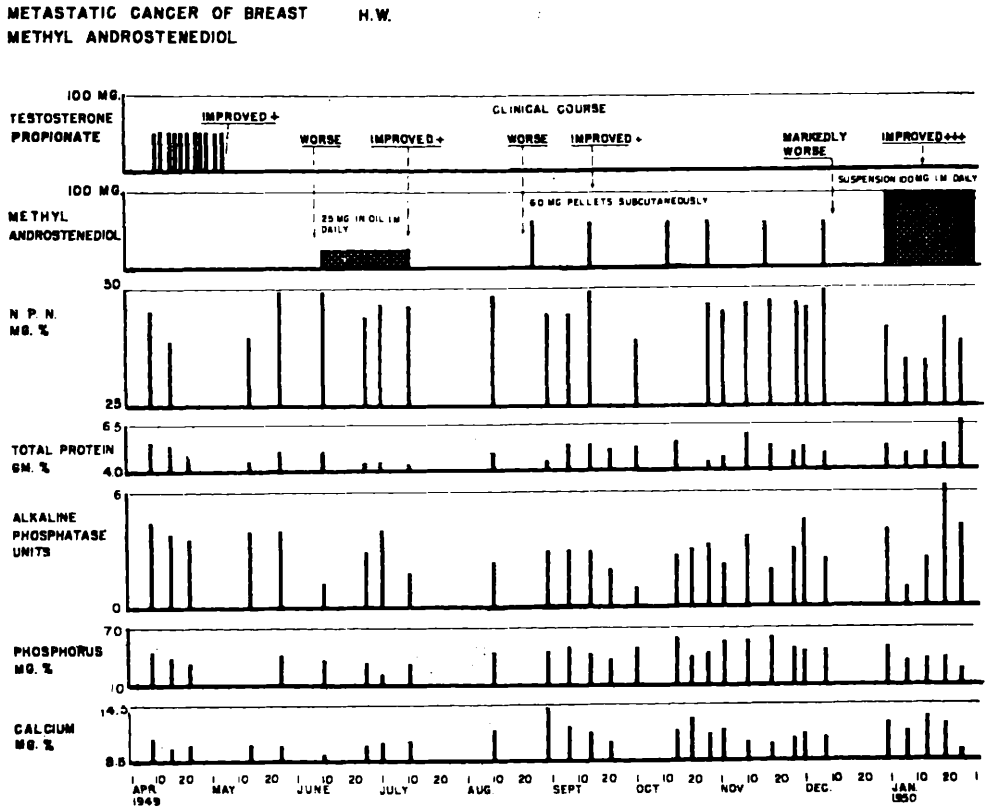

FIG. 4.
Chart of blood chemistry change as related to therapy and clinical changes. Patient H. W.

methylandrostenediol is a non-virilizing steroid hormone with moderate protein anabolic effect, and that it causes subjective well-being in patients with cancer of the breast. It did not bring about in our experience any of the undesirable biochemical phenomena such as water retention or hypercalcemia which often occur with testosterone. In at least 3 out of 7 cases of breast cancer objective regression of soft tissue and bone lesions was observed.

These brief clinical experiences do not justify conclusions as to the exact therapeutic value of this drug. However, they indicate the need for further critical evaluation on a larger scale.

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Alkaline Phosphatase Activity of Human Serum in Cancer.* (17841)

ADOLPH BERNHARD AND LOUIS ROSENBLOOM.
From the Achelis Laboratory of the Lenox Hill Hospital, New York City.

Elevated serum alkaline phosphatase values are generally accepted as indicating either bone disease(1) or liver damage(2-4). The role alkaline phosphatases play in uncontrolled growth has been postulated by Potter (5,6). Potter and Liebel(7) have shown

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TABLE I.
Statistical Analysis of Alkaline Phosphatase Activity of Human Serum. All values in mg %.

