THE SIGNIFICANCE OF THE BLOOD ACID AND ALKALINE PHOSPHATASE VALUES IN CANCER OF THE PROSTATE

BY

STANLEY WRAY

From the Department of Pathology, General Hospital, Middlesbrough

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The present series of observations is based on 500 miscellaneous cases of which 407 had prostatic lesions and the remaining 93 other conditions not related to the prostate. The ages of the patients varied from 21 to 95, but the majority were between 61 and 80 years of age (Table I).

TABLE I
PATIENTS INCLUDED IN THIS INVESTIGATION

Site of Lesion		Age Distribution	
Organ	No. of Patients	Age	No. of Patients
Prostate	407	21-45	17
Lungs	24	46-55	53
Bone (excluding prostatic secondary)	21	56-60	48
Stomach	20	61-65	81
Bladder	7	66-70	108
Diabetic	6	71-75	115
Liver	5	76-80	53
Central nervous system	4	81-85	20
Brain	3	86-95	5
Cerebrovascular system	3		
Total	500	Total	500

The purpose of this investigation was twofold: first to re-evaluate the clinical usefulness of the total plasma acid phosphatase and its formaldehyde stable fraction, and secondly to correlate serial laboratory findings, in particular the plasma alkaline phosphatase, with the clinical manifestations.

Acid Phosphatase

On each of the 500 patients the total plasma acid phosphatase and its formaldehyde stable fraction were estimated, the latter by the method described by Abul Fadl and King (1948), with results as shown in Table II. In this the unit values to the left of the centre dark line are within the normal range whilst those on the right are in the "doubtful" or "prostatic cancer" groups. It will be seen from the lower part of section A that,

with the estimation of the total value in those cases without prostatic cancer, 14 gave misleadingly raised results, but by estimating its formaldehyde stable fraction as shown in section B this figure became 8. These findings suggest that the latter test is a more reliable clinical guide in the investigation of "prostatic" conditions, as claimed by Abul Fadl and King (1948).

The eight patients who had a raised formaldehyde stable fraction were further investigated and urinary retention was found to have been present in all when the first estimation was made. It will be seen from section C that, when this test was repeated following relief of the retention, its value fell to normal in all but one case. This patient had carcinoma of the bladder infiltrating the prostate and periprostatic tissue and was differentiated from prostatic cancer on both clinical and histological examination

Thus, when the formaldehyde stable fraction of the acid phosphatase was estimated on blood taken after urinary retention had been relieved and

TABLE II
PLASMA ACID PHOSPHATASE (K.-A. UNITS PER 100 ML.)
IN 500 CASES

Plasma Phosphatase Test	Total	Units 0-5	Range (Units)
A. Total acid			5-1 upwards
Prostatic cancer	73 cases	28 cases	45 cases
Simple prostate and other conditions	427 ..	413 ..	14 cases
B. Formaldehyde stable fraction retention not excluded		Units 0-3	3-1 upwards
Prostatic cancer	73 ..	29 cases	44 cases
Simple prostate and other conditions	427 ..	419 ..	8 cases
C. Formaldehyde stable fraction retention excluded		Units 0-3	
Prostatic cancer	73 ..	30 cases	43 ..
Simple prostate and other conditions	427 ..	426 ..	1 case

after the exclusion on clinical grounds of other conditions already known to interfere with these findings (Woodard, 1952 ; Hock and Tessier, 1949 ; Huggins, Scott, and Hodges, 1941), no false results were obtained in the present series. The relief of the urinary retention before this test would seem to be a particularly important precaution because of its likely presence with prostatic lesions.

A further observation, in keeping with previously published work (Merivale, 1951), is that of the 73 patients who were known or later proved to have cancer of the prostate only 43, or 59%, gave a significantly raised acid phosphatase value when first seen. The normal findings were usually due to the absence of spread of the malignant process, but in at least four cases (5.5%) the malignant process had spread and it is possible that the normal value was the result of the presence of an excess of a thermo-labile acid phosphatase inhibitor which has recently been shown to be present in some instances (Hudson, 1954).

FIG. 1.—Alkaline phosphatase response following stilboestrol therapy in patient aged 69 with prostatic cancer with bone secondaries where the initial value was normal.

FIG. 2.—Alkaline phosphatase response following stilboestrol therapy in a patient aged 66 with prostatic cancer with bone secondaries where the initial value was raised. This shows the depression in the blood alkaline phosphatase occurring during the first week or ten days of therapy before the increased results are obtained.

Alkaline Phosphatase

The next consideration is that of the significance of a raised blood alkaline phosphatase level. As an initial test its value is of limited worth. Of 37 cases which had bone secondaries radiologically only 22, or 60%, gave a value greater than 15 King-Armstrong units. But when this investigation was made at weekly intervals on cases of prostatic cancer which were improving on stilboestrol therapy, a very definite pattern of response was obtained. This took one of two forms. In those cases where the plasma alkaline phosphatase value had been normal initially a rise started immediately after stilboestrol therapy began. After the peak the value fell to normal more slowly (Fig. 1). In those cases where the alkaline phosphatase was markedly raised to start with there was an initial fall in its value coincident with the start of stilboestrol therapy, but after a few days this downward trend reversed and the subsequent increase went beyond its initial value to attain a peak within 30 to 40 days followed by a gradual fall as in the former case (Fig. 2). Both these patterns of response have been shown to be constant in

cases of cancer of the prostate with bone secondaries when these are rapidly degenerating. This response has been called the alkaline phosphatase "kick" and has been shown to be present in 95% of such cases. This response was not seen in a control series of 20 patients who had bone secondaries from non-prostatic malignant tumours and in 10 cases of Paget's disease, although there were some atypical changes in some of the latter which are being further investigated.

