CHANGES IN THE BLOOD CHEMISTRY IN MALIGNANT DISEASE WITH SPECIAL REFERENCE TO CARBOHYDRATE TOLERANCE AND ALKALOSIS

PAULINE BEREGOFF

(Littauer Fellow in the New York University and New York City Cancer Institute)

The purpose of this investigation was to observe the alterations in the blood chemistry associated with malignant disease and to determine the value of such changes in the diagnosis of human cancer.

The first studies of sugar tolerance in malignant disease were conducted by Freund (1) in 1885 and by Trinkler (2) in 1890. These investigators found that cancer patients show a low tolerance for sugar and claimed the carbohydrate tolerance test to be of diagnostic value in cancer.

In 1919, Rohdenburg, Bernard and Krehbiel (3) studied the sugar tolerance in cancer patients and they found a low tolerance to sugar in all cancer patients that they examined, but as their series of cases was small, they did not base any contentions on their findings. In the same year Edwards (4) reported several cases of carcinoma in which the glucose tolerance test was low. He considered this test of greater value as a method of eliminating the presence of cancer than of establishing its existence. The failure to establish a specific glucose tolerance curve, as is found in cancer, he considered strong evidence against the presence of malignant disease. This investigator emphasized the fact that the disturbance in sugar metabolism consists not in the blood sugar content but in the ability of the organism to utilize a known quantity of glucose; the important factors being (1) how much of the excess sugar will be evident in the blood, (2) how early its high point be reached, and (3) how slowly it disappears from the circulation.

Reding and Slosse (5) in 1927 showed that cancer patients

possess a lower tolerance to glucose. In a series of 36 cases of untreated cancer, they found that after administering 50 grams of dextrose the average maximum increase of sugar in the blood was 91.8 milligrams per 100 cc. In normal individuals the blood sugar returned to its previous level within 90 minutes, whereas in cancer patients the fall was not complete until two hours or longer. It is interesting that the alteration of the sugar metabolism in cancer patients was accompanied by an alteration of the hydrogen ion concentration (pH) toward the alkaline side.

In 1928 Reding (6) attempted to demonstrate alterations in the blood chemistry of patients either suffering from cancer or having a predisposition to this disease. In each example he determined the pH, the total CO_2 (free and combined), and the concentration of the ionized calcium. He divided his cases into four groups as follows:

Group I: Twenty-five normals, the ages ranging between 21 and 68, with a negative family history for carcinoma. Their pH averaged 7.36; the total CO_2 averaged 63.2; and the ionized calcium averaged 22.43.

Group II: A total of 51 carcinoma patients, ages ranging between 34 and 60. The pH averaged 7.45, the CO_2 averaged 64, and the ionized calcium averaged 17. Alkalinity, fall of CO_2 and fall in the concentration of ionized calcium were constant phenomena associated with cancer.

Group III: A total of 31 patients in whom malignant tumors had been removed. The tests were made two months to three years after operation. The blood findings showed a similar average to those found in the untreated carcinoma patients. (Group II).

Group IV: Ten patients with benign tumors showed a pH of 7.42. The total CO_2 was 59.7 and the ionized calcium was 20.8.

These findings were subsequently confirmed by Reding and Slosse (7) (1929). Schreus (8) (1929) also reported that the blood chemistry of carcinoma patients showed a moderate alkalosis. He found that the pH in a series of 22 cancer patients averaged 7.42 and the alkaline reserve averaged 58.6. His

conclusions are the same as those of Reding (6) and Weiss (9), that a certain degree of alkalosis is present in all cancer patients.

Cori and Cori (10) have pointed out that abnormally large amounts of glycogen have long been known to be present in malignant tumors. The classical work of Warburg (11) of Berlin has shown a distinct difference in glycolysis of the cancer cell as compared with glycolysis in normal tissues. Warburg found that cancer cells exhibit a great increase in metabolism or glucose partition and that this partition deviates from the normal in that in cancer one molecule of lactic acid is reoxidized into glycogen and twelve molecules are cast off; while normally six molecules are reoxidized and three are cast off. The glycogen metabolism of cancer is about eight times that of working muscle and one hundred times that of a resting muscle. According to Warburg and to Cori and Cori the excessive amount of lactic acid produced by cancer cells points to abnormal carbohydrate metabolism in the cancer cell itself, whereas other observations indicate an abnormal carbohydrate metabolism in the organism as a whole.

