NUCLEAR DIGESTION AND URIC ACID EXCRETION IN A CASE OF TOTAL OCCLUSION OF THE PANCREATIC DUCT *

DANA W. ATCHLEY
BALTIMORE

The digestion of nuclear material and the production of purin bases therefrom has been discussed from three points of view: (1) the morphological destruction of the nucleus; (2) the digestion of the so-called nucleoproteids and nucleins; and (3) the splitting of nucleic acid. The localization of the third stage, namely, nucleic acid digestion, has been unquestionably settled by the demonstration of a nuclease in the erepsin of a dog (Nakayama,¹ 1904) and of its absence from the gastric and pancreatic juices (Levene and Medigreceanu,² 1911). Confirmatory evidence is afforded by the work of London and Schittenhelm³ (1910) who found no difference in the nucleic acid metabolism of a normal dog as compared with animals in which the stomach or the pancreas had been removed, or those with a ligated pancreatic duct.

The morphological destruction of the nucleus has been the subject of much controversy since the statement of Adolf Schmidt⁴ (1899) that the presence of undigested nuclei in the muscle fibers found in the feces was an evidence of decreased or absent pancreatic function. On this finding, Schmidt based a clinical test consisting of the feeding of small pellets of muscle tissue enclosed in silk bags. He recovered the tissue from the stool, sectioned, stained and examined it for nuclei. Intact nuclei were considered evidence of pancreatic achylia. Kashiwado⁵ (1911) modified this test by using thymus nuclei isolated by gastric digestion and stained with hematoxylin—these nuclei were mixed with lycopodium spores and administered in capsules. Kashiwado found in test-tube experiments that neither gastric juice (dog), extract of duodenal mucosa or duodenal juice would digest the nuclei, whereas pancreatic juice quickly accomplished this result. Strauch⁶ (1910), using muscle tissue, confirmed Kashiwado's results with the

* Submitted for publication Dec. 3, 1914.

* From the Medical Clinic of the Johns Hopkins Hospital.

1. Nakayama: *Ztschr. f. physiol. Chem.*, 1896, xli, 348.

2. Levene and Medigreceanu: *Jour. physiol. Chem.*, 1911, ix, 65.

3. London and Schittenhelm: *Ztschr. f. physiol. Chem.*, 1910, lxx, 10.

4. Schmidt: *Deutsch. med. Wchnschr.*, 1899, No. 49, p. 811.

5. Kashiwado: *Deutsch. Arch. f. klin. Med.*, 1911, civ, 584.

6. Strauch: *Deutsch. Arch. f. klin. Med.*, 1910, ci, 128.

exception that juice pressed from the intestinal wall seemed to have a slightly destructive effect on the nuclei, and Fronzig⁷ (1913), using the nuclei of frog's blood, held that his results agreed with the fundamental principle of the Schmidt test. There has, however, been a great deal of evidence pointing to an opposing view. Glaessner and Popper⁸ (1908) found that easily stainable nuclei persisted after digestion with the juice obtained from a pancreatic fistula in a girl of 17, while Hesse,⁹ as a result of test-tube experiments and of the insertion of a muscle cube into the stomach (1910), claims that gastric juice will digest nuclei. Van Westenrijk¹⁰ (1911) says that, in the dog, muscle tissue is digested *en masse* in the gastro-intestinal tract, and he holds that muscle tissue without nuclei is never to be found, no matter how the factors of digestion be varied. The clinical experience of many observers (Leech,¹¹ Pratt¹² and others) has been that the Schmidt test is in no way a dependable one, but the author of the test still (July, 1914) considers it of great value.

It was formerly held that the so-called nucleoproteid was a distinct entity, and several observers (Popoff,¹³ 1894; Milroy,¹⁴ 1896) demonstrated to their satisfaction that this hypothetical substance was not split by gastric digestion, whereas it was by pancreatic. Even in the 1914 edition of his *Lehrbuch der Physiologischen Chemie*, Abderhalden assumes two stages of nucleoproteid digestion: first, the formation of "nuclein" from nucleoproteid, accomplished by the stomach, and, secondly, the splitting of "nuclein" into nucleic acid and protein by the activity of the pancreatic juice. This theory of two distinct combinations of nucleic acid with protein has been quite definitely disproved by the work of Umber¹⁵ (1901), who showed that any nucleoproteid is easily split by pepsin or trypsin with the liberation of nucleic acid. Further proof is given by Walter Jones,¹⁶ who demonstrated that the combination of nucleic acid with a protein is merely that of a weak base and a weak acid and is easily reproduced in the test-tube.

When a patient on the medical service of the Johns Hopkins Hospital (whose history is reported below) was found to have a complete absence of pancreatic secretion in the intestinal tract, the idea was conceived that by feeding thymus gland and estimating the increased

7. Fronzig: *Ztschr. f. klin. Med.*, 1913, lxxvii, 84.

8. Glaessner and Popper: *Deutsch. Arch. f. klin. Med.*, 1908, xciv, 46.

9. Hesse: *Ztschr. f. exper. Path. u. Therap.*, 1910, vii, 91.

10. Van Westenrijk: *Ztschr. f. exper. Path. u. Therap.* 1911, viii, 353.

11. Leech: *Practitioner*, 1911, lxxxvii, 631.

12. Pratt: *Am. Jour. Med. Sc.*, 1912, cxliii, 313.

13. Popoff: *Ztschr. f. physiol. Chem.*, 1894, xviii, 534.

14. Milroy: *Ztschr. f. physiol. Chem.*, 1896, xxii, 307.

15. Umber: *Ztschr. f. klin. Med.*, 1901, xliii, 282.

16. Jones, Walter: *Nucleic Acids* (Monographs on Biochemistry, 1914).

output of uric acid in the urine, the possible necessity of the pancreas to any stage of nuclear digestion could be conclusively demonstrated. It has long been known that approximately 50 per cent. of ingested purins is excreted in the urine (Weintraud,¹⁷ 1895, and others).

