Pagophagia and Iron Lack

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Iron lack was associated with an unusual perversion of appetite characterized by the ingestion of extraordinary amounts of ice. Pagophagia is defined as the purposeful ingestion of at least one ordinary tray of ice daily for a period in excess of two months. The symptom appears to be related to iron lack and is completely resolved with amounts of iron less than those required for resolution of the anemia or replenishment of iron stores. The data on the rates of repair of mucosal cytochrome and blood-cell hemoglobin coincide with the temporal relationship between the resolution of pagophagia and the correction of iron-lack anemia.

The association of a wide variety of perversions of appetite, so-called pica, with various states of malnutrition has been known since ancient times. Cooper,[1] in her monumental review on pica, observes that Aetius, Royal Physician to Justinian I during the sixth century AD, presented the first documented description of pica in association with pregnancy.[2] Avicenna, "Prince of Physicians" during the tenth century AD, noted that pica was wonderfully benefited by "iron steeped in fine wine and strained through Hippocrates' sleeve."[3] Certainly, this must be the initial observation of the use of iron for a perverted appetite. Mason,[4] in describing the most appropriate treatment for dirt-eating encountered in the Jamaicans in 1863, discussed the use of a "bitter laxative . . . in a pint of which 8 or 10 grains of sulphate of iron is dissolved." Such perversions of appetite range from the edible to the inedible and, as described in the report of Cragin,[5] may border on cannibalism.

It is the purpose of this communication to describe an unusual perversion of appetite, characterized by a pathologic craving for ice in patients with iron lack. During the past two years more than 25 such patients have been evaluated at Wilford Hall US Air Force Hospital, and in each instance the patient has had an associated, clearly documented iron lack. Pagophagia, after the Greek *pagos* for frost or ice, and *phagein*, to eat, is here arbitrarily defined as the purposeful ingestion of at least one ordinary tray of ice daily over a period in excess of two months. Pagophagia appears to be invariably associated with iron lack, and in each instance was completely resolved by treatment with amounts of iron insufficient to correct the patient's anemia or deficient iron stores.

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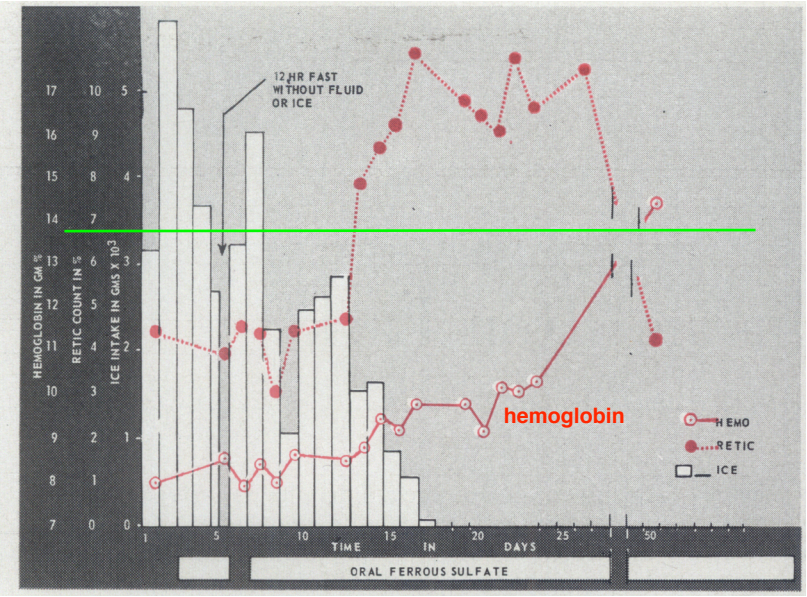
Materials and Methods

