THE BASAL METABOLISM AND HYPER-
GLYCEMIC TESTS OF HYPER-
THYROIDISMWITH SPECIAL REFERENCE TO MILD AND LATENT
CASES *

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A recent writer¹ has remarked that our position in the study of thyroid disease is about what it would be in regard to diabetes if we were without our laboratory data relative to the urine and the blood. It is well known² that in some very severe cases of thyrotoxicosis the thyroid gland is not definitely palpable, or at most not more so than in very many presumably healthy persons. This emphasizes the fundamental importance, if any emphasis were needed, of looking beyond the goiter for clinical data more distinctive and more strongly diagnostic than the clinical signs and symptoms usually present in thyroid intoxication.

Recent observations have confirmed the suspicion long entertained that other endocrine glands besides the thyroid play a more or less important rôle in exophthalmic goiter. This is especially true with reference to the thymus, the importance of which would almost seem to justify the term "thyroid-thymus syndrome" for this condition. Whether or not this term is too cumbersome, or possibly might too much exaggerate the relative importance of the thymus, it reflects a point of view which needs emphasis at the present time. For instance, Blackford and Freligh,³ on the basis of seventy-four necropsies, conclude that an enlarged thymus is present in 100 per cent. of patients under 40 years of age, and in about 50 per cent. of those above 40, in whom the average weight of the thymus was 13 gm. Matti⁴ says that the monopoly enjoyed by the thyroid in exophthalmic goiter is at an end. Halsted⁵ on the basis of a very large experience concludes that the important rôle played by the thymus in exophthalmic goiter is demonstrated beyond question by animal experimentation, and especially by the cures resulting from primary thymectomy and also from secondary thymectomy following thyroidectomy which alone had been unsuccessful.

There are two pressing needs in the study of thyroid disease. The first of these is the differential diagnosis of the so-called borderline cases and the determination of the toxicity of an existing definite goiter. Practically all cases of thyroid disease belong to this group at the outset for a variable period, which may be very short or very long—may in fact be measured by days or by years. A group of more or less vague symptoms, which might be either constant or intermittent, and consisting for the most part of tachycar-

dia, nervousness, and hyperidrosis, and a trifle later varying grades of debility and digestive disorders, and perhaps a little later still, mild, irregular febrile disturbances, formed the basis of the clinical diagnosis. These symptoms are, obviously, the expression of a toxemia with somewhat variable group reactions, and which may in many cases easily be due to any one of several different causes, and especially chronic infections.

The second pressing need is something besides the subjective sensations of the patient and the ordinary clinical manifestations, to enable us more accurately to measure the actual rise and fall of the thyrotoxic state, just as by the rise and fall of hyperglycemia and glycosuria in diabetes we follow the course of that disease. Owing to the neuropsychopathic character of so many of these thyrotoxic patients, it is essential that it should be objective in its nature. In my opinion the recent clinical application of the basal metabolism and alimentary hyperglycemia tests has very satisfactorily met these demands and marks an epoch in the study of hyperthyroidism.

BASAL METABOLISM

We will first consider the basal metabolism which is by far the more important of these two methods. By basal metabolism is meant that minimal quantity of metabolic change essential to the neuromuscular and secretory phenomena of what might be called the basal and necessarily continuous organic functions—respiration, circulation and secretion. Rest and food abstinence approximately eliminate all other metabolic activities. It has been well known since the classical work of Friedrich Müller⁶ and Magnus-Levy,⁷ about twenty-five years ago, that one of the most characteristic phenomena of hyperthyroidism was an increase in general metabolism, while hypothyroidism produced exactly the opposite result. This, of course, depends on the regulatory action of the thyroid secretion on metabolic processes, which apparently bear a direct relationship to each other. It is perfectly evident, therefore, that the optimum conditions of body function are dependent on a definite quantity of thyroid and synergistic secretions which can only vary within narrow limits without producing more or less serious disturbance.

