightly clad, in a constant-temperature room at 20°C. This produced a steady state of vasoconstriction so that vasodilation could be measured readily. Skin temperatures were read off a galvanometer. The specific molecules that produced flushing were those of nicotinic acid and its various salts. Pellagra could be treated effectively with nicotinamide, which did not produce the unpleasant flush (3).

The Self as Subject

As illustrated by this experience, autoexperimentation was usually the beginning of clinical research in nutrition. I have done hundreds of such experiments with no apparent ill effects. A near miss occurred, however, when I was a busy nutrition Fellow with many clinical and teaching responsibilities. For nearly two weeks I took a pellagra-producing diet and lost ten pounds in ten days, mostly from an inability to eat enough of the cornbread, hominy, fat back, and molasses to supply calories. I was exhausted and unable to do my work, so I stopped the test, which was not expected to produce results for months. This experience made me acutely aware of the other side of the patient-physician interaction. Therefore, in testing various compounds for effects on malnourished persons we ate or injected them into ourselves before giving them to patients. Later, extensive experiments of many kinds were done in the Army with the medical officers undergoing practically all of the test routines before or while our soldier subjects were tested.

The Inertia and Momentum of Clinical Signs of Malnutrition

Food provides material for constructing the fabric of the body and for the energy for the multitude of functions that constitute cell life. After growth is complete, repair and renewal require energy, as do the daily metabolic functions of the body.

Malnutrition begins when supplies are low. For water-soluble vitamins this occurs more rapidly than with fat-soluble vitamins, some of which are retained with great tenacity. A deficiency at the biochemical level begins to

interfere with various functions, causing pathophysiological changes. The organic lesions of niacin deficiency are at first microscopic but become grossly visible as clinical hallmarks of disease of gut, skin, and nervous system. Stomatitis and diarrhea occur. The initial changes in the skin of the malnourished look like a second degree burn, a mild scald, or a severe sunburn. The skin becomes pigmented, desquamates, and sometimes regenerates with the cracking of crazy-pavement epithelium. In localization, regional forces are important. A skin lesion may be progressing in one place while it is healing and regenerating in another. Individual variation in susceptibility is also significant.

It was logical to suppose that nicotinic acid played its role through its function in respiratory enzyme systems. For this reason it was important to find chemical methods to obtain information about the blood level of such enzymes. In 1939, Richard and Sue Vilter published with Tom Spies a microbiological method for determining the level of codehydrogenase (cozymase) in the blood and urine of pellagrins and normal persons (64, 65, 67). The assay of the enzymes was a logical approach to classification and measurement, but later clinical study provided most of the key information on nicotinic acid deficiency. Levels of these pyridine compounds were low in people with pellagra, but also in many persons with diabetes, leukemia, Roentgen sickness, and pneumococcal pneumonia (9, 64, 65). Sometimes the levels were decreased in other infections, in various fevers, and after extreme physical exercise.

It was a puzzling problem to Spies and others that while eating the pellagra-producing diets, pellagrins who are hospitalized might have their lesions improve or even disappear. It began to be obvious that the upset balance between demand and supply could be rectified temporarily by reducing the need as well as by normalizing or increasing the intake. Any agent given at this time that had no specific effect might be credited for the therapeutic improvement that followed.

Biosynthesis, which is important in ruminants, is much less significant in human beings since the colon, where most bacterial action occurs, is too far down the alimentary canal for very effective absorption.

Indirect effects of test substances must also be remembered in therapeutic testing. For instance, if nicotinic acid is given to someone with pellagra and beri-beri while the individual remains on a poor diet, digestion and absorption may improve enough so that thiamin is absorbed in quantities adequate to correct the thiamin deficiency and thus relieves the beri-beri (16).

Deficiencies may take months or years to produce clinical changes. It is not surprising that restoring the missing vitamins and providing a balanced diet do not always produce rapid effects. This is particularly true in lesions involving the nervous system. When a nerve cell is killed, no treatment can repair the damage. However, in many patients with the peripheral neuropa-

thies of beri-beri, slow improvement occurs over a period of months of carefully continued treatment (16).

