STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID TISSUES. I.

THE CHEMICAL METABOLISM OF NORMAL AND PATHOLOGICAL LYMPH NODES*

BY HENRY JACKSON, JR., M.D., FREDERIC PARKER, JR., M.D., AND EUGENE C. GLOVER, M.D.

WITH THE ASSISTANCE OF ISABELLE NEWTON

(From the Thorndike Memorial and Pathological Laboratories, Boston City Hospital, the Medical Service, Collis P. Huntington Memorial Hospital, and the Department of Medicine, Harvard University, Boston)

(Received for publication, June 25, 1930)

Warburg and his associates, Posener and Negelein (1924), have shown that within certain limits and with certain exceptions carcinomatous tissue has a unique and characteristic metabolism. They and Warburg (1925) found that normal tissues have a relatively high rate of oxygen consumption and a low aerobic glycolysis. Embryonic tissue has high respiration and, under anaerobic conditions, a high glycolysis, but it has only a slight destruction of sugar under aerobic conditions. Neoplastic tissue, on the other hand, has a rather low respiration rate and a high glycolysis under both aerobic and anaerobic conditions. These broad generalizations have been corroborated by Murphy and Hawkins (1925), Rona and Deutsch (1926), and others. The subject is more fully reviewed by Jackson (1929). Neither glycolysis nor oxygen consumption, however, proved to be an infallible guide to the nature of a given living tissue, so that Warburg (1927) resorted to a new value by which to differentiate neoplastic from normal tissue. He points out that when the Pasteur reaction functions at its maximum, the formation of exactly two molecules of lactic acid is suppressed when one molecule of oxygen is consumed, and on this basis he suggests a new value "U," which may be regarded as the

* The expenses of this work were in part defrayed by Mr. Edward Mallinckrodt, and in part by the DeLamar Mobile Research Fund, Harvard University.

theoretical aerobic glycolytic rate. This value U he finds rather constantly negative for normal tissue, in the vicinity of zero for embryonic tissue, and strongly positive for carcinomata.

In man the lymph nodes are subject to various pathological processes including what, for lack of a better term, we may call the malignant lymphomata, a classification which is used in this paper to include lymphosarcoma, Hodgkin's disease, reticulum cell sarcoma and lymphatic leukemia. Pathologists are not entirely agreed as to the nature of these rather varied, but at the same time similar, pathological processes. Some regard them as neoplasms, others as infectious granulomata. Other pathologists again would class some types in one group, some in the other. In this paper we are placing Hodgkin's disease, as defined below, by itself for comparison with the other types of lymphomata.

As a part of a general investigation of this group of diseases it occurred to us that a study of the chemical metabolism of pathological lymph nodes might throw some light on their fundamental nature. The metabolic processes might, we hoped, afford evidence as to whether various types of malignant lymphomata were neoplastic or infectious in origin. This paper deals with the results of the investigation of normal and pathological lymph nodes and primary tumors not involving lymph nodes, from 71 patients, and is the first of a series of papers dealing with various aspects of malignant lymphomata.

Methods

As soon as received from surgical operation, the tissue was cut into thin sections, averaging 0.3 mm. in thickness, by a specially devised knife consisting of two safety razor blades held parallel, but slightly apart, in a suitable metal holder provided with adjustments for aligning the blades. All such sections were immediately immersed in sterile, normal horse serum, at room temperature, preparatory to their transfer to the metabolism chambers. Sterile cultures of the lymph nodes in this horse serum lived as long and as well as in the patient's own serum. Paraffine sections were made of all lymph nodes examined.

The metabolism was carried out in all instances in a modified Thünburg respiration apparatus. Briefly this consisted of two small vials connected one with another by means of a long, very fine capillary tube containing a kerosene drop to serve as a direct indicator of the oxygen consumption. The tissue to be metabolized was floated in buffered normal horse serum in an inner chamber. The moat about this inner chamber contained 2 per cent NaOH which served to absorb all

carbon dioxide formed. The anaerobic glycolysis was determined in a small vial containing horse serum saturated with pure nitrogen which had been passed over red hot copper to free it from traces of oxygen. The serum used in the anaerobic experiments was first subjected to a vacuum to rid it of air and subsequently saturated with pure nitrogen. This anaerobic chamber was attached to the stand supporting the Thünburg apparatus. The whole apparatus, aerobic and anaerobic alike, was immersed in a constant temperature water bath at 37.5°C. and kept agitated by a suitable motor. All apparatus coming in contact with the tissue was chemically clean. That the possible presence of bacteria did not affect the results was evident from several specially devised experiments and also from the constancy, from period to period, of the tissue metabolism, as evidenced by the oxygen consumption. Following each experiment the tissue was washed free of serum, dried at 100°C., and weighed. From 5 to 25 mg. tissue was used. All weights refer to dry tissue.