Since that time a great deal of work has been done by various investigators in confirmation and elaboration of these facts. This work has for the most part been done in well-equipped hospitals and institutions with large and complicated apparatus requiring, for instance, the services of an expert gas analyst and, therefore, not at all practical for general clinical purposes. Taking advantage of the fact that heat production could be measured equally well if not more accurately by oxygen consumption alone than by direct calorimetry, Dr. F. G. Benedict⁸ has devised a portable and comparatively inexpensive apparatus which can be operated in any small hospital or office by any one reasonably familiar with laboratory technic. The introduction of this apparatus, which can be placed in the corner of any convenient room, the only accessory being a couch, places the entire medical profes-

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1. Du Bois, E. F.: Metabolism in Exophthalmic Goiter, *Arch. Int. Med.* **17**: 915 (June) 1916.

2. McGarrison, Robert: The Thyroid Gland in Health and Disease, New York, William Wood & Co., 1917.

3. Blackford, J. M., and Freligh, W. P.: The Thymus in Adults with Especial Reference to Goiter, *Collected Papers of Mayo Clinic* **8**: 507, 1916.

4. Matti, H.: Die Beziehungen der Thymus zum Morbus Basedowii, *Berl. klin. Wchnschr.* **51**: 1365 (July 20) 1914, abstr. by J. A. M. A. **63**: 812 (Aug. 29) 1914.

5. Halsted, W. S.: The Thymus in Exophthalmic Goiter, *Bull. Johns Hopkins Hosp.* **25**: 223, 1914.

6. Müller, Friedrich: Beiträge zur Kenntniss der Basedowischen Krankheit, *Deutsch. Arch. f. klin. Med.* **51**: 335, 1893.

7. Magnus-Levy: Gaswechsel bei Thyroidea, *Berl. klin. Wchnschr.*, **32**: 650, 1895.

8. Benedict, F. G.: A Portable Respiration Apparatus for Clinical Use, *Boston M. and S. J.* **178**: 667 (May 16) 1918.

sion under additional obligation to this distinguished investigator.⁹

The estimation of metabolism by measuring the units of heat production is made possible by the application of Rubner's law, that it is proportional to the body surface from which, with some exceptions, all heat not actually expended in energy production is radiated. The basis of this law is, of course, the universally accepted laws of the conservation and

Chart 1.—Basal metabolism in actual and suspected hyperthyroidism.

transmutation of energy and the radiation of heat. The chemical forces of the body, which represent the sum total of metabolism, are transmuted into heat, the excess of which over body requirements is radiated from the surface. The standard chosen is the number of calories per square meter of body surface per hour. The body surface is determined very simply by what is known as the "height-weight formula" based on two factors: namely, the height in centimeters and the weight in kilograms. By the use of the chart, plotted from this formula, as worked out by Du Bois,¹⁰ and the two factors of weight and height, the body surface expressed in square meters is instantly read without any calculation whatever. In the determination of oxygen consumption the patient is made to fast overnight and then to lie on a couch for thirty minutes or more to get rid of the respirable products of all metabolism other than basal, resulting especially from the voluntary musculature. The patient breathes through the mouth-piece connected with the open air for a few minutes in order to establish quiet normal breathing, after which the breathing is in and out of a spirometer bell. The oxygen and nitrogen only are rebreathed, for the carbonic acid is entirely removed from the expired air by being passed through an absorbent (soda-lime). The scale on the side of the spirometer bell is read at the beginning of the observation and again at the end of whatever period is chosen (usually ten minutes), both observations being made at the same point of time; that is, at the end of expiration. Since the carbonic acid gas has disappeared

and the nitrogen is not influenced, the difference in the readings on the spirometer scale accurately represent the amount of oxygen consumed. The volume of gas is then corrected for barometric pressure and thermometer readings in order to bring it to the standard of sea-level and zero centigrade. This corrected volume which is obtained by the use of logarithms, but which could undoubtedly be determined on the percentage basis with sufficient accuracy for all clinical purposes, is used as the basis of the indirect calorimetric calculation. Each liter of oxygen gas, with the above mentioned corrections, represents 4.825 calories of heat. From this the calories are calculated for one hour. By dividing the calories per hour by the body surface, determined as above indicated, we have the final result of calories per square meter per hour.