Because of the diversified metabolic missions of various cells, specific deficiencies may interfere with certain functions of cells before others. The study of nutrition is full of surprises. Krehl, Elvehjem, and colleagues (34) found that the essential amino acid, tryptophane, can be converted into niacin and thus can prevent or cure pellagra. This was a unique example of the conversion of an essential amino acid into an essential vitamin. On the other hand, an abundance of niacin does not take the place of tryptophane in human nutrition, so it is a one way street. It is of note that Goldberger suggested tryptophane deficiency as a contributory mechanism in the development of pellagra (31).

Vitamins undoubtedly may serve as placebos. The confidence engendered by coming to a famous nutrition clinic well-known for benefiting many persons may assist in generating great subjective improvement. Where most manifestations are subjective, the interpretation of improvement must be made in the light of this significant point. Hospitals have lost some of their terror and famous clinics have achieved famous cures. Faith has helped ailing humanity, as at Lourdes. Psychosomatic factors must be investigated, controlled, and evaluated, particularly where manifestations contain so much that is subjective (16).

My observations on pellagra led me to believe that a major source of the arguments and disagreements among observers resulted from significant variation in the quality of corn in different southern regions—i.e. from the amount of nicotinic acid and perhaps of tryptophane in the diet. Certainly when we learned about tryptophane a number of mysteries were cleared up. Diets with more nicotinic acid were sometimes associated with more pellagra, rather than the other way around. Later studies of bound niacin further clarified concepts.

It is still a matter of conjecture why mechanical defects such as intestinal shunts may be followed now by pellagra, now by beri-beri, now by macrocytic or microcytic anemia, or by apparently reasonable health in what seem to be precisely comparable circumstances (4, 6). (See the review by Young & Blass in this volume.)

Unilateral and Experimental Lesions Produced Without Sunlight

Goldberger, who made so many capital observations on pellagra, observed that atypical lesions may readily occur.

> It may be stated as the rule, that if the back of one hand, or one foot, one elbow, one knee, one side of the neck, one cheek, or the lid of one eye is affected then the corresponding part of the other side of the body is assumed to become similarly affected and affected

> to almost exactly the same degree. This rule, however, is not without many exceptions. It must not be hastily assumed, therefore, that the possibility of pellagra is necessarily excluded because the back of the head or of one foot or of one side of the neck alone seems to be involved or is involved to so slight an extent to be almost nothing in comparison with the other side.

Stannus, in his classic review of the theories of the cause of pellagra (62), observed that "the facts in regard to the distribution of the exanthem in pellagra may be stated in reality quite simply, though they appear to have escaped the observations of most pellagrologists. The exanthem tends to appear in those areas of the skin which in any particular individual have *undergone certain changes* as the result of the action *in the past* of traumata of various kinds including solar radiation, exposure to cold, friction, pressure, irritants, etc." This is also true of skin lesions in many other diseases.

I made a careful study in 1940 and 1941 of a series of patients who had asymmetric or unilateral lesions as well as bilaterally symmetrical ones (8). Five cases of asymmetric lesions were observed in persons with varicose veins that were more severe on one side than the other. Trauma, pressure, and irritation were found to be the cause in five other cases. Infection was responsible in two, paralysis was found in one, and no cause could be found in two. Asymmetrical lesions on the elbow occurred only in patients confined to bed who, if right-handed, rested on the left elbow. A one-sided lesion was associated with asymmetrical varicose veins in patients who were ambulatory. In none of the patients we observed was sunlight a provoking cause, although Plunkett (39) noticed that a one-sided exposure to sunlight or wind damaged the skin and gave rise to asymmetrical localization.