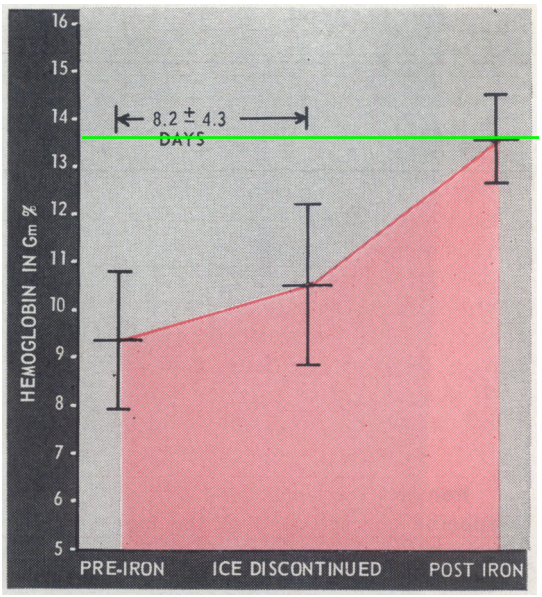
This communication concerns 25 patients, all but one of whom were studied as outpatients. Standard hematologic studies were performed. One patient was studied in the Metabolic Unit, during which time she had unlimited access to precisely measured volumes of ice, both day and night. The 25 patients studied were all women and, except for two with prior subtotal gastrectomies and one pregnant patient, all had severe hypermenorrhea as the etiological factor of their iron lack. Nineteen patients were carefully observed to the point when the pagophagia discontinued, and 13 to the optimum hematologic response.

For editorial comment, see page 552.

Seven patients were part of a single-blind study, measuring the influence of one dose of parenterally given iron on their ice consumption. The study covered three consecutive weekly periods, during which time the patients were seen in the Hematology Clinic once a week. They meticulously measured their daily consumption of ice in trays of ice, to the nearest cube, throughout the study. The total consumption of ice was calculated by measurement of the volume and number of cubes in a representative ice tray from each of the patients' freezers. The average ice tray contains 710 gm of ice. After one week (control) and again one week later, the patients were given a deep intramuscular injection. In each instance the initial injection was 5 cc of saline and the second was 5 cc of iron dextran injection. Each patient was apprised of the contents of the injections but was not apprised of their se-



1. Hospitalization graph of 35-year-old white woman (case 5). Open rectangle below days 3 through 5 represents histidine load.



2. Mean and one standard deviation of hemoglobin values prior to treatment with iron, within seven days of discontinuance of ice and at point of optimum response.

quence or the anticipated influence on their pagophagia. Complete blood cell counts, including red blood cell counts and reticulocyte counts, serum iron level, and total iron binding capacity were determined on each visit. Following the third week, oral iron therapy was started and patients were observed until they had achieved a maximum hemoglobin response.

Report of a Case

A 35-year-old white woman had a three-month history of ingesting six to eight trays of ice daily. The ice trays contained 710 gm of ice and her estimated daily intake was 5,680 gm. She recalled that during her first pregnancy, 17 years previously, she had had an unusual craving for ice for which she insisted that her husband arise regularly at 2 AM to crush ice for her. Similar problems arose with three subsequent pregnancies and cleared promptly with delivery. Three months prior to being seen, she became pregnant again with recurrence of pagophagia. The pregnancy terminated in two months with an incomplete abortion followed by dilatation and curettage; but in contrast to previous parturition, her craving for ice did not decrease, but rather increased. When seen initially, she had 8 gm of hemoglobin with clear-cut iron-lack anemia. A comprehensive laboratory evaluation failed to reveal other significant abberations. She was admitted to the Metabolic Unit for study. Her 24-hour ad libitum ice intake was scrupulously documented, and Fig 1 shows her ice consumption in grams $\times 10^3$ plotted on the bar graph. Her maximum 24-hour ice consumption was 5,800 gm. During the six-day control period she ingested an average of 3,884 gm of ice daily. On day 5, as indicated by the arrow, she had a 12-hour fast from ice and food, following which osmolar clearance studies indicated intact posterior pituitary function. The open rectangle below days 2 to 5 indicates a three-day histidine load which resulted in normal results for a formiminoglutamic acid test. Oral iron therapy was begun on the sixth day and reticulocytosis reached its maximum ten days later. On the 18th day of the study, 11 days following the start of therapy, at which time the patient's hemoglobin level was 9.6 gm/100 cc she refused all ice. On the 50th day of study all values had returned to normal.