The number of calories per square meter of body surface per hour varies normally with sex and age and perhaps other physiologic conditions. By the Du Bois or "height-weight" formula, the average figure for men is 39.7; for women, 36.9. In pathologic conditions and conspicuously in disturbances of thyroid secretion, these figures are subject to numerous variations. In hyperthyroidism the increase is striking; very mild cases, including the borderline group, and frank cases of thyrotoxicosis in the quiescent state, may show an increase up to 30 per cent.; mild cases, 30 to 50 per cent.; severe cases, 50 to 75 per cent., and very severe cases, 75 to 100 per cent. or more, following the classification of Du Bois excepting that the "mild" cases of Du Bois (below 50 per cent. increase of basal metabolisms) are subdivided into "mild" and "very mild" to correspond with his "severe" and "very severe" cases above 50 per cent. increase.

TABLE 1.—PARALLEL OBSERVATIONS ON BASAL METABOLISM AND BLOOD SUGAR IN ACTUAL AND SUSPECTED CASES OF HYPERTHYROIDISM

Case	Age	Calories per Sq. Meter from per Hour	Percentage of Variation from Normal	Blood Sugar		
				Fast-ing	First Hour	Second Hour
1. Mrs. M.	1263	60	35.2	- 4.6	0.125	0.119
2. Mr. S.	1775	44	37.9	- 4.5	0.089	0.093
3. Mrs. F.	1765	63	36.5	0		
4. Mrs. T.	1455½	38	37.2	0	0.770	0.090
5. Mr. S.	1747	38	40.7	+ 2.5	0.087	0.226
6. Miss J.	1776	24	39.0	+ 5.7	0.078	0.120
7. Miss K.	1727	27	39.9	+ 8.1	0.112	0.129
8. Mrs. R.	907	..	40.0	+ 8.4	0.089	0.139
9. Mr. R.	1778	33	43.7	+10.0		
10. Mr. S.	8	54	45.0	+13.3	0.090	0.150
11. Mrs. K.	1378	25	42.0	+13.8	0.071	0.072
12. Mrs. E.	1582	50	42.1	+14.0		
13. Mrs. E.	1740	34	43.7	+18.4	0.110	0.146
14. Mrs. Y.	1761	41	45.1	+22.2	0.084	0.194
15. Miss W.	1723	35	45.9	+24.4	0.094	0.233
16. Mrs. Y.	1700	43	48.3	+30.9	0.120	0.140
17. Mr. B.	1726	28	56.3	+41.9		
18. Mrs. C.	1708	32	55.9	+51.5	0.065	0.210
19. Mrs. H.	1752	35	59.0	+60.0	0.092	0.195
20. Mrs. B.	1549	29	64.8	+75.6	0.090	0.220

9. Dr. Janney of New York in his discussion of this paper raised a question which I overlooked in the closing discussion, and which I think deserves attention. He said that the metabolism observation even with the Benedict portable respiration apparatus was not easy. Certainly it is not easy. The greatest care and accuracy are required. For example, if the patient after resting half an hour should, without the knowledge of the clinician, arise from the couch and walk, say 20 feet, and close a window, it would raise basal metabolism about 15 per cent. If the metabolism observation was made after instead of before the 100 gm. of glucose, in the technic described in this paper, this would cause an increase of 5 per cent. The slightest error in measuring exactly the duration of the observation, or escape of air or oxygen around the mouth piece, would introduce substantial error. A failure to correct volume of oxygen to zero C. and sea-level barometric pressure, if such carelessness were conceivable, would make another increase of from 10 to 15 per cent. It will thus be readily seen that if careless or incompetent work should find its way into literature, under a mistaken impression of the simplicity of this procedure, it would be very deplorable.