Oxygen consumption was read directly on a calibrated scale attached to the capillary. Readings were taken every 5 minutes. The results are expressed in c. mm. per mg. hour. Glycolysis, or more accurately, sugar destruction during the experimental period was determined by the familiar method of Folin (1929). The figures given in the text are those actually observed, except that in those tumors in which there was considerable connective tissue stroma a suitable allowance was made as this tissue has a metabolism entirely negligible compared to that of the more active cells composing the rest of the tumor. The amount of stroma present was carefully estimated by two independent observers from paraffine sections. The observed metabolic figures were then multiplied by the appropriate factors. In only 14 of the 71 cases was the amount of stroma increased sufficiently to warrant the application of a correctional factor.

Experimental Results

Normal Nodes.—Four normal nodes were examined. The average aerobic glycolysis was 0.020 mg., the average anaerobic glycolysis 0.054 mg., and the average oxygen consumption 5.7 c. mm. In this small series of cases there was a marked uniformity of the results. The average value U was 4.1, a figure entirely consistent with that found by Warburg for normal lymphoid tissue, but slightly higher than that found in most normal tissues elsewhere in the body which, as has already been stated, usually have a negative U. These figures can probably be taken as representative of the normal lymph node, and must be used as a determining value for further correlations.

Lymphoma.—Under this heading we here include lymphosarcoma, lymphatic leukemia, lymphocytoma, lymphoblastoma, and reticulum

cell sarcoma, but not Hodgkin's disease. There were studied metabolically nodes from 14 such cases. In contradistinction to the normal nodes there was found to be a marked variation in the different factors making up the metabolism in these pathological cases. The average aerobic glycolysis was 0.063 mg., over three times that found in the normal series. Three cases had an aerobic glycolysis above 0.083 mg., and all of these cases were rapidly fatal, while in two cases the rate fell below 0.035 mg., and these also were highly malignant from a clinical point of view. No correlation, therefore, could be found between degree of malignancy and the rate of aerobic glycolysis. The nodes from case S-29-662 and those from case S-29-1574 gave almost identical figures for aerobic glycolysis, yet the former case is alive and well a year and a half later, while the latter case died in a few months. The average anaerobic glycolysis was 0.092 mg. One, a case of rapidly advancing lymphosarcoma (S-29-236), showed the extremely high figure of 0.206 mg., while another, a case of lymphosarcoma involving the stomach (S-29-1585), had a low figure of 0.047 mg. Again, no correlation can be traced. The oxygen consumption averaged 5.5 c. mm. per mg. hour with such extreme variations as 0.7 and 12.6, yet there was no apparent relation between the metabolic rates and either the pathological or the clinical findings. The value U averaged 11.8, thus placing these tumors tentatively in the neoplastic class. But again extreme variations occurred, as witness case S-29-100 A, a rapidly advancing and rapidly fatal lymphoma with metastases to bone which had a U value of —1.7, and, on the other hand, S-29-236, a lymphosarcoma with a U of +47 and fatal in approximately the same time as the first case. Again case S-29-662 had a U value well above the general average for this class and well within the limits set by Warburg for malignancy, yet the case responded in a remarkable way to high voltage X-ray therapy and has remained well over a period of nearly 2 years.