Results

Hypochromia and microcythemia were seen in all 25 patients (Table). The mean hemoglobin value was 9.36 gm per 100 cc ± 1.45. The mean hematocrit value was 33.04% ±4.35. The serum iron level averaged 28.8 μg/100 cc ± 13.3 and the mean saturation of the total iron binding capacity was 7.3%. Bone-marrow iron was absent in eight of eight patients so studied. Thirteen patients were observed to maximum hematologic response and all eventually had an optimal response to iron therapy alone. The mean maximum daily ice consumption for the 25 patients was 2,445.2 gm/24 hr ± 1,948.1 with a range from 550 to 5,800 gm. The minimum mean duration of consumption was 26.8 months with a range from two months to 18 years.

The period of time between the onset of therapy with iron and the discontinuance of all ice was documented in 19 of the 25 patients studied. The range was from 1 to 14 days with a mean of 8.2. Eight of the patients received iron orally and 11 received it parenterally. The average lag between the initiation of treatment and the refusal of all ice was 11.6 days ± 2.2 for those receiving iron orally and 5.7 ± 3.7 for those receiving iron parenterally. The difference between these two means is significant at the 0.01 level.

The mean and one standard deviation of hemoglobin prior to iron treatment, at a point within a week of the time of discontinuance of ice, and at the point of optimum response to iron therapy is plotted on Fig 2. There is no quantitative relationship between the degree of anemia or the level of serum iron and the volume of pagophagia.

The mean and one standard deviation of the daily ice consumption of the seven patients during the three weeks of the single-blind study are shown

in Fig 3. The mean ice consumption of each subject during the last three days of each period was used in the calculation of the mean and standard error of ice consumption for the group during each period. A statistical analysis of the difference between mean ice consumption during the control periods and those during which iron was administered revealed the difference to be significant with $P < 0.01$.

In six of the seven instances in which the patient received iron parenterally, the intake of ice was zero at the end of one week, having decreased to zero in one day in one patient, within two days in another, within four days in three patients, and within six days in one patient. In one patient there was no significant influence on the pagophagia as a result of one dose of iron parenterally but it did fall to zero at 14 days.

Comment

Although there has been mention of the use of iron in various forms as therapy for pica throughout recorded medical writings,[1-4] the exact relationship between the two has not been made clear. Certainly most authors have been more impressed with the relationship of malnutrition to pica than with the more specific association with iron lack or iron-lack anemia.[1] On the other hand, the analysis of the etiological characteristics of pica has led some to conclude that "dirt eating is simply a cultural trait like dipping snuff or smoking."[6] The widespread pica that occurs in animals may be difficult to attribute to cultural traits, but it appears to be no better understood than the human counterpart.[7]

The first definitive study undertaken to define the pica-iron relationship was the work of Lanzkowsky.[8] He showed that South African children with severe pica had severe anemia and that he was able to permanently resolve the pica with parenteral administration of iron. Gutelius et al[9] later showed, in a double-blind study, that iron and saline were equally effective in treating pica. Beron and Valero[10] and, more recently, McDonald and Marshall[11] have presented data which confirm the cure of pica in iron-lack anemic children with use of iron therapy. Recently Okcuoglu et al[12] studied Turkish villagers with pica and found that 60.4% of the group with pica, but only 17% of the control group, were anemic. There was, in addition, a broad overlap in the population, so that pica occurred in patients who were not anemic. As he was studying the relationship of pica to anemia, the absence of a clear-cut correlation resulted in his invoking such etiologic mechanisms as custom and habit. Certainly the absence of anemia does not rule out iron lack.