In the middle 1930s Spies had demonstrated that glossitis was a much more sensitive gauge of the clinical stage of pellagra than the skin; skin lesions might clear up while patients were eating a pellagra-producing diet. Such a diet might ultimately lead to skin lesions in persons not exposed to sun. Dermatitis in the pudendal region had been known for a long time. There was thus much argument about the specificity of sunlight in the disease. For this reason, early in 1941 I undertook to determine whether by reducing the blood flow to the skin and increasing its metabolism by the use of a heating pad the localization of skin lesions could be encouraged. This had to be done during the prodromal stage of the disease, perhaps months and certainly weeks before the clinical manifestations were expected. For one or two hours a day for a period of more than two weeks, I put a cuff on my arm, set the pressure well over the level of systolic blood pressure, and wrapped an electric heating pad around. After several days' testing the skin developed the so-called fire stains, or *erythema ab igne,* the reticulated, mottled, pigmented network seen in those who have used a hot water bottle or an electric heating pad for a long time or have sat long in front of an

open fire or a hot water radiator. No other manifestation occurred, and after a few weeks my arm resumed its normal appearance. I concluded that the method was probably safe to use in persons whose history led us to believe they would develop an annual relapse in pellagra. We used the tourniquet method of producing ischemia in several persons before encountering an example of neuropathy. This mishap occurred in a malnourished man in his early 30s who had had annual attacks of pellagra for several years. I used the method of heat and ischemia that I had used on myself, but only for 15 minutes. To my surprise and consternation, this produced a neuropathy that included both paralysis of the muscles and a loss of the sensations of touch and pain. Fortunately, the condition cleared up in a few hours. This led me to use simple sandbags to weight the electric heat pad. The weight of the sandbags in place 30 minutes was sufficient without heat to cause reactive hyperemia, indicating effective oxygen deprivation. No further neuropathy occurred, and we used the method in a study of thiamin metabolism and beri-beri. An effective variation of the method was to have the patient lie supine on a firm examining table. The weight of the leg induced ischemia on the back of the calf. In two of five persons with latent pellagra, the induction of ischemia plus heat produced changes in the skin that resulted in a unilateral lesion during a clinical relapse of the disorder in which bilateral dermatitis developed in other parts.

Secondary Pellagra

My studies of diarrheal diseases that give rise to pellagra got me interested in going over the records of all patients with pellagra in the modern period at Lakeside Hospital in Cleveland and at the Cincinnati General Hospital (6). This review was supplemented by an intensive literature search which I had been conducting for years on the history and current understanding of pellagra. Strictly secondary pellagra can be established only when a person on a fixed diet develops pellagra following the development of a disease and gets rid of the pellagra when the disease is reduced or cured. To be sure, the diet is likely to be marginal, but not in itself sufficient to produce the disease. The current state of medicine and science has generally determined current thoughts about pellagra. When first described, its cause was thought to be a toxin or poison on corn, analogous to ergot on rye (32a). In the last third of the 19th century infection dominated thoughts of etiology and convinced many that pellagra was an infection. Sambon incriminated the buffalo gnat. For sixty years the belief that pellagra was an infection prevented progress.

Clearly any disease can dispose to the development of pellagra by disorganizing a person's relationship to his environment. Disorders of the body politic give rise to war and famine, upheavals in personality lead to food

fads, dietary cults, and addiction to alcohol; other disabling upsets, including insanity, are important in the background upon which pellagra develops. Even epilepsy, hemiplegia, and parkinsonism may have pellagra engrafted upon them.

It is not easy to separate symptoms of pellagra from those of the diseases of the alimentary canal upon which it may be engrafted. We must consider intestinal hypermotility, decreased enzymatic digestion, inadequate absorption, abnormal bacterial flora, destruction or utilization of vitamins by bacteria, inactivation or binding by various constituents, liver damage and such abnormalities of function as nausea, vomiting, loss of appetite, infection and fever. Thus the alimentary canal from one end to the other can influence nutrition—e.g. damaged teeth or their absence, disease in the gullet, trouble in the stomach including cancer, ulcer, inflammation, syphilis, and a host of diseases of the remaining alimentary canal: parasitism, obstruction, granulomas, tuberculosis, ulcerative colitis, Crohn's disease, shunts, operations, strictures, and functional disorders of the alimentary canal. All such conditions cause conditioned malnutrition. Liver disease, operations, anesthesia, infection, and fever are all important. Women need more nutrients during pregnancy, lactation, and childbirth in order to produce the fetus and placenta and to supply milk later. In addition, a mother is likely to sacrifice her own food in order to feed her child. Hypertension, congestive heart failure, and radiation sickness have had meager systematic study but may have special mechanisms of reducing the pyridine coenzymes. Drugs, chemicals, hemorrhage, and a vast miscellany of nonspecific disorders may also condition occasional instances. It has not been possible to study in isolation a genetic liability to pellagra, mainly because people inherit not only their genes but also, to a surprising degree, their environments. During the period of the Birmingham studies among a large Negro population, blacks provided only 9% of all pellagra patients whereas in Ohio pellagra was two or three times as common in blacks as in whites. It has been my impression that in the old South blacks usually had white friends or a white family who were genuinely concerned with their well-being and saw to it that they got food.

