cation; Thomas D. Wood, chairman, Joint Committee on Health Problems in Education, National Education Association and American Medical Association; Willard W. Beatty, director of education, U. S. Office of Indian Affairs, recently president, Progressive Education Association; Frank P. Graham, president, University of North Carolina; R. A. Kent, president, University of Louisville; Roy G. Ross, general secretary, International Council of Religious Education; Donald J. Cowling, president, Carleton College; F. L. Bishop, Highway Education Board; John Q. Rhodes, president, Association of Motor Vehicle Administrators; Roger William Riis, public relations counsel; W. Roy Breg, executive secretary, Allied Youth; Thomas H. MacDonald, chief, United States Bureau of Public Roads; Russel E. Singer, general manager, American Automobile Association; Samuel Thorne, attorney; Thomas D. Thacher, attorney; Percy Jackson, attorney; Harold B. Hoskins, vice-president, Cannon Mills, Inc.; Edward W. Freeman, vice-president, Suchar Process Company; Edwin C. Jameson, president, Hamilton Fire Insurance Co.; Graham Edgar, vice-president, Ethyl Gas Corporation.

SPECIAL ARTICLES

INFLUENCE OF ADRENALECTOMY ON ANTERIOR PITUITARY KETOGENESIS IN RATS

IN 1934 Long and Lukens[1] first described experiments revealing that adrenalectomy produces a marked reduction in the ketone body excretion of the depancreatized cat. Since then a number of investigators have reported that adrenalectomy similarly affects the ketonuria consequent to phlorhizin intoxication,[2] pregnancy,[3] fasting[3] and the administration of extracts of the anterior pituitary gland.[3,4] This reduction in ketonuria has been attributed to a decrease in ketone body formation consequent to the removal of the adrenal cortex. However, several other interpretations of the decrease in ketonuria are possible without having recourse to the hypothesis that the adrenal cortex, or its hormone, is essential for ketogenesis.

The observation made incidentally by MacKay and Barnes[3] that the adrenalectomized rat may develop a ketonemia after the administration of an extract of the anterior pituitary gland suggested to us that the adrenals may not be essential to the ketogenic activity of anterior pituitary extracts. For that reason, a series of studies was started to investigate more closely the blood and urinary ketone body content of normal and adrenalectomized animals treated with a crude extract of the anterior pituitary gland.

Rats were adrenalectomized forty-eight hours before the administration of a crude extract of beef anterior pituitary glands (A.P.E.), and were given normal saline "ad lib" during the interval. No attempt was made to maintain these animals for periods longer than forty-eight hours before administering A.P.E., since we did not desire the secondary effects of an adrenal insufficiency to interfere with effects attributable to the absence of the glands *per se*. All animals, normal and adrenalectomized, were fasted for seventeen hours before the injection of A.P.E. subcutaneously and of saline intraperitoneally. Following the injections, the urine was collected for eight hours and its ketone body content determined by the method of Van Slyke and Fitz. At the end of the eight-hour period, the animals were bled from the aorta and the blood ketone body content was determined by the same method.

Our data, summarized in Table I, indicate that in the absence of the adrenal glands, A.P.E. administration is relatively ineffective in producing a ketonuria; an observation which is in accord with that of others. However, the blood ketone body content indicates no apparent disturbance in the ability of adrenalectomized rats to manufacture these substances. In fact, if anything, the blood ketone content of the adrenalectomized rats is greater than that of the normal animals. That of the adrenalectomized rats is 5.7 mgm per cent. higher than that of the normal group, the ratio of the difference of the means to the standard error of this difference being 2.53.

TABLE I

Experimental group	No. of rats	Average weight gms.	Fasted hours	Blood ketones* 8 hours after A.P.E. mgm per cent.	Urine ketones* 8 hours after A.P.E. mgm per 100 gm
Normal	20	191	17	18.2	5.9
Adrenalectomized .	17	163	17	23.9	0.9

* Expressed as acetone.

One possible explanation of these data is that presented by MacKay and Barnes,[5] who postulated that adrenalectomy results in an increased ketolysis, which in turn is responsible for the decrease in ketonuria. However, the fact that the blood ketone content is at least as great in our adrenalectomized animals as it is in the normal group makes it obvious that irrespective of whether ketolysis is or is not increased, the same

[1] C. N. H. Long and F. D. W. Lukens, SCIENCE, 79: 569, 1934.

[2] G. Evans, *Am. Jour. Physiol.*, 114: 297, 1936.

[3] E. M. MacKay and R. H. Barnes, *Am. Jour. Physiol.*, 118: 184, 1937.

[4] E. G. Fry, *Endocrinology*, 21: 283, 1937.