Dudley Jackson (12) has claimed that the character of the sugar curve may serve as an indicator of the response that may be expected to radiation and surgery. He states that when the sugar fails to rise to a high maximum and when the return to the fasting level occurs within a period of three hours the response of the tumor is more beneficial and recurrences are less likely.

MATERIAL

A total of 281 known cancer patients, a group of 25 unknown (Chart No. 4) preoperative cases and 25 normal individuals were studied. The diagnosis is confirmed by microscopical examination in 90 per cent of the cases. In those cases in which no biopsy is available the disease is so far advanced clinically that the diagnosis is beyond doubt. The twenty-five normal controls gave a negative family history for carcinoma.

TECHNIC

The glucose tolerance test was performed by the method first introduced by Jacobson. The following procedure was adopted: (1) Five cc. of blood was taken by venipuncture in the morning before breakfast in order to determine the normal blood sugar content; (2) ninety-five grams of dextrose dissolved in 200 cc. of water or tea was administered by mouth; (3) a second venipuncture was performed forty-five minutes after the glucose administration and the sugar content determined by the Folin and Wu method; (4) two hours after the glucose administration a third venipuncture is performed and the sugar content determined; (5) three hours after the sugar administration a fourth specimen of blood is obtained and the sugar content determined. The figures representing the number of milligrams of sugar per 100 cc. of blood are plotted in the form of a curve. In a normal carbohydrate curve (Chart No. 1) the maximum point is reached at the forty-five minute interval. The curve returns to its base line within a period of two hours.

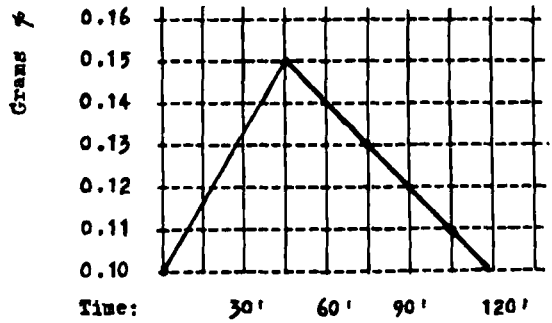

CHART 1. AVERAGE CARBOHYDRATE CURVE IN TWENTY-FIVE NORMAL INDIVIDUALS. The maximum point, 0.15 gms. per 100 cc. of blood, is reached 45 minutes after glucose ingestion. The blood sugar returns to normal within two hours.

The pH. was determined by Cullen (13) as well as by Hastings and Sendroy (14) colorimetric method. The total CO_2 (free and combined) was determined by the Van Slyke method. The concentration of the ionized calcium was determined by Rona and Takahashi (14) formula:

$$Ca++ = K\frac{H+}{CO_3H_2}.$$

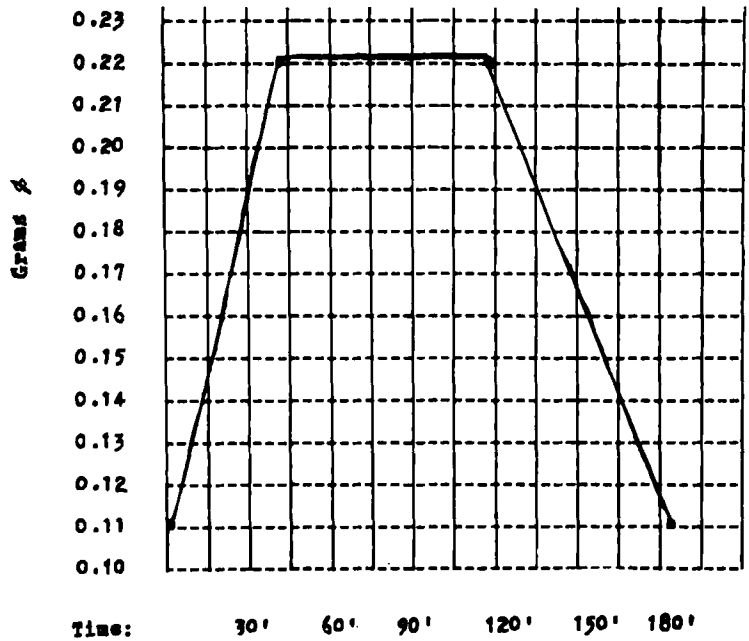

CHART 2. AVERAGE CARBOHYDRATE CURVE IN 300 KNOWN CANCER PATIENTS. The average maximum glucose content is 0.22 gms. per 100 cc. of blood. The sugar content fails to return to its normal level within two hours but reaches its previous normal only after three or four hours.

DISCUSSION

Low glucose tolerance, alkalosis and calcium deficiency, uniformly present in cancer patients indicate a perverted metabolic function which appears to be dependent upon disturbances in the mechanism of internal secretions.

Reding and Slosse believe that alterations in the glucose tolerance mechanism, the acid-base and ionic equilibrium, are disturbances independent of the tumor itself, precede its appearance and constitute a general disposition to cancer. They also believe that this predisposition is hereditary and caused by endocrine deficiency. They state that alkalosis is not due to abnormal cellular metabolism but to a breakdown in the normal mechanism of neutralization by a balance of carbonic acid and bicarbonate, and consider the parathyroids of primary importance in the regulation of the blood reaction.

Underhill (16) believes that calcium salts may play an important rôle in the regulation of the carbohydrate metabolism. It is well known, for instance, that glycosuria evoked by long continued injections of sodium chloride into the blood, may be checked promptly by the intravenous administration of diluted solutions of calcium chloride. Calcium salts have been closely associated with the function of the thyro-parathyroid mechanism. MacCallum and Voegtlin (17) have demonstrated a loss of calcium in the body after extirpation of the parathyroids together with cessation of tetany symptoms after calcium injections. Underhill confirmed these results and in addition demonstrated that the blood sugar content may be restored to normal, temporarily, by calcium administration. In our experiments it was noticed that when there is sufficient calcium, the blood sugar is normal, and that when there is diminished calcium the blood sugar tolerance is lowered. Thus calcium seems to play an important rôle in maintaining the equilibrium of the sugar regulating mechanism.

CHART 3.

Summary of Blood Findings in Cancer Patients.

No. of Patients	Lesion	Glucose Tolerance	Average pH	Av. Tot. Ca. Ion	Av. Tot. CO_2
45	Ca. breast	11–20–20–19	7.45	17.5	56.2
35	Ca. cervix	12–23–23–20	7.43	17.2	59.6
35	Ca. rectum	10–17–17–17	7.47	17.0	57.5
20	Ca. tongue	10–18–18–17	7.43	18.0	58.6
20	Ca. tonsil	10–21–21–20	7.44	18.0	55.6
15	Ca. prostate	11–18–19–18	7.45	16.5	60.1
2	Ca. penis	11–17–17–17	7.50	16.9	55.4
1	Ca. thyroid	10–17–17–16	7.50	18.2	58.3
13	Ca. vagina	11–16–17–16	7.51	19.0	59.1
5	Ca. ovary	11–18–18–17	7.44	18.3	58.5
5	Ca. uterus	11–18–18–17	7.44	18.2	57.2
5	Ca. bladder	10–17–17–16	7.44	16.5	56.2
26	Epithel. skin	10–16–16–15	7.42	17.0	57.1
15	Epithel. lip	10–17–17–16	7.40	18.5	56.2
1	Ca. parotid	10–16–16–15	7.42	16.1	55.2
1	Endothel. brain	10–17–16–16	7.50	18.0	56.4
13	Lymph. sarcoma	11–17–18–17	7.48	18.5	57.4
20	Ca. colon, sigmoid	11–23–24–23	7.42	17.5	58.7
4	Ca. larynx	10–15–16–16	7.46	17.5	58.2
Total No. 281					
Average.....			7.44	17.54	57.65

The ages of the patients ranged between 28 and 68.