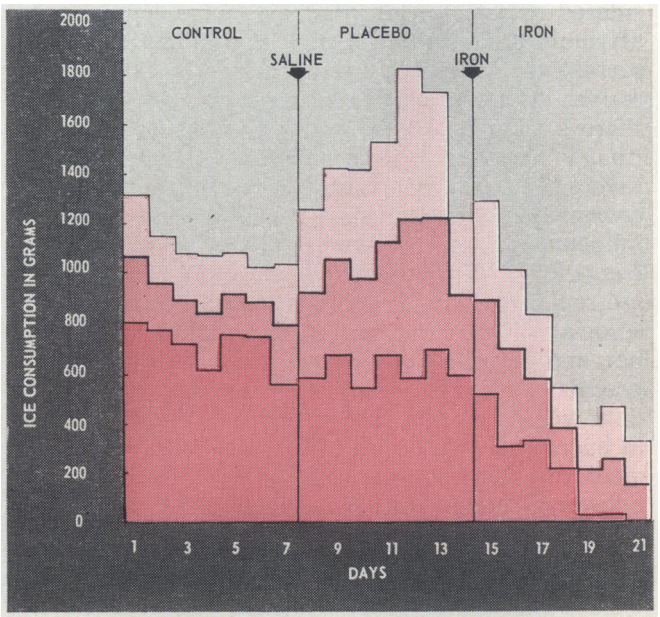
The association of severe iron-lack anemia and hypokalemia in association with the ingestion of large amounts of white clay (geophagia) was studied by Mengel et al.[13] The authors attributed the hypokalemia as well as the iron-lack anemia to chelation of both dietary potassium and iron. They further observed that the geophagia diminished with iron treatment, but contended that the iron-lack anemia was *due to* the geophagia. Blum et al[14] similarly related the anemia of habitual starch eat-

Results of Studies Prior to Iron Therapy

Patient	Maximum Daily Ice Intake (Gm)	Duration of Ice Intake (Mo)	Hemoglobin (Gm/100 cc)	Serum Iron (μg/100 cc)	Total Iron Binding Capacity (μg/100 cc)	Marrow* Iron
1	700	2	9.1	8	288	ABS
2	1,750	7	11.2	14	355	...
3	3,050	3	7.4	31	329	...
4	2,200	6	6.7	9	346	...
5	4,500	12	8.0	59	373	ABS
6	1,000	30	8.5	31	440	...
7	3,000	12	8.8	33	QNS†	ABS
8	3,500	174	10.4	36	408	...
9	9,600	"All life"	9.9	56	420	ABS
10	3,600	48	9.5	22	600	...
11	4,410	24	11.8	20	445	...
12‡	710	24	10.5	36	564	...
13‡	2,840	24	10.2	40	576	...
14‡	710	6	13.2	44	372	...
15‡	2,800	120	10.3	30	384	ABS
16‡	1,600	216	7.6	20	435	...
17	3,000	"Since childhood"	9.4	32	360	...
18‡	710	12	8.0	49	504	ABS
19‡	550	2	7.8	20	480	...
20	800	12	9.0	19	450	...
21	2,800	12	9.8	21	576	...
22	2,000	"Years"	9.9	25	447	...
23	1,000	3	8.8	19	489	ABS
24	720	24	9.0	29	450	...
25	3,500	"Years"	9.4	18	512	ABS
Mean	2,445.2	36.8	9.36	28.8	441.8	...
Standard Deviation	1,948.1	58.9	1.45	13.3	84.1	...
No.	25	21	25	25	24	...

*ABS indicates bone-marrow iron absent.
†QNS indicates quantity not sufficient.
‡Included in single-blind study.

3. Mean and one standard deviation of the daily ice consumption of seven patients during 21 days of the single-blind study.



ers to a 50% reduction in iron absorption as a result of the starch. On the basis of the calculations of Harris[15] one would find it somewhat difficult to attribute the severe iron lack, as seen in these patients, solely to a 50% reduction in dietary iron absorption.