Hodgkin's Disease.—Eighteen cases of typical Hodgkin's disease were studied. We class as Hodgkin's disease those nodes which show the typical multi-nucleated giant cells described by Dorothy Reed and by Sternberg. The tumor in some of the cases was very cellular, while in others it was sclerosed. The average aerobic glycolysis was 0.052 mg., slightly lower than the corresponding figure for all other types of lymphoma. There was a remarkable tendency for the figures to vary

about the average within narrow limits, the lowest being 0.030 mg. and the highest 0.067 mg. The average oxygen consumption was 5.8 c. mm. The anaerobic glycolytic rate was 0.074 mg., again slightly lower than that in the other lymphomata. The value U averaged 7.3, slightly above the corresponding value for normal nodes but definitely below that for tuberculous nodes which was 10.3. From this it might be inferred that Hodgkin's disease was infectious in nature, or at least not neoplastic, but it should be remembered that the lymphosarcoma S-29-100A had a value U of only —1.7, and another lymphosarcoma infiltrating the stomach and the parotid had a value of 3.4. On the other hand, a case of sclerosing Hodgkin's disease (S-29-1152), responding well to X-ray therapy, showed in the node a value U of 19.6, while another case, histologically similar and clinically rapidly fatal (S-29-1556) had a low value of 0.9. So it must be recognized that no very clear evidence is obtained as to the fundamental nature of the lesions from these data.

Tuberculosis.—Four cases of the cellular type of tuberculosis were studied. Necrotic or very fibrous nodes were excluded for obvious reasons. Here it was found that the average aerobic glycolysis was 0.055 mg., and the average anaerobic 0.090 mg. The oxygen consumption ran high, averaging 8.2 c. mm., while the U averaged 10.3. Nye and Parker (1930) have produced in animals lesions consisting of closely packed mononuclear cells identical with, or very similar to, those found in cellular tuberculosis. The lesion is particularly prominent and particularly pure in the lung, and examination of the involved lungs from these animals showed that they had an aerobic glycolysis of 0.05 mg. and anaerobic of 0.09 mg., a U of 15. The similarity between these figures and those of human tuberculosis is obvious, and the figures indicate that the type cell rather than the etiological agent or the fundamental nature of the disease is responsible for the character of the metabolism. If one attempts to classify tuberculosis on the basis of Warburg's figures one is forced to admit that here again is an obvious exception to his general rule; for the observed figures alone would indicate rather sharply that the process is neoplastic.

Carcinoma.—Thirteen cases of carcinomata involving lymph nodes were examined. Here again, as in the case of Hodgkin's disease, due allowance was made, when necessary, for the presence of large amounts of physiologically inactive connective tissue. The average aerobic

glycolysis was 0.088 mg., a figure far higher than any other tissue previously examined, but rates as low as 0.032 mg. (S-29-1042) were found in a slowly growing, highly differentiated epidermoid carcinoma. Five cases had an aerobic glycolysis above 0.100 mg., and 10 were above 0.060 mg. The average anaerobic rate was 0.142 mg., but varied considerably. With one exception, case S-29-1042 again, all were above 0.068 mg., and six cases yielded figures which were above 0.150 mg. Oxygen consumption was consistently low, averaging 4.1 c. mm. As was to be expected from Warburg's work, the value U was very high, averaging 24, well over twice that for lymphoma and entirely in confirmation of Warburg's findings. The highest U value was 40.4 in a rapidly growing, highly malignant epidermoid carcinoma (S-28-2468). There seemed, indeed, to be some general correspondence between the value U and the degree of malignancy. Thus, S-29-1049, S-28-168J, and S-28-2468 all had a U value above 35 and were all highly malignant, while S-28-2524 and S-29-1042 were relatively benign, slow growing tumors, and each had a value below 11. But the rule was by no means invariable. Roughly the same crude parallelism could be traced between malignancy and anaerobic glycolysis, though again there were certain exceptions.

Sarcoma.—In all, thirteen cases of sarcoma were studied. In most cases the tumors investigated were primary foci and not metastatic in lymph nodes. The metabolism was striking and interesting, in that all figures were low. The average aerobic glycolysis was 0.017 mg., with comparatively little variation except in S-29-1803, where the figure was 0.036 mg. The average anaerobic glucose destruction was 0.037 mg., again varying closely about the mean. The U value averaged only 4.9 and the oxygen consumption only 2.4 c. mm. It is be noted that all these figures are far below those of carcinoma. To be sure, S-28-1803 with a U of 12.6 comes into the malignant class, but the majority fell far short of it and yet they were all highly malignant tumors. S-29-2965, a melanotic sarcoma, had an anaerobic glycolytic rate of but 0.056 mg. with a U of but 7.4, yet it was one of the most rapidly growing tumors ever seen in this laboratory. The conclusion is obvious. Sarcomata do not appear to behave metabolically in the same manner as do carcinomata, and from their relatively low metabolic rates it is difficult to understand wherefrom they derive the great energy which must be required to favor their growth and