10. Du Bois, Delafield, and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. 17: 863 (June) 1916.

Table 1 and Chart 1 illustrate the range of cases studied and give the general grouping of the cases. Perhaps the most important feature is the relatively large proportion of cases belonging to the mild and very mild or borderline group. As indicated above, the main purpose of this clinical study was the differential diagnosis and positive identification of the cases in this group, which frequently cannot be done by the ordinary clinical methods. There will be found, with some exceptions, a striking parallelism between the percentage increase of basal metabolism and the relative intensity of the thyrotoxicosis. This parallelism

is so close that the percentage increase of the basal metabolism seems to serve as a reliable guide in the classification of the cases and an accurate measure of the fluctuations that may occur either spontaneously or as a result of treatment.

In the study of basal metabolism it is important to remember that like all physiologic processes in either normal or pathologic conditions, it is subject to marked variations. This variation, however, offers no greater difficulties here than in other procedures, such as the

Chart 2.—Sample curves illustrating types of alimentary hyperglycemia in thirty-one cases of hyperthyroidism: A, blood sugar fasting; B, blood sugar one hour after 100 gm. of glucose; C, blood sugar two hours after 100 gm. of glucose.

tests for albuminuria, glycosuria, the Wassermann test, variations in temperature, etc. When properly correlated with the general clinical syndrome it may be regarded as one of the most reliable and scientifically accurate aids available in any field of diagnosis, and is of inestimable value not only in establishing the diagnosis but in studying the clinical course of this disease.

ALIMENTARY HYPERGLYCEMIA

The occurrence of alimentary hyperglycemia in hyperthyroidism has been known since the work of Tachau¹¹ in 1911. At that time and until quite recently, the methods of blood analysis were too cumbersome for clinical use. The recent investigations of Lewis and Benedict,¹² Myers and Bailey,¹³ and others, however, placed this work on an entirely different and clinically practical basis, and stimulated both experimental and clinical investigations along this line. With the aid of these very simple and accurate colorimetric methods the entire subject of blood sugar content has been worked over afresh within the last few years.

Living in a thyroid zone and confronted almost daily by the diagnostic difficulties above mentioned, I was attracted by the method described in the paper by Denis, Aub, and Minot.¹⁴ This method seemed entirely practical. The test, as outlined by them, can be completed in a little more than two hours, or if immediately preceded by the basal metabolism observation, which is my method of choice, the entire procedure will require less than three hours, most of this time being spent in waiting.

The fasting blood is first taken; then the patient is given 100 gm. of glucose. In one hour a second blood specimen is taken, and in another hour a third, which by this technic completes the blood study. The urine

also is examined at the end of the first and second hours, and may be examined for several hours longer, although the glycosuria is a question involving the renal glucose threshold rather than the thyroid question.

Under normal conditions, in the average person in the fasting state, 100 gm. of glucose does not produce a hyperglycemia lasting as long as one hour. At least, this was the result in fourteen of my own cases, and in sixteen of those recorded by Denis, Aub, and Minot.¹⁴ Hamman and Hirschman,¹⁵ however, obtained an alimentary hyperglycemia in normal persons following 100 gm. of glucose, the crest of the wave occurring in from twenty to forty minutes but still remaining to some extent at the end of one hour or longer. In view of these facts, it must be regarded as possible that a transient hyperglycemia occurred during the first hour in observations made according to the methods used in this paper, disappearing at the end of the first hour.

Whatever may be the fact in regard to normal persons, there seems to be no question that in hyperthyroidism after the ingestion of 100 gm. of glucose there is almost invariably a marked hyperglycemia, the crest of the wave occurring at the end of the first hour, or at least recognized then by this method, with a sharp fall in 70 per cent. of my cases by the end of the second hour. This curve was found in twenty-two of thirty-one cases (about 70 per cent.) of hyperthyroidism. In six cases (20 per cent.) the hyperglycemia continued to rise until the end of the second hour. In three cases only (or about 10 per cent.) the hyperglycemia did not occur until the end of the second hour. These curves are represented graphically in Chart 2, based on Tables 3 and 4. The delayed hyperglycemia shown by the curves represented in Types 2 and 3 is probably the result of retarded absorption