Substrate used	No. of patients	Range	Mean	Stand. Dev.
Adenosinetriphosphate				
(1) Normals	17	.5-3.1	2.2	.7
(2) Non-malignant	81	.1-6.4	2.2	1.2
(3) Cancer	51	1.2-21.0	6.2	5.7
(4) After removal of malignant tumor	28	.8-3.5	2.4	1.0
Yeast adenylic acid				
(1) Normals	52	.9-2.9	1.9	.5
(2) Non-malignant	161	.5-19.5	2.6	2.3
(3) Cancer	106	1.4-21.6	5.4	4.3
(4) After removal of malignant tumor	28	.9-3.5	2.4	.5
β-glycerolphosphate				
(1) Normals	24	1.4-3.7	2.3	.7
(2) Non-malignant	37	1.2-15.5	3.4	2.9
(3) Cancer	37	2.0-20.5	5.8	4.2
(4) After removal of malignant tumor	14	.7-3.4	2.5	.7

that in cancer tissue there exists, in high concentration, an enzyme capable of hydrolyzing ATP. Meister(8,9) reported that serum adenosinetriphosphatase hydrolyzes ATP with a maximum activity at pH 8.9. The enzyme is accelerated in liver disease and in patients with bony metastasis from prostatic carcinoma. We have found that similar dephosphorylation occurs with yeast adenylic acid and β-glycerolphosphate, and have studied the serum phosphatase activity using these substrates, in normal, in non-cancerous, and in individuals with neoplastic malignant disease.

Methods and materials. Substrates were adenosinetriphosphate, (*Tetra Sodium Salt* of ATP, Rohm and Haas, Phila., Pa.), yeast adenylic acid (Schwartz Laboratories, N. Y.), and β-glycerolphosphate (Eastman Kodak Company, Rochester, N. Y.), each in a concentration of 3.38 micromols per 2.5 ml of veronal-HCl buffer pH 8.9. This concentration gave optimum activity under our experimental conditions.

Procedure. 0.5 ml of non-hemolyzed serum is pipetted into each of 2 tubes. As a control one of these tubes is inactivated at 57°C for ½ hour. The control, the non-inactivated serum and the buffered substrate are brought to 37°C. 2.5 ml of substrate is added to each tube, the contents mixed, stoppered and incubated at 37°C for 2 hours. The inorganic phosphorus is determined by the method of Fiske and Subbarow(10). When ATP was used all determinations were made simultaneously to obviate errors due to spontaneous hydrolysis(11). Preliminary studies showed that dephosphorylation of the various substrates was proportional to the amount of serum used, and to the incubation period. The enzyme activity of the serum was not affected by refrigeration. Variations in the amount of phosphorus released in 2 hours were sufficiently great to establish a difference in enzyme activity between cancerous and non-cancerous individuals. The amount of phosphorus release selected as indicative of a significant increase in phosphatase activity for each of the substrates employed, (this value will be referred to as the S.I.)

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TABLE II.
Distribution of Patients with Malignant Tumors According to the Significant Increase.

Substrate used	Site of tumor	No. of cases	Significant above	Increase below
Adenosinetriphosphate	Liver and pancreas	6	6	0
	♂ G.U. System	6	6	0
	♀ " "	5	4	1
	Gastro-Intestinal Tract	17	8	9
	Breast	4	2	2
	Lung	5	2	3
	Misc.	8	5	3
Yeast Adenylic Acid	Liver and Pancreas	14	14	0
	♂ G.U. System	11	8	3
	♀ " "	8	6	2
	Gastro-Intestinal Tract	40	28	12
	Breast	11	9	2
	Lung	11	6	5
	Misc.	11	7	4
β-glycerolphosphate	Liver and Pancreas	4	4	0
	♂ G.U. System	5	3	2
	♀ " "	6	4	2
	Gastro-Intestinal Tract	11	8	3
	Breast	5	4	1
	Lung	1	1	0
	Misc.	5	5	0

was the mean plus twice the standard deviation of the normal group. The normals consisted of healthy laboratory workers, nurses and internes.