Pellagra in Ohio Hospitals in 1941 and 1949

I did two studies (5, 15) of pellagra in Ohio Hospitals, in Cleveland and Cincinnati (1942) and the other in Cincinnati (1949), where pellagra had been under intensive study for nearly 15 years and underestimation of its frequency, therefore, was unlikely when we studied the effectiveness of new remedies. During the depression in Cleveland and Cincinnati the disease was prevalent, constituting one or two percent of the admissions to the medical services. The figure doubled if readmissions were counted. Despite emphasis on early signs of deficiency, the 1949 study disclosed a spectacular

decrease in the frequency beginning between 1939 and 1940. In 1939, 44 pellagrins were admitted to the Cincinnati General Hospital. In 1940 there were three, and by 1946–1947 none. Changes in the vitamin content of white flour began in 1942, two years after pellagra experienced its sharp decline. Vitamin tablets were not used by the Cincinnati patients. The improvement of the economy with retooling for World War II must have improved the diet of many persons who during the depression rarely had food adequate in quality or quantity.

The Birmingham Scene

The social milieu of Birmingham, its southern culture and graces, made it a pleasant place to work. The many visitors to the Spies clinic were entertained as guests at the Mountainbrook Country Club—not only scientists and nutritionists but also publicists, those in pharmaceutical and manufacturing firms, and a number of private persons who were generous and sometimes lavish contributors to the work of Tom Spies and the nutrition clinic. It was my good fortune to more or less fall into the responsibility of looking out for visitors, meeting them at trains and planes and otherwise spending time with them. In this way I had the uncommon and pleasant experience of getting to know Paul DeKruif (26), John Steinbeck, and others who spent weeks or months there gathering information. De Kruif, the gifted author of *Hunger Fighters,* wrote many popular articles about the colorful Dr. Spies and his nutrition clinic. (I do not think Steinbeck ever used his experience in a book.) Joseph Goldberger's widow, who belonged to a prominent New Orleans family, was a charming guest enormously interested in anything having to do with pellagra, nutrition in the South and, naturally, her husband. From the back numbers of the *Southern Medical Journal* I compiled into one volume all the pellagra articles by Goldberger I could find; this volume, supplemented with his papers in the US Public Health Reports, made a nearly complete file of Goldberger's published studies. Mrs. Goldberger was astonished that we knew so much about her husband, that our admiration of him was so great, and that his contributions had been every bit as valuable as she believed. Despite a steady inflow of bourbon whiskey, DeKruif was a vivid and entertaining conversationalist; and once one had penetrated the protective cover of the very shy Steinbeck, whose face was disfigured with acne scars, he, too, was delightful, perceptive, and extremely warm and gentle as well as profoundly intelligent. Just as knowing history gives us a clearer view of reality, so knowing individuals gives us special insights into their creative works and achievements.

In the spring of 1940, Tom Spies told me that I was to present a paper at the New York meeting of the American Medical Association (AMA) and discuss a hundred patients with diarrheal diseases who had developed pella-

gra (4). I had been in the clinic only a couple of months and could not find any satisfactory records. It was clear to me that we needed to devise accurate, quantitative clinic records and that I would have to find some way of straightening out the strange fascination with round numbers that seemed to exist in the clinic. The only records available had been those kept by the excellent nurses and social workers in the clinic, so I designed a record that became the standard nutritional form in the clinic and is displayed in Spies's paper in the 1943 handbook (38).

I was interested in a variety of clinical observations by that time on fingernails, skin mottling, the triple response, and vascular spiders. These, therefore, were included on the form. The nutrition clinic in Birmingham was the focus of such enormous interest that visitors from all over the country, indeed from many parts of the world, were coming and going. Each was given a copy of the nutrition form, and I became inadvertently responsible for a rather casual assumption that anything found in a pellagra clinic must have something to do with pellagra. Some of the visitors even wrote learned articles about vascular spiders and such things as signs of pellagra. It took a long time to get this heresy removed.