TABLE 2.—EVIDENCE OF NO HYPERGLYCEMIA IN NON-HYPERTHYROID CASES

Case	Fasting	After 100 Gm. Glucose		Remarks
		1st Hour	2d Hour	
Mr. F. 1655	0.065	0.080	0.107	Doubtful
Mr. S. 1775	0.068	0.105	0.093	
Miss A. 1175	0.125	0.100	0.100	
Mrs. H. 1386	0.096	0.094	0.095	
Miss M. 1627	0.095	0.090	0.100	
Mr. B. 1660	0.077	0.080	0.082	
Mr. S. 1711	0.065	0.065	0.060	
Mr. M. 1608	0.073	0.081	0.087	
Miss K.* 1727	0.112	0.129	0.113	
Mrs. A. 1751	0.089	0.097	0.091	
Miss R. 1707	0.090	0.091	0.088	
Mrs. M.* 1263	0.125	0.140	0.119	
Mrs. K. 1378	0.071	0.072	0.092	

* Cases 1263 and 1727 show an absolute hyperglycemia, but it will be noted that the fasting blood sugar is quite high, raising a question of an associated pathology.

due to gastro-intestinal conditions. It suggests the possibility of a belated hyperglycemia occurring in some of the cases in which it does not appear within the two hour period. This is apparently a valid criticism of this technic. My answer is that in the forty-five cases of actual or suspected hyperthyroidism forming the basis of this section of this paper, there were thirteen (Table 2) which did not show a hyperglycemia within two hours, and in none of these could the diagnosis of hyperthyroidism be established on other grounds, although two or three still look suspicious.

15. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar, Arch. Int. Med. 20: 761 (Nov.) 1917.

11. Tachau: Deutsch. Archiv. f. klin. Med. 104: 445, 1911.
12. Lewis and Benedict: J. Biol. Chem. 20: 61, 1915.
13. Myers and Bailey: J. Biol. Chem. 24: 147, 1916.
14. Denis, W.; Aub, J. C., and Minot, A. S.: Blood Sugar in Hyperthyroidism, Arch. Int. Med. 20: 964 (Dec.) 1917.

In practically every case in which the diagnosis of hyperthyroidism seemed to be reasonably well established on other grounds, including the basal metabolism observations, a definite hyperglycemia occurred not later than the second hour, and in 90 per cent. of the cases within the first hour. As a routine procedure, therefore, I believe that the two hour period is sufficient.

In doubtful cases, and especially when the determination of basal metabolism cannot be made, the alimentary hyperglycemia test, as above outlined, may prove to be of considerable value. Of course diabetes, alcoholism, etc.,¹⁶ must be excluded.

SUMMARY

The differential diagnosis of many mild, atypical or very early cases of thyrotoxicosis by means of the ordinary clinical signs and symptoms can only be made with varying degrees of probability. The need is, therefore, very great for definite objective data, either decisive or very strongly corroborative, not only to determine diagnosis, but to estimate therapeutic results. The clinical application of basal metabolism and alimentary hyperglycemia satisfies these demands in a very scientific, practical and satisfactory manner.

Basal metabolism, or the metabolism of the fasting body in the resting state, can be quickly and accurately determined by measuring the oxygen consumption with the Benedict portable respiration apparatus. The average normal heat production, which is an accurate index of metabolism, is about 39.7 calories for men and 36.9 for women by the "height-weight" formula per square meter per hour under the conditions indicated. Physiologic variations of not more than 10 per cent., and nearly always much less than this, may occur in either direction.