It would be difficult to dissociate completely pica and iron-lack anemia on the basis of the literature to date. The major question relates to whether the iron-lack anemia causes the pica, as suggested by the data of Lanzkowsky,[8] Beron and Valero,[10] and McDonald and Marshall,[11] or that pica causes the iron-lack anemia as suggested by Mengel et al[13] and Blum et al.[14]

There are several features of the association of pagophagia and iron lack, as seen in this study, which are of particular interest. All of the patients had iron lack but not all would be considered to have anemia according to most standards, including those of Okcuoglu et al.[12] The period of time between the initiation of therapy and the refusal of ice is surprisingly brief. It appears to be shorter with parenteral than with oral iron therapy. In the single-blind study, a 500-mg dose of iron dextran injection was given parenterally. All but one patient completely stopped the pagophagia within a week. Pagophagia is clearly resolved with astonishingly small doses of iron and, in each instance, a dose less than that required to correct either the iron-lack anemia or the iron stores. The female population of this study reflects the relative incidence of iron lack in our population. We have seen pagophagia in both men and in children.

On the basis of these data, it would seem that iron-lack anemia did not cause the pagophagia, since *not all* patients were anemic and the problem was resolved with doses of iron insufficient to restore iron balance. It is further difficult to believe that the pagophagia caused the iron-lack anemia because of the relatively benign nature of frozen water. Even if decreased absorption could be considered as a significant etiologic factor, it is hard to attribute impaired absorption to swallowed ice. Ice certainly reaches body temperature by the time it arrives at the stomach and contains no more adulterants than does the local water per se. Because iron, in very small doses, reverses the pagophagia before there is a real change in the hemoglobin, it is conceivable that the pagophagia is related to the influence of iron on some compound other than hemoglobin. Various heme-containing compounds are replaced at rates divergent from hemoglobin in association with iron repletion. Catalase,[16] myoglobin, and cytochrome C[17] are examples of such compounds studied in relation to iron lack. Jacobs'[18] data would indicate that cytochrome oxidase levels in buccal mucosa began to increase within one day after the initiation of iron therapy. Dallman and Schwartz[17] found that the cytochrome C of intestinal mucosa in rats with iron deficiency returned to control levels within two days, as compared to the eight days required to correct the rat's anemia.

Although there are no data to support the relationship of pagophagia to mucosal cytochrome, the temporal relationship of the resolution of pagophagia and anemia in the human parallels the studies in the rat.

In summary, it would seem that there may be a variety of etiologic mechanisms participating in the pica of various types. Cultural influences are undoubtedly real.[6,9,12] Aggravation of iron lack by malabsorption could play some role in the problem.[13,14] Certainly the ingestion of toxic substances would make a major contribution to the anemia. It would appear, however, that in the relatively pure form of pica, known as pagophagia, the mechanism is related to iron lack and not specifically to iron-lack anemia. In addition, pagophagia neither results from nor causes iron-lack anemia.

The term *pagophagia* was conceived by David J. Kudzma, MD, "a local Greek scholar."

Generic and Trade Names of Drug

Iron dextran injection—*Imferon.*

References

1. Cooper, M.: *Pica: A Survey of the Historical Literature as Well as Reports From the Fields of Veterinary Medicine and Anthropology: The Present Study of Pica in Young Children and a Discussion of Its Pediatric and Psychological Implications*, Springfield, Ill: Charles C Thomas, Publisher, 1957.

2. Aetius-Aetios of Amida, cited by Cooper.[1]

3. Avicenna, cited by Cooper.[1]

4. Mason, D.: On Atrophia A Ventriculo (Mal d'Estomac) or Dirt Eating, *Edinburgh Med Surg J*, April 1833, pp 289-296.

5. Cragin, F.W.: Observations on Cachexia Africana or Dirt Eating, *Amer J Med Sci* **17**:356-369 (No. 8) 1835.

6. Dickins, D., and Ford, R.N.: Geophagy (Dirt Eating) Among Mississippi Negro School Children, *Amer Soc Rev* **7**:59-65 (Feb) 1942.

7. French, M.H.: Geophagia in Animals, *E Afr Med J* **22**:152-163 (April) 1945.

8. Lanzkowsky, P.: Investigation Into the Aetiology and Treatment of Pica, *Arch Dis Child* **34**:140-148 (April) 1959.

9. Gutelius, M.F., et al: Nutritional Studies of Children With Pica: II. Treatment of Pica With Iron Given Intramuscularly, *Pediatrics* **29**:1018-1023 (June) 1962.