advance. If one figures, according to the method of Hawkins (1925) the energy requirements of a rapidly growing carcinoma such as S-29-1049, one finds that it produces anaerobically 0.093 calories per mg. dry weight per hour, aerobically 0.206 calories. The same calculations applied to such an extremely rapidly growing sarcoma as S-29-2965 show that anaerobically it produces but 0.020 calories and aerobically only 0.022 calories. Again the distinction, metabolically speaking, between carcinomata and sarcomata is obvious. They do not behave in the same manner. It should be noted, however, that even carcinoma itself does not appear in such experiments as these to expend much energy in growing. Aerobically the average energy output of these series of carcinomata was 0.033 calories per mg. hour, anaerobically 0.054 calories. The respective averages for sarcomata were 0.018 and 0.014 and for benign tumors 0.049 and 0.006.

Benign Tumors.—Three benign tumors were investigated. As was to be expected, their metabolism was low, the aerobic glycolysis being 0.010 mg., and the anaerobic 0.017 mg., and the U 3.9—figures, it should be noted, not far from those of the highly malignant sarcoma. Their oxygen consumption averaged 2.4 c. mm.

The degree of differentiation of various cells seemed rather definitely connected with the degree of difference between the aerobic and anaerobic glycolysis.

For instance, Cases 9, 19, 33, 38, and 40 were tumors (carcinoma, lymphoma, etc.) composed of undifferentiated cells, and their percentage difference was only 1 per cent, the highest being 8 per cent. On the contrary, Cases 1, 8, 11, 12, 15, 16, 21, 30, 37, 41, 42, and 78 were all tumors composed of well differentiated cells, and the average difference was 167 per cent. Case 12 (S-28-2431) constituted an exception in that it was a highly differentiated tumor (epidermoid carcinoma) with a split of only 11 per cent. No correspondence was found to exist between the oxygen consumption and the maturity of the cells, though Glover, Daland and Schmitz (1930) have found with white blood cells of both the myeloid and lymphoid series a definite increase of oxygen consumption with increasing maturity. This they found to hold true only when the cells were studied in whole blood but not when they were suspended in Ringer's solution. For various reasons they believed that whole blood gave more accurate information. Exceptions to this general rule (the greater the difference between

aerobic and anaerobic glycolysis the greater the degree of cell differentiation) occurred in almost all the sarcomas, as witness S-29-1913, a highly differentiated tumor with a split of 0, and S-28-2721, an undifferentiated cell tumor with a split of 127 per cent.

DISCUSSION

It was hoped that evidence might be thrown on the question as to whether the malignant lymphomata are of infectious or neoplastic origin from this study of the aerobic and anaerobic glycolysis and the oxygen consumption of 71 lymph nodes and tumors. Careful comparisons have been made between the microscopic pathology and the metabolism. The various metabolic rates were found to vary over so large a range that few generalizations can be made. There was, in general, a steady rise in both the aerobic and anaerobic glycolysis from the normal nodes through Hodgkin's disease, the lymphoblastomata and tuberculous nodes to carcinomata. The sarcomata and benign tumors had very much lower rates. Their glycolysis, indeed, is not even of the same order of magnitude as that of the carcinomata. Much overlapping existed, however, so that from the metabolism alone one can not infallibly predict in which class the tissue will fall. Some lymphomata, for instance, had metabolic rates greater than those of some cancers. The oxygen consumpton seemed to bear little or no relation to the pathological picture. It was rather consistently low in carcinoma and tended to be high in tuberculosis and some cases of Hodgkin's disease. The value U was over twice as high in the carcinomata as in any other pathological class, but here again overlapping existed to a considerable extent so that a diagnosis of neoplasm could not be made on this basis alone. The U value for sarcoma was definitely low, in no way approaching that of other malignant disease. The high metabolic rates found for tuberculous nodes indicated very clearly that the type of cell, rather than the nature of the underlying process, determined the character of the chemical changes. This fact was further borne out by the figures found for the rabbit lungs filled with mononuclears. Neither speed of growth nor degree of malignancy could be predicted from the glycolysis or oxygen consumption.

The metabolic processes in the sarcomata were of unusual interest. The figures of our thirteen cases approached those of benign tumors and were in no way similar to those of carcinomata. Yet some of these

sarcomata were extremely malignant and rapidly growing. The number studied is small and it is quite possible that further investigations will show that some human sarcomata have as high or even higher metabolic rates than do carcinomata of equal malignancy. Such is not our finding at present and further observations on sarcomata are in progress.

