We have observed that the serum proteins of patients with advanced prostatic cancer rapidly return to or toward normal values following deactivation of the neoplasm by anti-androgenic procedures. While there exists a variety of methods, more or less satisfactory, for observing these changes, perhaps none is so simple or so useful as the determination of the lowest percentage of blood serum to gel after heating under standard conditions. The use of this assay method is the subject of the present paper.

One of the central problems in the chemotherapy of cancer is to obtain methods of measuring neoplastic activity and the effects of medicines thereon, with precision and sensitivity, preferably with simplicity. Advanced prostatic carcinoma of man is peculiarly adaptable for quantitative studies of activity and, conversely, partial or complete inactivation of the tumor by therapeutic agents. In the past this neoplastic activity could be measured by two modalities which reflected local events in and near the carcinoma. When this neoplasm has metastasized, the level of acid phosphatase in serum is often increased. A common site of metastasis of this tumor is bone marrow, a tissue wherein the neoplasm thrives and usually stimulates the growth of osteoblasts, which process in turn results in an elevation of alkaline phosphatase in the serum. When one investigates these enzymatic levels in the blood concurrently over a period of days, he measures the relative production of acid phosphatase by the metastases (an activity of the cancer) and the response of adjacent nonmalignant bone tissue to the presence of that tumor (local reactivity of normal host cells). Unlike these measurements of essentially local changes, albeit occurring in many places, a determination of the least percentage of thermocoagulable protein reflects the over-all state of certain plasma proteins, especially albumin, and hence is an indicator of the efficiency of general physiologic mechanisms and balances.

It has been shown that the transformation of serum under the influence of heat to form a cohesive jelly depends largely, if not exclusively, on its content of serum albumin. Changes in serum albumin frequently occur in patients with cancer, but unfortunately no method exists whereby the quantity of albumin in serum may be determined with precision. The simple determination of the quantity of albumin present does not completely characterize this protein, because albumin possesses the property of binding anions to itself, a peculiarity only shared by certain rare \( \gamma \)-globulins among the serum proteins. Both the quantity of protein and certain associated anions such as deoxyribonucleate affect the thermocoagulability of albumins.

The determination of the lowest thermocoagulable percentage of serum is a simple and highly reproducible physical method of investigation of serum proteins. Its determination yields a primary value. The implications of the results from the standpoint of physical chemistry are complex. In our experience with clinical patients a decrease in the least coagulable percentage of serum always means an improved physiologic state, while a higher percentage always implies deterioration. Its determination is one objective way of measuring general damage or freedom therefrom, but it is unspecific with respect to the nature of the damaging agency.

METHODS

Nineteen patients with untreated cancer of the prostate in this series were classified in two categories: (a) early cancer was defined as small nodular carcinomas confined to the anatomical limits of the prostatic gland; (b) advanced cancer included all cases with metastases or appreciable extension outside of the site of origin.

The following determinations were made on the blood serum of the patients: total protein by the
micro-Kjeldahl technic of Ma and Zuazaga (11); albumin after precipitation of globulins with 28 per cent sodium sulfate by use of the Weichselbaum (18) modification of the Howe (5) method; acid and alkaline phosphatases by the method of King and Armstrong (10); anion binding of serum with the equilibrium dialysis of phenolsulfonephthalein (8); and least coagulable percentage of serum (6).

The upper limit of values derived from examination of the sera of more than 500 normal adults in this laboratory are for acid phosphatase, 4.5 King and Armstrong units per 100 milliliters of serum; for alkaline phosphatase, 11 units; least coagulable percentage of serum, 20 per cent.

In certain cases diethylstilbestrol was administered intramuscularly in solution in sesame oil; orchietomy was done under local anesthesia.

OBSERVATIONS

Serum—least coagulable percentage and level of phosphatases.—The results are summarized in Table 1. There were twelve cases in this series (63 per cent) with elevated values for thermal coagulation percentage; of the seven men with normal coagulable percentage, one patient had elevated phosphatases. There were six cases in the series (32 per cent) with elevated phosphatase levels, one of whom had normal coagulation values. Thus, five patients had both elevated phosphatase and coagulation findings; four cases of advanced prostatic cancer had both normal phosphatase and coagulation values.

The data show that elevated coagulation percentage values of serum are more common in cancer of the prostate than elevation of acid and alkaline phosphatases.

The effect of orchietomy on the least coagulable percentage of serum.—Bilateral orchietomy was performed 10 times in patients with elevated coagulation values. Without exception there was a decrease in coagulation percentage within 2–5 days; a typical example is shown in Chart 1. The changes in the coagulation percentage were usually spectacular and were evident at an earlier period than significant changes in total protein or albumin content.