10. Beron, R., and Valero, A.: Pica and Hypochromic Anemia: A Survey of 14 Cases Seen in Israel, *Harefuah* **61**:35-39 (July 16) 1961.

11. McDonald, R., and Marshall, S.R.: The Value of Iron Therapy in Pica, *Pediatrics* **34**:558-562 (Oct) 1964.

12. Okcuoglu, A., et al: Pica in Turkey: I. The Incidence and Association With Anemia, *Amer J Clin Nutr* **19**:125-131 (Aug) 1966.

13. Mengel, C.E.; Carter, W.A.; and Horton, E.S.: Geophagia With Iron Deficiency and Hypokalemia: Cachexia Africiana, *Arch Intern Med* **114**:470-474 (Oct) 1964.

14. Blum, M.; Orton, C.; and Rose, L.: The Effect of Starch Ingestion on Excessive Iron Association, abstracted, *Ann Intern Med* **68**:1165 (May) 1968.

15. Harris, J.W.: *Iron Lack Anemia in the Red Cell*, Cambridge, Mass: Harvard University Press, 1963, p 64.

16. Balcerzak, S.P.; Vester, J.W.; and Doyle, A.P.: Effect of Iron Deficiency and Red Cell Age on Human Erythrocyte Catalase Activity, *J Lab Clin Med* **67**:745-756 (May) 1966.

17. Dallman, P.R., and Schwartz, H.C.: Myoglobin and Cytochrome Response During Repair of Iron Deficiency in the Rat, *J Clin Invest* **44**:1631-1638 (Oct) 1965.

18. Jacobs, A.: Iron Containing Enzymes in the Buccal Epithelium, *Lancet* **2**:1331 (Dec 16) 1961.

EDITORIALS

Insulin and Proinsulin: Relations and Implications

In the late 1940's and early 1950's, Sanger demonstrated that the insulin molecule comprised two chains, A and B, linked by disulfide bridges. Two possibilities for the evolution of this kind of structure suggested themselves. The first was that the two chains were made separately in the beta cell and then united to form the final product. Subsequent investigations lent indirect support to this hypothesis. Isolated separately from crystalline insulin, the A and B chains—neither having biologic activity by itself—were made to reunite, with resulting return of activity.[1] Similarly, the joining of separate A and B chains in the in vitro synthesis of insulin also resulted in a compound with measurable hypoglycemic properties which neither chain alone possessed.[2] Perhaps, then, this was the way the beta cell made insulin.

The second possibility, not necessarily excluding the first, was that the insulin molecule was a derivative of a larger precursor molecule which itself might or might not have biologic activity. Such a large molecule, termed "proinsulin," has recently been isolated and characterized at the University of Chicago.[3] It was found originally in a human islet cell adenoma and now has been detected in normal pancreas, in normal blood and urine, and in the plasma of an adult-onset diabetic patient. It has a molecular weight of 8,000 to 10,000 compared to insulin's 6,000, and it yields true insulin on tryptic digestion in vitro. Its biologic activity is very low. Most importantly, it cross-reacts with true insulin in the immunoassay for insulin, so that when one measures plasma insulin by this widely used method one may be also measuring unknown amounts of the relatively inactive proinsulin. This disturbing situation throws into doubt the interpretation of all previous immunoassay studies of "insulin" secretion and plasma concentrations in normal as well as pathologic conditions such as diabetes, prediabetes, starvation, obesity, and various endocrine disorders.