Such metabolic rates as are reported here represent the chemical activity of the tissue during a relatively brief period of tissue existence. They do not necessarily represent the requirements of growth. One of the essential characteristics of neoplastic tissues is their unlimited, chaotic and purposeless growth. To study the chemistry of growth rather than that of mere existence one must determine the metabolic rates of tissues over a long period of time in tissue cultures. This is being done as a continuance of the present study.

CONCLUSIONS

From a study of the metabolism of 71 lymph nodes and tumors one may conclude:

1. The nature of a tumor can not be predicted from the metabolism because too much overlapping of metabolic rates exists between the pathological groups.

2. There is no evidence metabolically one way or another as to whether malignant lymphomata of any type should be classed as neoplastic or as infectious processes.

3. The degree of cell differentiation can in most cases be foretold by the percentage difference between the aerobic and the anaerobic glycolysis. The greater the differentiation the greater the percentage difference. Sarcomata in general constitute an exception to this rule.

4. The degree of malignancy in carcinoma, but not in other tumors, can, with certain exceptions, be predicted from the height of the value U.

5. Human sarcomata appear to have a metabolism far more closely comparable to that of benign tumors than to that of carcinomata. They do not behave as malignant tumors under the Warburg classification. Their energy requirements are not of the same order as those of carcinoma.

6. One can not from the value U or from the glycolytic rates predict whether or not a tissue should be classed as neoplastic.

7. Warburg's findings for carcinomata are confirmed and amplified.