Urinary Pigments in Pellagra

One of the interesting misinterpretations of the early studies was in the Beckh, Ellinger & Spies (BES) tests for pigments in the urine of pellagrins (25). In Spies's article, "The Principles of Diet and the Treatment of Disease" in the 1943 American Medical Association Handbook of Nutrition, he stated that the BES Test for porphyrins in the urine was of "considerable clinical use in detecting small quantities of abnormal pigments" in persons with subclinical and clinical deficiency states. While it is perfectly true that the BES Test will be positive in people who excrete much corproporphyrins and other porphyrins, Cecil Watson and his colleagues (69) in Minneapolis demonstrated that in most malnourished persons the main pigment was indole acetic acid or its chromogen, again a tryptophane-related compound.

In 1940 I presented a paper on the subject before the American Society for Clinical Investigation, but by this time it was recognized that the test was not in any sense diagnostic of porphyrin. My paper may have increased interest in the matter, since I discussed the notion of photosensitivity and pellagrous dermatitis. At this time it was not clear that exposure to sunlight was unnecessary to the production of the pellagraderm.

Adenylic Acid

Many studies were done with adenylic acid from yeast and muscle in malnourished patients (55). We reported improvement of ulcers in the mouths of several patients following daily intravenous administration of 50

mg of adenylic acid. Because the adenylic acid produced disagreeable symptoms we did not recommend its use clinically. Such lesions generally healed promptly in pellagrins after administration of nicotinic acid and an improved diet. Often ulcers were swarming with Vincent's organisms and this condition also cleared up. Neither diet nor adenylic acid administration was effective in treating the ordinary aphthous ulcer or canker sore, a lesion that produces discomfort out of proportion to its usual small size.

Roentgen Sickness

In 1944 Bean, Spies & R. W. Vilter (9) published a series of studies on irradiation sickness—the nausea, vomiting, headache, cramps, diarrhea, and general feeling of illness that may follow therapeutic irradiation. We found that persons on a diet very poor in B-complex vitamins developed Roentgen sickness that could be prevented or ameliorated by giving supplements of nicotinic acid or thiamin a few days before irradiation. Well-fed persons had no untoward reaction to 400 roentgen units administered from a distance of 27 cm.

Glossitis

In the effort to compare the speed with which various compounds, diets, or procedures brought about the healing of glossitis, Vance and I published a table in the *Journal of Clinical Nutrition* in 1953 (18) indicating the rapidity with which glossitis underwent characteristic improvement (Table 1).

Ration Testing For Military Use

My introduction to ration testing in the Army in 1942 was to follow Ancel Keys in the California desert and study the acceptibility of the K-ration. He had written a favorable report. We found that one could track a light tank batallion on maneuvers by following a trail of discarded K-rations. In

Table 1 Speed with which various compounds, diets, or procedures bring about the healing of glossitis

Agent	Time for effect
Cozymase	few minutes to several hours
Nicotinic acid	few hours to days
Tryptophane	few hours to days
ACTH + diet	one to three days
Rest in bed	one to three days
Crude liver extract	one to five days
Yeast	three to fifteen days
Diet alone	three to thirty days

the winter of 1942–1943 it became obvious to everyone that the US battle rations were not good. In North Africa our military debut was anything but a success. In order to get into each day's ration and preferably each item a proportion of the daily vitamin requirement while staying within the space and weight allowances it was necessary to make the ration biscuits with yeast, liver extract, and soybean flour. They had a very high satiety value, soon became rancid, and thus were not eaten. Then serious difficulties arose. The Surgeon General ordered me to write a critique of Army Emergency Rations. I emphasized two disregarded facts (7): (*a*) A ration is no good if it is not eaten. All the vitamin king's horses and all the procuring king's men cannot feed an Army if the soldier will not eat the food provided. Soldiers are people and eat things they are familiar with. (*b*) Variety encourages eating. I emphasized that a ration had to be palatable; it must "fill the belly," and be usable in extremes of heat and cold. The fare should consist of common foods, bland and not heavily seasoned. I was directed to design a ration and, using a thousand soldiers, test it against the various rations already procured (11). I obtained from the large food stores a list of the 20 most popular meal items purchased by the American housewife. From the list I selected foods that could be procured readily and developed a ration in which there was no repetition of major item for nine meals. Such meals as chicken stew and ham with lima beans were most popular.