Results. In Table I, the results of our studies of phosphorus release in 2 hours using ATP, yeast adenylic acid and β-glycerolphosphate as substrates are recorded. With ATP the S.I. was found to be 3.6 mg%, 90 of 98 patients known to be free from neoplastic malignant disease had values below this figure. Of the 28 patients in whom the phosphatase was determined after removal of a malignant tumor only 2 showed a greater release than 3.6 mg%. Using yeast adenylic acid, the S.I. was found to be 2.9 mg%, and in 181 out of 213 non-cancerous subjects the value was below this figure. After removal of a malignant tumor, only 2 out of 28 patients showed a value greater than 2.9 mg%. Using β-glycerolphosphate substrate, the S.I. was 3.7 mg%. 54 of 61 of the non-cancerous subjects had a value below this figure. All of the 14 patients whose phosphatase was determined after removal of a malignant tumor showed a normal response. In individuals with some form of neoplastic malignant disease, the phosphatase was determined before surgical intervention or other treatment was instituted and the diagnosis was confirmed by biopsy or post mortem examination. These data are presented in Table II, and are classified according to the site of the tumor and whether the phosphatase activity is above or below the S.I.

Discussion. The sera of normal, the vast majority of non-cancerous individuals, and all cases of pregnancy showed a normal dephosphorylation. The main exceptions were those with diseases of the liver and pancreas, (the majority of whom were jaundiced) and those with endocrine disturbances, particularly thyroid disease. The S.I. of the cancer group was not influenced by the age or sex of the individual, nor by the site, type or degree of the malignancy. The greatest phosphorus release was found in those with tumors of the liver and pancreas, most of whom were jaundiced and those with malignancies of the genito-urinary system. In those with carcinomas of the gastro-intestinal tract showing normal phosphatase activity, the majority involved malignancy of the recto-sigmoid. In contrast over 92% of all the patients from whom a malignant tumor had been previously removed and were symptom free, the dephosphorylation of the various substrates was within normal limits. If all cases of known jaundice are excluded from our results, the same relationship between cancerous and

non-cancerous individuals still holds true. The p value, as calculated by the statistical method of Fisher(12), of the normal, of the non-cancerous, and of patients after removal of a malignant tumor showed no difference, but was statistically significant when compared with that of the cancer group.

No specific reaction for adenosinetriphosphatase could be demonstrated. Yeast adenylic acid substrate gave the most consistent results, it is a stable compound, not subject to spontaneous hydrolysis in acid solutions and has a much lower S.I. than that of the other substrates. These factors might be of some value in the differential diagnosis of neoplastic malignant disease. Under our experimental conditions the dephosphorylation of the β-glycerolphosphate was lower than in the usual Bodansky procedure(13). No specificity or differentiation of serum alkaline phosphatase could be established, since the same serum gave similar dephosphorylation regardless of the substrate employed. The relationship of phosphorus release between cancerous and non-cancerous individuals was not influenced by substrate used.

Summary. The sera of normal and non-cancerous individuals have the same magnitude of dephosphorylation. In patients having a malignant tumor, phosphorus release of the serum was generally higher than the normal and non-cancerous group. The highest values were found in patients with tumors of the liver, pancreas and genito-urinary system. The sera of patients from whom a malignant tumor had been previously removed showed a phosphorus release which was identical with the normal and non-cancerous group.

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Histamine as Possible Chemical Mediator for Cutaneous Pain. Dual Pain Response to Histamine. (17842)

SOL ROY ROSENTHAL.

From the Institution for Tuberculosis Research, University of Illinois College of Medicine, and Research Foundation, Chicago, Ill.

This is the eighth in a series of studies that support the theory of histamine or a histamine-like substance as the chemical mediator for cutaneous pain, be it direct or referred(1-7). It has been demonstrated(7) that as little as 54 molecules of histamine (0.01 ml of 10^{-18} base) introduced into the superficial layers of the skin will cause painful responses, and that the intensity of the response is directly proportional to the concentration of histamine. The sensations considered previously were of the latent type only. In the present study both the immediate and latent responses to histamine in human subjects are considered.

Methods. Care of materiel. Scrupulous care was taken in the cleaning of the glassware, needles, etc. All glassware was cleaned in sulphuric acid potassium dichromate solution. The needles were placed in running water for 4 to 6 hours and then rinsed by forcing 10 cc of distilled water through them. After sterilization and before use, needles

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