[5] E. M. MacKay and R. H. Barnes, *Am. Jour. Physiol.*, 122: 101, 1938.

degree of ketonuria should occur in both instances. Since a decreased ketonuria occurs in adrenalectomized animals and since ketogenesis apparently is undisturbed, ketolysis can not be regarded as the factor responsible for the decreased ketonuria.

A more plausible explanation for the discrepancy between the ketone body excretion and the blood ketone level is that following the removal of the adrenal glands, the renal threshold for ketone bodies is markedly increased. Thus, even with identical blood ketone levels the adrenalectomized animal will excrete less ketone bodies than will the normal. This is in accord with the observations of many investigators who have demonstrated that adrenal insufficiency is characterized by marked abnormalities in renal function,[6] and hence it is not surprising that these renal disturbances manifest themselves by an inability of the kidney to maintain its normally low threshold for ketone bodies.

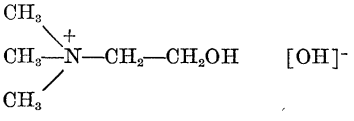
Our data suggest the conclusion that the adrenal gland *per se* is not essential for the ketogenic activity of extracts of the anterior pituitary gland and that an increase in the renal threshold for ketone bodies is responsible for the decreased ketonuria observed in the adrenalectomized animals treated with A.P.E. However, this does not exclude the possibility that in late stages of adrenal insufficiency secondary changes in liver function ensue, with a consequent decrease in ketogenesis. These and other studies will be published in greater detail elsewhere.

I. ARTHUR MIRSKY

METABOLIC LABORATORIES,
INSTITUTE FOR MEDICAL RESEARCH,
THE JEWISH HOSPITAL, CINCINNATI, OHIO

THE CHEMICAL NATURE AND NOMENCLATURE OF CHOLINE DERIVATIVES

CONSIDERABLE confusion exists as regards the nomenclature and understanding of the chemical nature of compounds of the choline type. Choline is an organic homologue of ammonium hydroxide, but the name suggests an amine. Perhaps because of this inappropriate



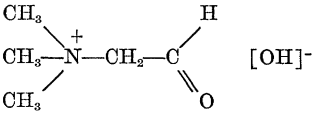
name it is not generally appreciated that choline, like tetramethylammonium hydroxide, is a very strong base, comparable with the caustic alkalies. Like sodium hydroxide, choline reacts with hydrochloric acid to form a chloride, a term which should be used in preference to "hydrochloride." Like sodium chloride, in aqueous solution the chloride salt of choline is neutral in reaction and dissociates into cations and anions. Strictly speaking, choline salts should no more be termed "choline" than should sodium chloride be referred to as "sodium," or ammonium chloride as "ammonium." The term "choline hydrochloride" is incompatible with the structure of this "onium" compound and the use of such terminology (by research workers and manufacturers) contributes to the erroneous idea that the chloride salt contains loosely bound hydrochloric acid which should be neutralized before biological use. It is obvious that these comments apply equally forcibly to the various derivatives of choline such as acetylcholine, "mecholyl," etc.

Ordinary nitrogenous compounds containing tri-(co)valent nitrogen form "salts" with hydrochloric acid by the addition of the hydrogen ion through a covalent link (shared electron doublet), making the molecule a cation and enabling it to hold the chloride ion by electrovalency. Such "salts" are termed hydrochlorides, although the nomenclature appears to have no justification except that of common usage, for "salts" with other than simple halogen acids are not so designated, for example, codeine phosphate, strychnine nitrate, etc.

In compounds of the choline type the four-covalent-one-electro-valent state is constant, an anion being ever present, whether it be hydroxide, chloride or bicarbonate. Substances of this type are classified as onium compounds and the names of the salts are derived in the same manner as are those of sodium hydroxide; for example, choline chloride, trimethyl-β-hydroxyethylarsonium bromide, tetramethylphosphonium sulfate, etc.

The importance of the charged nitrogen atom is evidenced not only by derivatives of choline, but also by such biologically significant compounds as vitamin B_1 and the nicotinic acid amide portion of the coenzyme system.

The nomenclature of the biological oxidation products of choline is unfortunate. Betaine aldehyde, the primary product of oxidation, has a particularly undesirable name, since it implies that the compound pos-



sesses the properties of a betaine, which is not the case. In aqueous solution betaine aldehyde and its salts are electrolytes, dissociating into cations and anions.

The name "betaine" (pronounced *bē′ tȧ in*) is generically applied to a large group of compounds having a zwitterion structure similar to that of the compound termed betaine specifically, the latter being the secondary oxidation product of choline.

[6] A. Grollman, "The Adrenals," pp. 170 and 180. Williams and Wilkins Company, Baltimore, 1936.