I was then put in charge of a ration test in the Pike National Forest. Our subjects were the 201st Infantry Regiment, whose officers had seen combat in a 20-month stay in the Aleutians and were serious about discipline and training. Expert consultants included John B. Youmans, Virgil P. Sydenstricker, Frederick J. Stare, W. Henry Sebrell, Julian Ruffin, R. H. Kampmire, W. F. Freedman, and M. Corlette. We organized a complicated experiment involving 10 physical fitness tests, 30 biochemical tests, and a complete nutritional examination, recording 200 items on every soldier. By means of a questionnaire each ration item was rated at each meal. The regiment's six companies, separated from each other so there was no opportunity to exchange food, underwent a rigorous training program. Daily records of ration evaluation, biochemical tests, the fitness scores and evaluations by the officers were transferred to IBM cards and sent to the Corps Area Headquarters in Omaha, Nebraska, from which we got reports twice a week. We compared rations as issued, one ration per day of varying calorie content (some being 20% greater than others), with rations issued so that each man received the same number of calories per day. Rapid data processing enabled us to complete a book nearly 250 pages long for distribution 3 months after the test. We found no vitamin deficiencies. The sun and the semiarid weather chaffed the soldiers' lips, and trauma to their gums from chewing K-ration biscuits at first caused concern. The biochemical tests

revealed no abnormalities; physical fitness improved; muscle mass increased. The thin soldiers gained weight, those of average weight added muscle and lost fat, and the heavy ones lost a great deal more fat than they gained in muscle mass. Every tenth soldier, the total coming to about 100, was examined independently on four occasions by at least three different clinicians. After careful instructions and agreement on the criteria for diagnosis, we published a detailed account of the subjective factors in these clinical examinations in nutrition which had accounted for some of the polemics of the past. These are important in all clinical judgments. Since then, diagnostic variability has been demonstrated in measurement of blood pressure, interpretation of X-rays, and numerous other clinical matters. Extremes present no problem of observer differences, but borderline manifestations—potentially so important in finding trouble early—are difficult. On our Army ration evaluation team, each observer had a pattern of diagnostic habits. The less experienced tended to overdiagnose and the more experienced found no significant lesions.

The surprising outcome of this study was that military authorities in Washington procured the new and improved C-ration, shipped millions of dollars worth to the Pacific, and sent me with three colleagues to test various old and new rations in ten different places in the Pacific, including observations made on Iwo Jima and Luzon on soldiers immediately out of combat (12–14). The most spectacular results we saw were in the 38th Infantry Division in Luzon, who had been fighting the Japanese for four and a half months, subsisting on the improved C-ration. The soldiers, though low on praise, were still eating the food. They had the best physical fitness record of any group we tested and exhibited no clinical or biochemical abnormalities.

The rations had been designed without much sophisticated metabolic theory but with practical common sense. Here was a unique example of the recognition of a clinical Army problem, a diagnosis, a proposal for change in the form of preventive therapy, a test under conditions of training but not combat, a procurement of the ration, and a final study right out of combat. The food did indeed work in the circumstances for which it was designed.

The development of large-scale rations tests and the improvement of Army emergency rations were a natural outgrowth of the work I had done in the field of nutrition in association with Spies, the Vilters, and many others. Several important lessons came from these studies. The most important, but little recognized, was that the acceptability of a ration is essential for its use. It is better to have an imperfect ration that is eaten than a theoretically perfect one that is not eaten or is eaten only in unbalanced fractions.

Tropical Nutrition

Our ration study group (R. E. Johnson, C. R. Henderson, L. M. Richardson, and myself) in the US Army and that of R. M. Kark and associates in the Canadian Army used identical reagents and methods to demonstrate that there was no form of deterioration peculiar to the tropics (33). Isolation, boredom, homesickness, and abuse of alcohol were just as prevalent in various parts of the United States as they were in tropical regions. Such deterioration as occurred was not related to any peculiar tropical requirement for food or supplements.