TABLE I

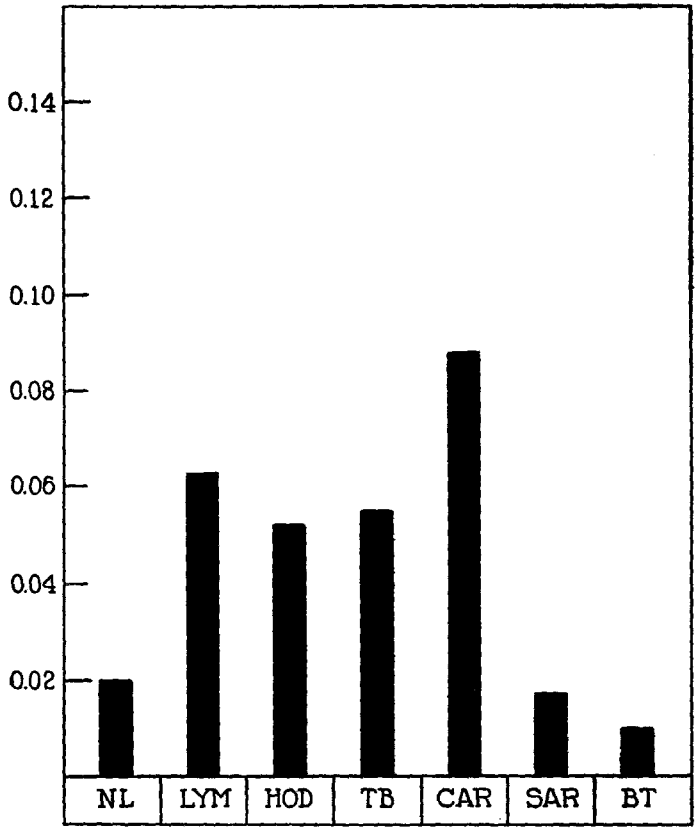
No.	Path. No.	Per cent active tissue	*Aerobic glycolysis	*Anaerobic glycolysis	†Oxygen consumption	"U"	Aerobic-anaerobic split per cent	Diagnosis
1	28-168J	50	0.116	0.172	3.2	36.6	48	Carcinoma
2	28-157R	100	0.071	0.117	6.4	16.4	65	Rabbit lung mononuclears
3	28-158R	100	0.050	0.106	5.2	16.1	110	" "
4	28-159R	100	0.051	0.100	5.1	15.0	96	" "
5	28-1686	100	0.034	0.037	2.0	4.5	9	Lymphoma
6	28-1804	100	0.066	0.082	4.4	11.7	24	Hodgkin's
7	28-2093	100	0.041	0.062	4.6	5.8	46	Hodgkin's
8	28-2347	100	0.009	0.014	1.0	2.5	56	Carcinoid
9	28-2348	100	0.069	0.069	5.0	7.5	0	Hodgkin's
10	28-2370	100	0.024	0.033	0.6	6.5	37	Normal node
11	28-2385	100	0.017	0.028	2.3	2.4	65	Arachnoidal fibroblastoma
12	28-2431	50	0.140	0.156	6.4	20.6	11	Carcinoma
13	28-2454	100	0.096	0.126	9.5	12.2	31	Tuberculosis
14	28-2467	100	0.055	0.082	1.8	17.9	51	Hodgkin's
15	28-2468	60	0.087	0.198	4.5	40.4	127	Carcinoma
16	28-2475	30	0.114	0.138	2.1	30.3	21	Carcinoma
17	28-2494	100	0.078	0.100	7.5	10.0	28	Hodgkin's
18	28-2516	100	0.040	0.069	4.4	8.4	73	Tuberculosis
19	28-2524	30	0.096	0.096	8.4	7.2	0	Carcinoma
20	28-2554	100	0.026	0.044	4.8	1.4	70	Endothelioma
21	28-2596	100	0.028	0.051	3.7	5.3	82	Normal nodes
22	28-2611	60	0.054	0.075	7.8	3.1	40	Reticulum cell sarcoma
23	28-2625	100	0.050	0.090	5.5	11.5	80	Hodgkin's
24	28-2665	100	0.067	0.096	6.4	11.2	43	Hodgkin's
25	28-2703	100	0.049	0.056	5.3	3.6	16	Hodgkin's
26	28-2707	100	0.019	0.040	2.1	5.8	110	Meningioma
27	28-2721	100	0.014	0.032	1.4	5.2	127	Sarcoma
28	28-2758	50	0.070	0.123	7.0	16.8	61	Carcinoma
29	28-2775	100	0.014	0.024	2.8	0.4	71	Fibrosarcoma
30	28-2795	100	0.056	0.078	5.1	9.3	39	Reticulum cell sarcoma
31	28-2917	75	0.076	0.082	3.7	13.6	8	Carcinoma
32	28-2931	100	0.077	0.106	6.8	11.7	35	Hodgkin's
33	28-3075	100	0.019	0.042	2.4	5.7	121	Normal node