TABLE 3.—EVIDENCE OF HYPERGLYCEMIA IN LATENT BUT SUSPECTED HYPERTHYROIDISM

Case	Fasting	After 100 Gm. Glucose		Remarks
		1st Hour	2d Hour	
Miss H.	766	0.086	0.190	
Miss S.	1602	0.075	0.190	
Miss H.	1654	0.070	0.140	
Mrs. F.	1616	0.070	0.140	
Mr. A.	1570	0.090	0.168	
Mrs. H.	1640	0.080	0.200	
Mr. W.	1641		0.116	
Mrs. T.	1644	0.066	0.122	
Mr. B.	1664	0.091	0.233	
Mr. B.	1663	0.070	0.070	
Miss B.	1673	0.075	0.081	
Mrs. P.	1721	0.132	0.191	
Mrs. F.	1612	0.060	0.149	
Mr. B.	1724	0.096	0.200	
Mrs. G.	1690	0.099	0.138	
Mrs. S.	1733	0.083	0.137	
Mrs. Y.	1761	0.084	0.194	
Mrs. R.	907	0.089	0.139	
Mrs. T.	1455½	0.077	0.090	
Mr. S.	1747	0.087	0.226	
Mrs. F.	1740	0.110	0.146	

Maximum increase

Minimum increase, 33%

In hyperthyroidism there is an increase up to 100 per cent. or more, according to the severity of the intoxication, which varies in different cases, and in the same case at different times.

In hyperthyroidism there is a diminished tolerance of carbohydrates with alimentary hyperglycemia, and also with glycosuria whenever the hyperglycemia exceeds the renal glucose threshold of the individual case.

16. In view of Pemberton's very valuable contribution made at this session, we must add arthritis to the list, and further studies may possibly add still more. The alimentary hyperglycemia test can only be regarded, then, as confirmatory, our main reliance being placed on basal metabolism.

In every case of hyperthyroidism studied (thirty-one cases) the blood sugar content was increased within two hours from 50 to 200 per cent.

In 70 per cent. of thirty-one cases the maximal rise occurred at the end of the first hour, with a more or less sharp decline at the end of the second hour, proving that the crest had been reached and passed.

The very few cases in which hyperglycemia is highest at the second hour may be explained by gastric hypomotility and slow intestinal absorption.

TABLE 4.—EVIDENCE OF HYPERGLYCEMIA IN FRANK HYPERTHYROIDISM

Case	Fasting	After 100 Gm. Glucose		Remarks
		1st Hour	2d Hour	
Mr. C.	1649	0.060	0.128	
Mr. S.	1684	0.065	0.086	
Mr. S.	8	0.090	0.150	
		0.078	0.176	
		0.090	0.220	
Mrs. B.	1549	0.054	0.180	
Mrs. G.	1597	0.090	0.126	
			0.063	
Miss C.	1708	0.065	0.210	
Mrs. L.	1719	0.083	0.157	
Miss W.	1723	0.148	0.203	
		0.094	0.233	
Miss H.	1752	0.092	0.195	
Miss J.	1776	0.078	0.120	
Mr. C.	1649	0.089	0.165	
		0.070	0.096	
Mrs. G.	1597	0.054	0.180	

Postoperative

Highest increase 233%
Postoperative
At end of rest treatment
period

Postoperative

The failure of the hyperglycemia to rise proportionately to the increased metabolism and to bear any direct relationship to the intensity of the thyrotoxicosis suggests that it is an indirect phenomenon due perhaps to overexcitation of other organs, for example, the pancreas, which in exceptional cases fails to respond to the thyroid stimulation.

The application of these tests will probably reveal a much greater incidence of hyperthyroidism than has formerly been recognized, and will especially enable us to make a clear diagnosis between toxic and nontoxic goiters. While a final diagnosis is altogether a question of clinical judgment, and should not be made exclusively in the laboratory; and while neither increased metabolism nor alimentary hyperglycemia is pathognomonic of hyperthyroidism, yet, when rationally correlated with the remaining clinical data, they together make as clear-cut a diagnosis of hyperthyroidism as a positive Wassermann does of syphilis in a suspected case.