CHART 4

Blood Findings in a Group of Unknown Preoperative Cases

Patient	Provisional Diagnosis	Final Diagnosis	Glucose Tolerance	pH	Tot. Ca. Ion	Tot. CO_2
H.M.	Luetic	Ca. penis	10–17–17–16	7.42	16.5	60.0
C.Q.	Ca. uterus	Fibroma uterus	10–15–10–10	7.38	22.0	66.5
C.T.	Ca. stomach	Exploratory negat.	10–15–10	7.37	20.7	64.5
R.F.	Tumor breast?	Ca. breast	11–23–23–22	7.46	16.5	58.2
E.G.	Sarcoma bone	Mult. cart. exostos.	10–15–10–10	7.37	17.2	63.5
J.H.	Lesion of tongue?	Inflammatory	10–15–10–10	7.38	19.7	65.6
T.M.	Hypernephroma	Tuberculosis of kidney	10–16–10–10	7.36	20.5	67.5
H.L.	Lesion of tendon	Seb. cyst.	10–15–10–10	7.37	22.5	68.2
J.W.	Sarcoma??	Adenitis	10–17–10–10	7.38	20.5	65.5
J.G.	Infected gums	Ca. gums	10–26–25–24	7.48	16.7	59.4
F.A.	Hodgkin's	Sarcoma	11–28–28–27	7.50	18.2	58.6
H.P.	Ca. lung	Inflammatory	10–16–10–10	7.37	19.5	66.7
J.R.	Luetic adenitis	Ca. adenitis	11–23–23–22	7.43	17.2	60.2
G.V.	Rectal polyp	Ca. rectum	11–25–25–24	7.54	15.3	56.5
M.R.	Lesion of prostate?	Ca. prostate	11–22–23–22	7.43	15.6	55.7
N.Y.	Lesion of uterus?	Ca. cervix	11–23–23–20	7.45	16.5	59.6
S.F.	Luetic?	Ca. lip. lues.	10–22–20–20	7.42	16.5	60.2
C.G.	Luetic	Ca. cervix	11–20–20–19	7.46	17.5	59.2
M.C.	Lues	Ca. cervix	10–22–21–20	7.46	16.2	60.0
M.C.	Lesion of stomach?	Ca. stomach	11–26–25–25	7.49	16.0	54.2
M.G.	Lesion breast?	Mastitis	10–16–10–10	7.37	22.0	64.2
G.S.	Lesion breast?	Mastitis	10–15–10–10	7.36	21.5	63.6
G.P.	Lesion breast?	Mastitis	10–14–10–10	7.37	22.1	65.2
M.R.	Gumma of larynx	Ca. larynx	11–25–25–23	7.50	16.2	58.9
P.L.	Lesion breast?	Mastitis	10–15–10–10	7.37	21.2	63.7

The ages of the patients ranged between 22 and 65 years.
This chart demonstrates the value of the tests in cancer diagnosis.

Our experiments and those of others indicate, that the mechanism regulating carbohydrate metabolism is sensitive to disturbances in the acid-base equilibrium and calcium reserve in the blood or tissues. A hyperalkaline pH corresponds to a reduced concentration of calcium and a low sugar tolerance.

CONCLUSIONS

1. A series of 300 patients have been studied in whom the blood shows a tendency towards alkalosis, low carbohydrate tolerance, deficiency in calcium and a low carbon dioxide content.

2. All bloods of cancer patients examined in these experiments exhibited a positive carbohydrate curve and a tendency to alkalosis. However, positive carbohydrate curves were obtained in other pathologic states such as hyperthyroidism, acromegaly and diabetes but in these conditions no alkalosis was demonstrable. As an indication of the presence of malignant disease a positive carbohydrate curve is significant only in the presence of alkalosis.

3. Examinations of the blood of 25 individuals not suffering from cancer, yielded a negative carbohydrate curve in every instance and the pH of the bloods was within normal limits. The concentration of the ionized calcium averaged 22.6 mgm. per liter.