* Expressed in mg. per 10 mg. dry weight per hour.

† " " c. mm. per mg. dry weight per hour.

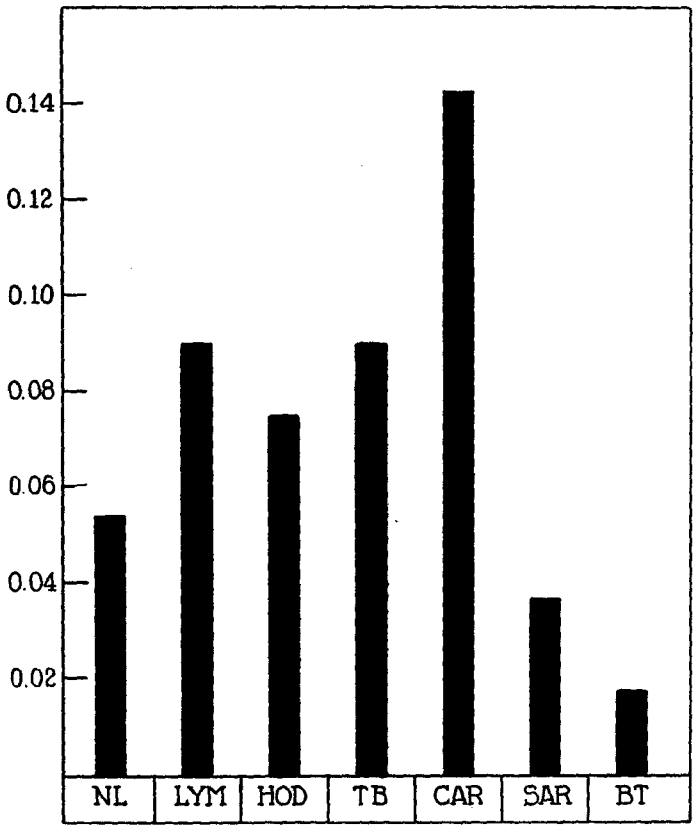
TABLE I—*Concluded*

No.	Path. No.	Per cent active tissue	*Aerobic glycolysis	*Anaerobic glycolysis	†Oxygen consumption	"U"	Aerobic-anaerobic split per cent	Diagnosis
34	29-100A	100	0.090	0.093	12.5	−1.7	3	Lymphoma
35	29-236	100	0.083	0.206	1.8	47.9	149	Lymphoma
36	29-266	20	0.115	0.115	4.5	17.8	0	Carcinoma
37	29-365	100	0.059	0.075	2.5	13.8	27	Lymphoma
38	29-399	100	0.044	0.045	0.7	9.8	2	Lymphoma
39	29-585	100	0.022	0.095	1.6	20.5	330	Lymphoma
40	29-628	100	0.001	0.012	4.4	−8.5	1000	Glioma
41	29-639	100	0.010	0.090	11.8	−1.1	800	Normal node
42	29-640	100	0.030	0.054	4.7	4.1	64	Hodgkin's
43	29-662	100	0.077	0.136	8.6	16.8	77	Lymphoma
44	29-1027	100	0.019	0.074	4.0	10.5	290	Tuberculosis
45	29-1042	75	0.032	0.048	2.0	10.0	50	Carcinoma
46	29-1049	50	0.150	0.250	29.5	35.5	67	Carcinoma
47	29-1152	100	0.047	0.100	2.7	19.6	112	Hodgkin's
48	29-1279	100	0.100	0.100	6.4	12.2	0	Lymphoma
49	29-1556	100	0.025	0.031	3.4	0.9	32	Hodgkin's
50	29-1574	100	0.071	0.071	6.4	4.9	0	Lymphoma
51	29-1585	100	0.047	0.047	4.8	3.4	0	Lymphoma
52	29-1754	100	0.068	0.079	9.7	0.3	14	Hodgkin's
53	29-1778	100	0.059	0.105	2.3	20.9	78	Carcinoma
54	29-1802	100	0.047	0.057	4.3	5.6	21	Hodgkin's
55	27-1803	100	0.036	0.077	3.3	12.6	114	Fibrosarcoma
56	29-1834	100	0.043	0.068	8.9	−0.9	58	Hodgkin's
57	29-1913	100	0.016	0.016	1.2	2.9	0	Fibrosarcoma
58	29-2066	33	0.042	0.168	3.9	34.2	300	Carcinoma
59	29-2309	20	0.050	0.200	10.0	30.0	300	Carcinoma
60	29-2368	100	0.032	0.067	5.3	6.1	110	Hodgkin's
61	29-2636	100	0.041	0.054	4.9	1.6	32	Hodgkin's
62	29-2651	100	0.046	0.065	6.5	3.3	41	Hodgkin's
63	29-J-1	100	0.014	0.024	1.9	2.2	41	Osteogenic sarcoma
64	29-J-2	100	0.010	0.015	0.8	2.1	50	Sarcoma
65	29-2866	100	0.030	0.060	2.3	10.4	100	Fibrosarcoma
66	29-2965	100	0.024	0.056	3.3	7.4	133	Melanotic sarcoma
67	30-396	100	0.018	0.060	3.9	7.2	232	Myxofibrosarcoma
68	30-600	100	0.062	0.120	10.4	9.2	94	Lymphoma
69	30-682	100	0.011	0.027	1.2	4.3	60	Fibrosarcoma
70	30-768	100	0.061	0.108	12.6	30.0	77	Lymphoma
71	29-664	50	0.012	0.046	9.6	−7.7	28	Melanotic sarcoma