Of special physiologic interest are the changes in plasma levels of proinsulin (or a closely related substance) observed in two normal subjects following ingestion of glucose. Proinsulin appeared in the circulation in only small concentrations at the 15-minute interval but came to constitute from one third to one half of the total "insulin" at the one- to two-hour period. Similar results were obtained in the single diabetic patient studied.[4]

Several speculative questions come to mind. Will further investigation show that adult-onset diabetic patients and obese subjects secrete a larger proportion of the feebly acting proinsulin in response to glucose than do normal subjects? If so, would it account for the puzzling paradox of their late secretion of normal or greater amounts of "insulin" as currently measured? In the prediabetic state, is the beta cell deficient (perhaps genetically) in the enzyme that breaks down proinsulin to insulin? If so, would the secretion of proinsulin in partial replacement of the full complement of true insulin force the beta cell to overproduce both and thus lead eventually to its exhaustion?

Answers to these questions and others may come when the presently complicated methods (gel filtration, fractional column chromatography, and electrophoresis) for separately measuring proinsulin and true insulin have been simplified for more general use.

1. Dixon, G.H., and Wardlaw, A.C.: Regeneration of Insulin Activity From the Separated and Inactive A and B Chains, *Nature* **188**:721-724 (Nov 26) 1960.

2. Katsoyannis, P.G., et al: Insulin Peptides. X. The Synthesis of the B-chain of Insulin and Its Combination With Natural or Synthetic A-chain to Generate Insulin Activity, *J Amer Chem Soc* **86**:930-932 (March 5) 1964.

3. Steiner, D.F., and Oyer, P.E.: The Biosynthesis of Insulin and a Probable Precursor of Insulin by a Human Islet Cell Adenoma, *Proc Nat Acad Sci USA* **57**:473-480 (Feb) 1967.

4. Roth, J.; Gorden, P.; and Pastan, I.: Big Insulin: A New Component of Plasma Insulin Detected by Immunoassay, *Proc Nat Acad Sci USA* **61**: 138-145 (Sept) 1968.

Pica and Iron Deficiency

When the poet lamented that there was "nothing to eat but food," he was obviously unaware of pica. Yet habitual eating of ordinarily indigestible, nonnutritious substances is as old as man. Lying in his sarcophagus with grass in his esophagus, King Nebuchadnezzar who "did eat grass as oxen" (Daniel 4:33) presents a notable biblical example. Dirt eating and other appetite aberrations have been recorded by Aetius (sixth century AD) and Avicenna (tenth century AD) and by a number of observers during the 19th and 20th centuries.

Substances comprising the pica collection are numerous and varied, but two—earth and ice—are of special medical interest because their ingestion is often associated with anemia. In both appetite perversions the anemia is that of iron deficiency characterized by hypochromia, microcytosis, and sideropenia. The two conditions, however, present differences in geographic distribution and ethnic background. And, according to some authorities, they may also differ in the nature of their association with iron deficiency.

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In this country, pagophagia (*pagos* = ice) is probably the commonest form of pica associated with anemia. Reynolds et al[1] studied 38 consecutive patients (28 women, nine men) with iron-deficiency anemia who were referred for investigation to a hematology clinic at Travis Air Force Base in California. Twenty-three of the patients admitted daily ingestion of two or more glasses of ice during the current and the previously diagnosed periods of anemia. Their anemia could readily be explained by overt or occult blood loss, and they were rid of the abnormal craving for ice after a short period of iron therapy. Thus, pagophagia could hardly have caused the anemia. Both conditions may possibly have been interrelated by such factors as tissue-enzyme deficiency.

In this issue (p 513), Coltman provides further support for this concept. He studied 25 women with pagophagia at Wilford Hall US Air Force Hospital. Not all were anemic, but every patient manifested iron deficiency which was accounted for by blood loss. Iron administration in doses insufficient to correct the anemia or to replenish body stores promptly eliminated all craving for ice. Coltman concludes that the relationship between pagophagia and anemia cannot be explained in simple terms of cause and effect relationship. Heme-containing enzymes, such as buccal cytochrome oxidases, which are affected by iron deficiency and are promptly replenished by iron, may provide a linking mechanism.