4. It would appear from these experiments that the carbohydrate tolerance test and the hydrogen ion concentration are of greater value in eliminating the presence of malignant disease than of proving its existence.

Note: It is with great pleasure that I acknowledge my indebtedness to Dr. Max Cutler, Director of Cancer Research of the New York City Cancer Institute, for the many helpful suggestions offered throughout the course of this work and for facilities which enabled me to conduct the problem.

REFERENCES

1. FREUND, E.: Zur Diagnose des Carcinoms. Wien. med. Blätter, 1885, viii, 268.
2. TRINKLER, N.: Ueber die diagnostische Verwertung des Gehaltes an Zucker und reducirender Substanz im Blute vom Menschen bei verschiedenen Krankheiten. Centralbl. f. d. med. Wissenschaft, 1890, xxviii, 498.
3. ROHDENBURG, BERNARD AND KREHBIEL: Sugar tolerance in cancer. J. A. M. A., 1919, lxxii, 1528.

4. EDWARDS, S.: Blood sugar tolerance in cancer. Ind. Med. Ass., Fort Wayne, 1919, xii, 296–298.
5. SLOSSE, A., ET REDING, R.: Étude des altérations humérales dans le cancer et le précancer. Bull. Acad. Royale de Med. Belgique, 1927, vi, 605.
6. REDING, R.: Acido-basic and ionic equilibrium. Cancer, Bruxelles, 1928, v, 97–132.
7. REDING, R., ET SLOSSE, A.: Des caractéres généraux de l'état cancéreux et précancéreux. Bull. Assoc. franç. pour l'étude du Cancer, 1929, xviii, 122–148.
8. SCHREUS, H. T.: Acid-base equilibrium in cancer. Strahlentherapie, 1929, xxxiii, 243–248.
9. WEISS, E.: Über Genese und Wesen des Krebsen. Ztsch. f. d. Ges. exp. Med., 1917, viii, 295–308.
10. CORI, C. F., AND CORI, G.: On carbohydrate metabolism and malignant tumors. Proc. Soc. Exper. Med. & Biol., 1924, xxii, 254–255.
11. WARBURG, O.: Verbesserte Methode zur Messung der Atmung und Glykolyse. Biochem. Zeitsch., 1924, clii, 51–63.
Ibid. Versuche an überlebendem Carcinomgewebe. Klin. Wochen., 1923, xi, 776.
12. JACKSON, D.: Carbohydrate metabolism in cancer. Texas State Med. J., 1929, xxiv, 622–629.
13. CULLEN, G. E.: Hydrogen ion concentration of the blood in health and disease. Williams & Wilkins Co., 1926, xi, 75.
14. HASTINGS, A. B., AND SENDROY, J.: The effect of variation in ionic strength on the apparent first and second dissociation constants of carbonic acid. J. Biol. Chem., 1925, lxv, 445–455.
15. RONA, P., UND TAKAHASHI, D.: Beitrag zur Frage nach dem Verhalten des Calcium im Serum. Bioch. Ztschr., xlix, 370.
16. UNDERHILL, F. P.: The role of calcium in the regulation of blood sugar content. J. Biol. Chem., 1916, xxv, 447–461.
17. MACCALLUM AND VOEGTLIN: On the relation of tetany to the parathyroid glands and to calcium metabolism. J. Exper. Med., 1909, xi, 118–151.

[NOTE: The author has omitted from her bibliography several important papers which do not confirm her work, as, for example: WOODARD, H. Q.: Some observations on the pH of blood in cancer, J. Cancer Research, 1930, xiv, 319–323; CORRAN, J. W., AND LEWIS, W. C. M.: The hydrogen-ion concentration of the whole blood of normal males and of cancer patients measured by means of the quinhydrone electrode, Biochem. J., 1924, xviii, 1358; MILLET, H.: Measurements of the hydrogen-ion concentration of normal, foetal, and neoplastic tissues by means of the glass electrode, J. Biol. Chem., 1928, lxxviii, 281. ED.]