ABSTRACT OF DISCUSSION

DR. JOHN C. HEMMETER, Baltimore: It is a great pleasure to listen to a paper that aims to have physiologic facts for its foundations. Dr. McCaskey's aim is simply to afford a new and practical method of diagnosis in doubtful cases of diseases of the thyroid. He assumes that the processes of oxidation in hyperthyroidism are increased and that there is a hyperglycemia two hours after 100 gm. of glucose are injected into the circulation and that this hyperglycemia is pathognomonic. I have seen the apparatus Dr. McCaskey employed for the respiring of a measured amount of oxygen by a resting subject. I saw no means for the absorption of the humidity that the patient himself gives off to the expired air. It makes a good deal of difference in the carbon dioxide absorbed by lime and the patient's own humidity. If it increases that of the respired gas to 80 it will increase the percentage of blood sugar by 13 per cent. of the normal. I would suggest some provision to account for this change in the blood sugar due to the humidity gradually accumulating in the spirometer, i. e., if the expired air actually reenters the spirometer. I do not wish to go through all the argu-

ments of sugar metabolism from Claude Bernard, Pavy and Otto Cohnheim and our own men down to Folin, Frederick M. Allen and others, but I hold that when you inject 100 gm. of sugar into an individual, a hyperglycemia two hours thereafter is physiologic. Therefore the method requires revision and further investigation. H. J. Hamburger (Groningen, Holland) in the most recent investigations which have come to me in the last ten days is opposed to this view of colloidal blood sugar. He says that all sugar when injected into the animals that have a separate circulation in the glomeruli from that of the renal tubules, as in the frog, behaves like sodium chlorid, and he gives further evidence that sugar exists in the blood just like sodium chlorid—not in combination. Postprandial hyperglycemia can be found in 90 per cent. of normal people. That there is an excess of blood sugar that can be caused by injecting 100 gm. of dextrose directly into the circulation can be ascertained by using several of the most modern methods for blood sugar determination. The whole matter has been gone over by McCleod in his recent book on biologic chemistry as applied to medicine. The excessive oxidation in hyperthyroidism appears to be well established by many biochemists. But in this very fact when associated with hyperglycemia we have a paradox and that paradox is one of the most puzzling things in medicine. Here we have a furnace that will burn anthracite coal and refuses to burn paper although you blow in pure oxygen. Of all the foods the carbohydrate molecule is the easiest to split up under above conditions, and the organization splits up the protein molecule, the most difficult, and even oxidizes the carbohydrate molecule moiety of the proteid molecule. It reminds one of a simile from a verse in the "Ancient Mariner"—"Water, water, every where, nor any drop to drink"—"Sugar, sugar every where, and not a milligram to oxidize."

DR. LEWELLYS F. BARKER, Baltimore: These two tests—that for measuring basal metabolism and that for measuring the glucose content of the blood—are certainly valuable tests in clinical diagnosis, especially for deciding upon the existence of what we call "overactivity of the thyroid gland." The methods, to the uninitiated, sound complex. They are, in reality, fairly easy to perform; and it is interesting that clinical men have devised simple modes of making measurements that formerly involved a very complicated technic. The basal metabolism is certainly increased in severe forms of exophthalmic goiter, and the sugar content of the blood, also, seems to be increased. Dr. Hemmeter has suggested that the existence of a hyperglycemia implies a state in which the body cannot split the carbohydrate molecule. May it not rather be simply that the sugar molecule, in some states at least, is mobilized more quickly than under normal conditions. For if the body, in the state under consideration, can split, as he says, the protein molecule and can burn the carbohydrate moiety of this protein molecule, why should it not be able, in the same state, to split the sugar molecule itself. The hyperglycemia might then be looked upon as the result, merely, of a sudden and rapid mobilization of sugar. Whether the increased basal metabolism and the hyperglycemia are due to the direct action of thyroid products, or are indirect results of thyroid activity, remains to be seen. We must think of the influence of the thyroid products on the cell metabolism all over the body, on the one hand; and, on the other, we must keep in mind the influence of the thyroid products on the activity of the other endocrine glands. I would mention one relationship, especially that of the thyroid to the suprarenal gland. Many of the phenomena that we speak of as hyperthyroidism may, in reality, be due to hypersuprarenalism, and it may be that some of our clinical tests for thyroid activity measure directly rather the suprarenal activity, and only indirectly the thyroid influence. I simply point out some of the difficulties, though I think that the tests are really valuable in internal medicine and I hope that they will be much more employed, and that we may come to some agreement as to what the results they yield may mean.