The effect of diethylstilbestrol on least coagulable percentage and phosphatases of serum.—This estrogen was administered intramuscularly to five pa-

### Table 1

<table>
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<th>Acid and Alkaline Phosphatases and Least Coagulable Percentage of Serum in 19 Untreated Cases of Cancer of the Prostate</th>
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<td>Acid and Alkaline Phosphatases</td>
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The effect of diethylstilbestrol on least coagulable percentage and phosphatases of serum.—This estrogen was administered intramuscularly to five pa-

The clinical condition of this patient with prostatic cancer was greatly improved by the anti-androgenic therapy, and the amelioration was reflected in the increase of anion binding and the decrease of the coagulation percentage; no striking change however occurred in the acid phosphatase level.

In 4 cases the least coagulable percentage of serum decreased (Chart 2), although less rapidly than after orchietomy, the first improvement being observed after 8–10 days of treatment. In one case (Chart 3), stilbestrol induced massive retention of water with anasarca; although the activity of the cancer was inhibited, as was shown by the serum phosphatases, the clinical condition
Changes in nonenzymatic plasma proteins are more common in advanced prostatic cancer than are elevations of acid or alkaline phosphatases. These changes were observed simply and accurately by determining the least thermocoagulable percentage of serum. An increased percentage always indicated deterioration of physiologic mechanisms, and a decreased percentage reflected improvement. Usually following anti-androgenic control of the cancer, the least coagulable percentage of serum returns rapidly toward normal values.

Orchiectomy induces changes in nonenzymatic proteins of the serum more rapidly in cancer of the prostate than the administration of estrogen. The minimal effective dosage of diethylstilbestrol in human prostatic carcinoma, therefore, is in the vicinity of 0.25 mg. when injected intramuscularly each day. Increasing the dose level to 5 mg. daily did not increase the therapeutic efficiency of this estrogen.

DISCUSSION

In a series of patients with gastric cancer subjected to a removal of the tumor, it was found (4, 12) that the abnormal a-globulin and fibrinogen values returned to normal within a few weeks after the surgical operation, while an increase of serum albumin was extremely slow even in patients maintained in positive nitrogen balance. By contrast in the present series of patients with advanced prostatic cancer, the least coagulable percentage of serum improved within a few days after anti-androgenic control.

CONCLUSIONS

Changes in nonenzymatic plasma proteins are more common in advanced prostatic cancer than are elevations of acid or alkaline phosphatases. These changes were observed simply and accurately by determining the least thermocoagulable percentage of serum. An increased percentage always indicated deterioration of physiologic mechanisms, and a decreased percentage reflected improvement. Usually following anti-androgenic control of the cancer, the least coagulable percentage of serum returns rapidly toward normal values.

Orchiectomy induces changes in nonenzymatic proteins of the serum more rapidly in cancer of the prostate than the administration of estrogen. The minimal effective dosage of diethylstilbestrol in human prostatic cancer is close to 0.25 mg. daily when this medicine is administered intramuscularly; increasing the dosage to 5 mg. daily did not enhance the effect of this estrogenic substance.

REFERENCES

3. Gutman, A. B., and Gutman, E. B. An "Acid" Phosphatase Occurring in the Serum of Patients with Metastasizing
4. HOMBURGER, F., and YOUNG, N. F. Studies on Hypopro-
  teinemia. I. Hypoproteinemia in Patients with Gastric
  Cancer; Its Persistence after Operation in the Presence
5. HOWE, P. E. The Use of Sodium Sulfate as the Globulin
  Precipitant in the Determination of Proteins in Blood.
6. HUGGINS, C.; CLEVELAND, A. S.; and JENSEN, E. V. Ther-
  mal Coagulation of Serum in Diagnosis. J.A.M.A., 143:
7. HUGGINS, C., and HODGES, C. V. Studies on Prostatic
  Cancer. I. The Effect of Castration, of Estrogen and of
  Androgen Injection on Serum Phosphatases in Metastatic
  Carcinoma of the Prostate. Cancer Research, 1:293—97,
  1941.
8. HUGGINS, C.; JENSEN, E. V.; PLAYER, M. A.; and HOPP-
  EKORN, V. D. The Binding of Phenolsulfonephthalein by
  Serum and by Albumin Isolated from Serum in Cancer.
9. KAY, H. D. Plasma Phosphatase in Osteitis Deformans
  and in Other Diseases of Bone. Brit. J. Exper. Path., 10:
  255—60, 1929.
10. KING, E. J., and ARMSTRONG, A. R. Convenient Method for
    Determining Serum and Bile Phosphatase Activity.
11. MA, T. S., and ZuZAGA, G. Micro-Kjeldahl Determina-
    tion of Nitrogen: A New Indicator and an Improved Rapid
12. PETERMANN, M. L., and HUGGINS, K. R. Electrophoretic
    Studies on the Plasma Proteins of Patients with Neo-
   plastic Disease. I. Gastric Cancer. Cancer, 1:100—105,
    1948.
13. WEISCHERBAUM, T. E. An Accurate and Rapid Method
    for the Determination of Proteins in Small Amounts of
    1948.
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