CASE REPORT

The patient's history and the clinical findings were as follows:

History.—M. W., aged 42 (Med. No. 33,205), a Russian Jew, married, was admitted to the hospital Oct. 20, 1914. The family and personal histories were unimportant. The patient complained of a persistent, painless jaundice (with one slight remission in the first month) lasting for nine months and accompanied by dark urine, rather frequent, soft, clay-colored stools, and 90 pounds loss of weight.

Examination.—On examination he was found to be a large-framed man, fairly nourished, but whose skin corroborated the statement of loss of weight. The skin and conjunctivae were intensely jaundiced. The heart and lungs were negative. The liver was large, extending from the sixth rib to the crest of the ilium in the nipple line, smooth, firm and sharp-edged. The gall-bladder was definitely palpated projecting about 2 inches below the liver margin. No other masses were felt; there were no signs of collateral portal circulation. The reflexes were normal. Rectal examination was negative. The temperature, pulse, respiration and blood-pressure were normal.

Blood: White blood-cells, 13,360; polymorphonuclears, 71 per cent.; hemoglobin (Sahli), 83 per cent.; fragility of the red blood-cells, normal; Wassermann reaction, negative; Widal reaction, negative.

Urine: Dark-brown; trace of albumin; few granular casts; bile tests strongly positive.

Stools: Large soft, clay-colored, frequent (while in the hospital the patient averaged three stools daily). Microscopically, marked increase of neutral fats and fatty acids, with the neutral fat clearly predominant; many undigested muscle fibers; hydrobilirubin, negative.

Calmette tuberculin test (1 per cent. and 5 per cent.), negative.

Gastric Analysis: No free HCl; total acidity, 9; no blood or lactic acid; much yeast.

The special pancreatic tests were as follows:

Duodenal contents were obtained with an Einhorn tube and the ferment activities determined by the methods of T. R. Brown.¹⁸

Trypsin, absent (digestion with 1 per cent. casein solution).

Lipase, absent (digestion with 1 per cent. monobutyryl solution).

Diastase, trace, probably salivary (digestion with one-tenth per cent. soluble starch).

Feces: Brown's¹⁸ technic was used here also.

Trypsin, absent.

Lipase, trace; probably from the lower intestinal tract.

Diastase, absent.

Urine: Diastase, 50 units (high) by Brown's¹⁸ method. Trypsin, absent.

Schmidt-Kashiwado nuclei test, negative (spores recovered).

Blood sugar, 100 mg. per 100 c.c. (normal).

Carbohydrate Tolerance: 100 gm. glucose gave no glycosuria.

17. Weintraud: Berl. klin. Wchnschr., 1895, xxxii, 405.

18. Brown, T. R.: Johns Hopkins Hospital Bulletin, 1914, xxv, No. 281.

The patient was discharged Nov. 4, 1914, with the diagnosis of "carcinoma of the head of the pancreas, obstruction of the common bile duct and obstructive cirrhosis of the liver."

The history of nine months of persistent, painless jaundice, associated with a loss of weight, and the clinical findings of a dilated gall-bladder, acholic stools and bile in the urine, point toward a carcinomatous obstruction of the common bile-duct. The inability to demonstrate any of the pancreatic ferments in either the duodenal juice or the feces, coupled with the frequent, large, fatty stools showing many muscle fibers, justifies the assumption that there was a complete absence of the external secretion of the pancreas from the intestinal tract of this patient.

The following experiment was therefore carried out: October 27, the patient was put on a purin-free diet containing 2,900 calories, and the daily uric acid output of the urine determined by means of the Folin-Schaeffer method. On the fifth day (October 31) 150 gm. of fresh calf's thymus were given with the noon meal and the same amount was given on the sixth day (November 1). The purin-free diet was resumed on the succeeding days. The results are found in the accompanying table.

Date	Diet	Total Urine c.c.	Uric Acid gm.
October 27	Purin-free	1,565	0.82
28	Purin-free	1,418	0.76
29	Purin-free	1,420	0.76
30	Purin-free	1,380	0.51
31	Plus 150 gm. of thymus	1,660	1.32
November 1	Plus 150 gm. of thymus	1,540	1.25
2	Purin-free	1,485	0.15
3	Purin-free	1,279	0.14

The first day's results may be excluded, for a constant level of excretion under the purin-free diet had not been reached at this time. The maximum truly endogenous output was, therefore, 0.76 gm., and the excess of excretion over this amount on the two thymus days was 0.52 gm. and 0.48 gm. By the principle that 50 per cent. of ingested purins is excreted as uric acid in the urine, 150 gm. of calf's thymus should cause an exogenous excretion of approximately 0.6 gm. of uric acid over the endogenous level. It can be safely said, therefore, that there was practically a quantitative recovery of the exogenous uric acid. This finding conclusively demonstrates that there was digestion of thymus nuclei with the production of the uric acid in the urine in the absence of both bile and pancreatic juice.

SUMMARY

The results of this experiment prove that in the human being the digestion of nuclear material, the purin metabolism and the uric acid formation do not depend on the presence of the pancreatic secretion in the intestinal canal. This finding, together with the negative result of the test in this case, and in many other reported cases, definitely points out the worthlessness of the Schmidt nuclear test for pancreatic function.

518 North Broadway.