The Canadian study of Kark and associates in Southeast Asia demonstrated that animal protein, riboflavin, and ascorbic acid levels were definitely lower in East Indian natives and Japanese prisoners than in US troops. Racial and religious dietary preferences resulted in lower values for hemoglobin, serum proteins, serum and urine ascorbic acid, and urinary riboflavin in Indian soldiers than in Americans; but interestingly enough, no classical disease of nutritional deficiency was found. Japanese prisoners were seriously malnourished, and many had vitamin deficiency diseases. A regiment of Gurkhas with the highest fitness record and almost no physical signs of deterioation or malfunction had much lower values of serum protein and urinary riboflavin than US troops. Food habits, customs, and adaptation must explain this.

Establishment of a Metabolism Unit in Iowa

After extensive clinical research on nutrition and human work and climate physiology in World War II, I established a metabolism unit at Iowa City, where P. C. Jeans had done such splendid work in pediatric nutrition. Kate Daum's section dealt with the biochemistry of nutrition, to which was added my own interest in B-complex vitamin deficiencies and the use of vitamin antagonists (16–22, 24, 35, 63). We published extensively on pantothenic acid deficiency and later on combinations of pantothenic and pyridoxine deficiency. We were trying hard to see whether vitamin antagonists would produce vitamin deficiencies that might be important in reducing antigen-antibody reactions and, thus, play a useful role in organ transplant. We did, indeed, find that many antibody reactions were diminished or prevented by the combination of pantothenic acid and pyridoxine deficiency. The catch was that this deficiency also prevented normal wound healing, perhaps partly owing to local infections. Thus the idea had to be discarded because of interfering complications.

Moral and Ethical Problems in Human Experimentation

I discussed Walter Reed and human experiments in the Garrison Lecture (24). Nearly thirty years before that I had presented my concern with moral

responsibilities in clinical research in the Presidential Address of the Central Society for Clinical Research in November, 1951 (17a). This has recently been updated in the December 1981 issue of the *Journal of Laboratory and Clinical Medicine* (17b). Though I saw no examples of disregard for the patients' safety and well-being in studies in Birmingham or Cincinnati, this owed more to the backgrounds and training of those involved than to any formal evaluation or obtaining of written consent. During World War II we had done all manner of experiments on physical fitness, adaptation to extremes of heat and cold, and water and salt requirements; we had done extensive ration tests involving a great variety of clinical, biochemical, and performance evaluations without formally obtaining consent, though the procedures had been explained to the subjects in detail. Though an occasional soldier departed without leave, in general the morale was splendid and the rate of AWOL was much smaller in our experimental subjects than in the units from which they were drawn. We agreed with the English investigator, L. J. Witts, who believed that if one does any investigation on oneself first then it is permissible to do it on others after genuine efforts to explain it to the subjects and after obtaining informed consent. No set of formal and codified rules or laws will be satisfactory in all cases, particularly if the experimenters do not have high ethical standards.

Despite the fact that we tested on ourselves the drugs we used and the compounds that had been effective in animal experiments, we made no systematic efforts to get what we now call informed consent, nor was there any document for the patients to sign. The only signed releases I saw were those that physicians and patients signed for photographs or moving pictures for education and promotion. The subject usually was paid, as token payment, a dollar and signed without any question. There was exhibited a further very important, but scarcely studied influence of faith and belief at the nutrition clinic in Birmingham, Alabama, where the famous Dr. Spies had created an effect resembling, but by no means as evident as that at Lourdes. This similarly exists in some centers today, centers of legitimate as well as pseudoscientific nutrition fame.

From the moral and ethical point of view, the fact that we had tested new compounds or diets on ourselves, orally or by injection, made us feel, in those informal days of confidence and trust, that we had done what was required to safeguard our subjects. I believe that most if not all of our studies would have been approved by the array of committees set up today to monitor moral and ethical guides in experiments on volunteers. I am unaware of any harm that resulted from our studies. A great deal of good resulted.

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