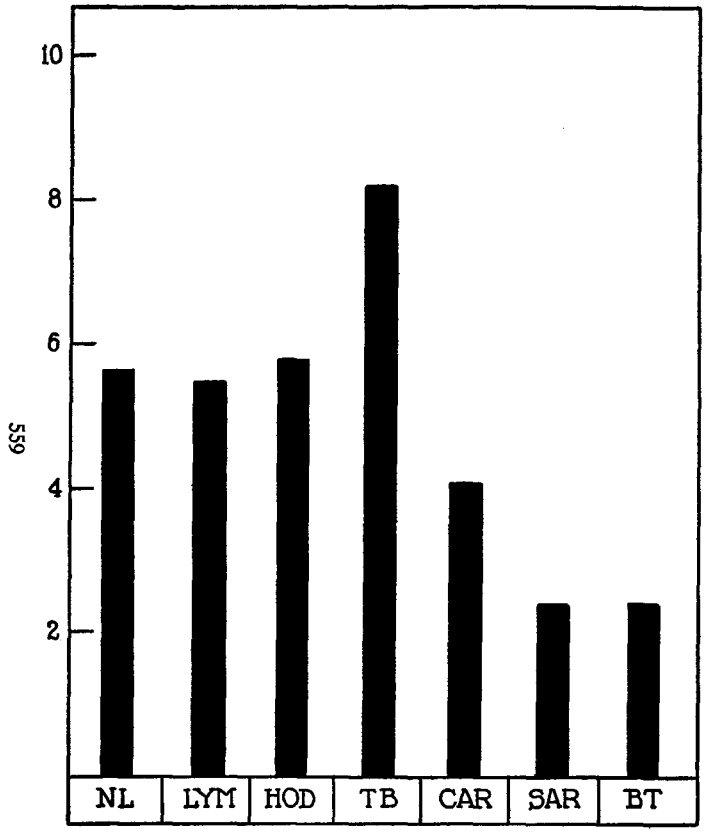
Aerobic glycolysis mg. per mg. hour

CHART 1



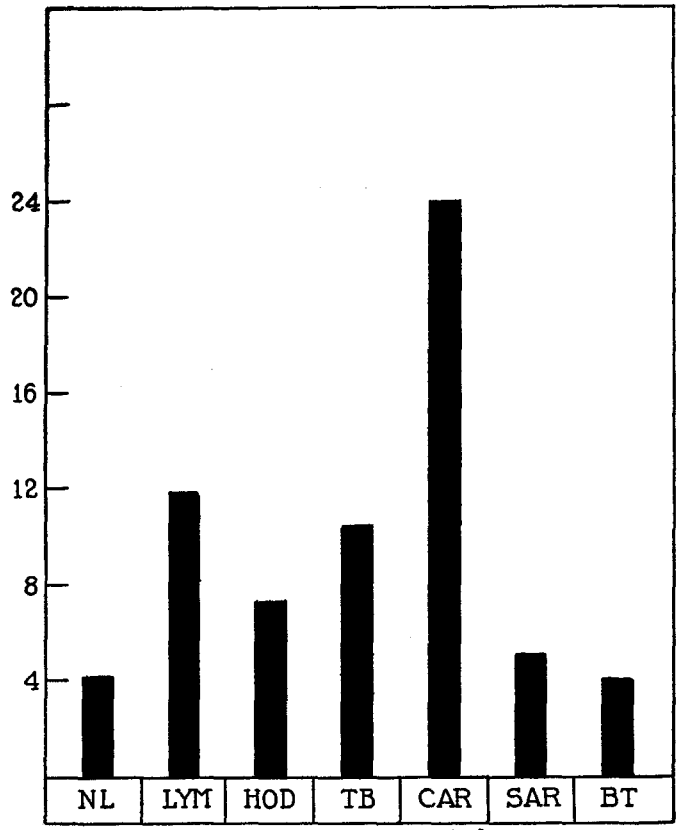
Anaerobic glycolysis mg. per mg. hour

CHART 2



Oxygen consumption c.mm. per mg. hour

CHART 3



Warburg's value 'U'

CHART 4

BIBLIOGRAPHY

1. Folin, O., *J. Biol. Chem.*, 1929, **82,** 83.
2. Glover, Daland, and Schmitz, *Arch. Int. Med.*, 1930, **46,** 46.
3. Hawkins, J. A., *J. Gen. Physiol.*, 1925, **9,** 771.
4. Jackson, H., Jr., *New England J. Med.*, 1929, **201,** 294.
5. Murphy, J. B., and Hawkins, J. A., *J. Gen. Physiol.*, 1925, **8,** 115.
6. Nye, R. N., and Parker, F., Jr., *Am. J. Path.*, 1930, **6,** 381.
7. Rona and Deutsch, *Klin. Wochenschr.*, 1926, **5,** 1216.
8. Warburg, Posener, and Negelein, *Biochem. Zeitschr.*, 1924, **152,** 309.
9. Warburg, O., *Klin. Wochenschr.*, 1925, **4,** 12.
10. Warburg O., *Biochem. Zeitschr.*, 1927, **184,** 484.