DR. NELSON W. JANNEY, New York: With regard to the blood sugar tolerance test it has been the experience of myself and co-workers that by standardizing the technic it

is possible to get more definite and accurate results than previously obtained. We now give, as already reported, 1.50 gm. sugar dissolved in 2.5 c.c. of water per kilogram of the patient's body weight, adding the juice of one lemon for flavoring. The fasting blood sugar value is obtained immediately before and one and two hours after taking the sugar lemonade. We thus find the normal blood sugar level to run from 0.12 to 0.14 per cent. without glycosuria. I wish to call attention to a very important point not yet presented in this discussion, namely a criticism of the value of the blood glucose tolerance test in diagnosis. Its value in this respect is problematical for myself and others have repeatedly observed abnormally high blood sugar curves in various conditions, i. e., pituitary disorders, Addison's disease, and other less clearly defined endocrinopathies. Unfortunately, therefore, this test, though frequently indicating an abnormal carbohydrate metabolism in hyperthyroidism, is by no means pathognomonic of that condition. We should, I feel, await with caution and patience more extended observations in this most interesting field.

DR. GEORGE W. McCASKEY, Fort Wayne, Ind.: In regard to Dr. Hemmeter's remarks, no matter whose figures he quotes, 0.3 per cent. as the normal blood sugar has certainly been discredited entirely. This figure was obtained by imperfect methods in use at that time. It has only been possible in the last few years by the use of the colorimeter to clinically determine the blood sugar content accurately. I believe we can do it now very closely. As to the factor of humidity in metabolism observations, I am not a physicist, but have made all the corrections indicated by Dr. Benedict. The fact that in forty-five consecutive cases the fasting blood sugar content is about what it ought to be, shows that there was no gross error, and even admitting any error, this error will be the same in both fasting and alimentary glycemic test, and that is all that is really necessary for the purposes of this clinical study, as it makes the comparative values reliable. Dr. Barker, I think, hit the nail on the head when he said that the hyperglycemia is not directly caused by the thyroid excess. I believe that the thyroid with other synergistic members of the endocrine system may modify other functions, such as the internal secretion of the pancreas, or the glycogenic or storage function of the liver, and in that way account for changes in blood sugar content. It is not simply a question of oxidation. It may be, among other things, mobilization, as Dr. Barker said. A failure on the part of the storage function of the liver or the voluntary musculature may account for the hyperglycemia. Dr. Jamey's criticism that a certain amount of glucose should be given per kilogram of body weight is well taken and is probably important. As a matter of fact, however, it did not seem to modify clinical results. Dr. Geyelin found glycosuria when the glucose intake exceeded 1.8 gm. per kilogram of body weight per hour. This is not a thyroid question at all, but a question of the renal glucose threshold, which Denis, Aub and Minot have established at about 0.17 or 0.18 per cent. blood sugar. Undoubtedly the scientific way to do this is to give a certain amount of sugar per kilogram of body weight, although in none of my thirteen normal cases did a hyperglycemia occur with a uniform intake of 100 gm. of glucose irrespective of body weight, unless the fasting blood sugar was already high. This is probably best accounted for by the enormous reserve function which apparently enables a patient weighing, say one hundred pounds, to promptly metabolize 100 gm. of glucose as readily as a patient weighing 150 pounds. It is perfectly obvious that if the glucose were increased, a point would be reached at which one patient could metabolize it and the other could not.

War Diet and Diabetes.—Bouchardat in France and Klemperer in Germany, reported at the time of the Franco-Prussian war in 1870, that under the dietetic restrictions entailed by the war, the course of diabetes was as a rule less severe. Elias and Singer have recently published similar observations. In the *Wiener klinische Wochenschrift* they state that classifying their cases by age and grade and comparing the course before and since the war began, demonstrate an unmistakably favorable influence from the war diet.