As distinct from ingestion of ice, that of earth or clay has a well-defined ethnic and geographic background. Geophagia has been reported among female villagers in Turkey; in the United States in some Southern states, mainly among Negro women in the low-income group; and in South Africa. Some authorities have attributed the anemia to dietary lack engendered by an appetite-curbing clay-filled stomach. Others have ascribed it to intestinal parasites. Mengel et al[2] have traced it to interference with iron absorption by the ingested clay—a concept which receives some support from recently conducted radioactive-iron-absorption studies.[3]

Though impressive, the evidence for different mechanisms in the anemias of pagophagia and geophagia is inconclusive. Reported cure of the latter by orally administered iron[4] tends to minimize the difference. Indeed, anyone venturing dogmatic assertions on this subject may end up eating his words (logophagia), or—if he is a betting man—his hat.

1. Reynolds, R.D., et al: Pagophagia and Iron Deficiency Anemia, *Ann Intern Med* 69:435-440 (Sept) 1968.

2. Mengel, C.E.; Carter, W.A.; and Horton, E.S.: Geophagia With Iron Deficiency and Hypokalemia: *Cachexia Africana*, *Arch Intern Med* 114:470-474 (Oct) 1964.

3. Minnich, V., et al: Pica in Turkey: II. Effect of Clay Upon Iron Absorption,[1,2,3] *Amer J Clin Nutr* 21:78-86 (Jan) 1968.

4. McDonald, R., and Marshall, S.R.: Iron Therapy in Pica, *Pediatrics* 34:558-562 (Oct) 1964.

Thomas Cadwalader (1708-1779)

Thomas Cadwalader, second only to Benjamin Franklin as a leading citizen of Philadelphia in the 18th century, was the son of a Welshman who came to America with William Penn on his second voyage. Cadwalader attended the Friends' Public School in Philadelphia and Rev. William Tennant's academy at Bensalem, Bucks County, before being apprenticed for two years to his uncle, Dr. Evan Jones.[1] His medical training was continued in Europe; there he studied anatomy and dissection under Cheselden and may have attended courses at the University of Rheims, France, for a short time. When Cadwalader returned to Philadelphia in 1730, he brought with him his European training, but no medical degree, inasmuch as this was not a prerequisite to practice in his day. With his personal charm and a good family name, he soon rose to eminence as a leader in medicine and an outstanding citizen. He supported Kearsley, Zachary, and Bond in advocating inoculation against the smallpox and, filling a critical void in the medical training available in Philadelphia, offered a series of dissections for interested students. William Shippen, Sr. attended the demonstrations as did Cadwalader's nephew, John Jones.

Although Cadwalader seemed destined to practice and reside in Philadelphia, his marriage in 1738 to the daughter of a land owner in Trenton township, New Jersey, induced him to move to his father-in-law's estate. Although maintaining ties with Philadelphia, he did not return to Pennsylvania permanently until 1750. Meanwhile, he published one of the earliest medical treatises and a report on one of the first autopsies in America. The two contributions appeared in a volume from Benjamin Franklin's press, with the preface indicating his residence as "New-Jersey, Trenton, March 25, 1745." The original manuscript was prepared with two possible prefaces and is treasured as one of the rare documents in the Library of the College of Physicians of Philadelphia. The volume, entitled *An Essay on the West-India Dry-Gripes; with the Method of Preventing and Curing that Cruel Distemper. To which is added, an Extraordinary Case in Physick*, included three case reports and detailed procedures for management of the "iliac passion." Cadwalader's discussion of the malady, associated with drinking of rum distilled in lead utensils, gave no suggestion that the base metal was the pathogenic agent. Nevertheless, the presentation was comprehensive and described encephalopathy, peripheral paralysis, constipation, and abdominal pain —features of lead intoxication.[2]

The *European* Physicians give an Account of a Disease similar to the *Dry-Gripes*, calling it *Cholica Pictonum*, because most frequent at *Poictiers*. They are both attended with excessive griping Pains in the Pit of the Stomach and Bowels, which are much distended with Wind; violent and frequent Reachings to vomit, sometimes bringing up small Quantities of bilious Matter; at other times there is a Sensation, as if the Bowels were drawn together by Ropes; great Costiveness, and frequently a continual Inclination to go to Stool without voiding any Thing.