It is suggested that this response or alkaline phosphatase "kick" is the result of an interaction of two opposing vital processes. On the one hand, due to the presence of osseous deposits, bone regeneration becomes more marked and the plasma alkaline phosphatase concentration tends to increase. On the other hand, from the results obtained it would seem that the secondary deposits of prostatic cancer may themselves be producing a substance which depresses the bone regenerative activity and thus tends in turn to depress the alkaline phosphatase. If this depressant factor is produced by, or stored in, the prostatic cancer cells, a sudden flood of it would be liberated when these cells are ruptured and one would then expect the alkaline phosphatase level to be rapidly, though temporarily, decreased. Similarly it is suggested that when this cell dissolution ceases the bone regenerative activity, which was formally held in check by the depressant factor from the cancer cells, now reacts vigorously and causes the marked plasma alkaline phosphatase elevation observed. As the process of healing runs its course the rate of bone reaction subsides and so does the alkaline phosphatase value.

At this stage a not dissimilar phenomenon should be mentioned, that of the depressant action on the haemoglobin coincident with the presence of prostatic cancer metastases. When the haemoglobin level is estimated at regular intervals in a case of prostatic cancer with bone secondaries which are responding to hormone therapy, it is found that in some cases the value falls rapidly before and during the first week or two of therapy and thereafter rises dramatically, whether or not anti-anaemic therapy is given (Wray, 1945). Correlating the haemoglobin with the alkaline phosphatase value, it was seen that the reversal of the trend in the haemoglobin coincided approximately with the peak of the alkaline phosphatase "kick." It is possible that there is some link between the two and that the same or a similar factor which is causing depression of bone regeneration may also be causing depression of the haemopoietic function of the bone marrow.

In order to test the clinical implications of these findings the results obtained from repeated and regular estimations of blood acid and alkaline phosphatase values were graphically recorded in 53 cases of prostatic cancer followed over periods from two to seven years. In addition the same procedure was undertaken in two control groups of cases, one of 20 patients who had malignant conditions with secondary bone deposits other than prostatic cancer, and the other of 12 patients who had benign conditions. From these investigations it is suggested that the graphically recorded results may be used in the following ways.

Confirmation of Diagnosis (Fig. 3).—The finding of a plasma formaldehyde stable acid phosphatase value greater than 5.0 K.-A. units after all interfering factors have been eliminated, especially urinary retention, is very strong evidence in favour of cancer of the prostate. Values between 3 and 5 units are in the suggestive range. But, when in a patient with an initially raised formaldehyde stable acid phosphatase this value is seen to be rapidly falling on oestrogen therapy and in addition there is a characteristic alkaline phosphatase "kick" at or about whose summit an initially falling haemoglobin rises again, there is no doubt that the case is one of prostatic cancer with bone secondaries.

FIG. 3.—Typical response to stilboestrol therapy in a patient aged 66 with cancer of the prostate with bone secondaries. This shows a rapidly falling acid phosphatase; an initially raised alkaline phosphatase becoming temporarily depressed followed by a peak and then a gradual return to normal, associated with a declining haemoglobin value which increased after the first three weeks of stilboestrol treatment without any anti-anaemia therapy.

FIG. 4.—This graph shows an alkaline phosphatase response on stilboestrol therapy associated with a haemoglobin which at first deteriorated and then improved in a patient aged 62 with known bone secondaries. The acid phosphatase was normal throughout and the cause of the osseous secondaries was not apparent at first. Prostatic cancer was indicated from these findings and was later proved to be present.

Aid in Doubtful Cases.—When bone secondaries are seen radiographically but the primary source is not apparent the presence of an alkaline phosphatase “kick” following stilboestrol therapy would suggest that the secondaries are of prostatic origin, whereas its absence would be some evidence against such a source. An example of the former is given in Fig. 4, where the acid phosphatase level was normal throughout and yet on stilboestrol a well-marked alkaline phosphatase “kick” was present. Cancer of the prostate was later confirmed. An example of the converse is seen in the case depicted in Fig. 5, where there was no indication of any change in the alkaline phosphatase when stilboestrol was being given, although secondary deposits had been demonstrated radiographically. As a result of this test it was suggested that the metastases were unlikely to be of prostatic origin. Shortly after this investigation small opacities were visible radiologically in the right chest and the patient died soon afterwards with a typical bronchial carcinoma.

Assessment of the Degree of Spread of a Known Prostatic Cancer.—As the alkaline phosphatase “kick” was obtained in 95% of cases with bone secondaries it can be used as an additional guide as to the presence or otherwise of osseous extension. A point worthy of mention here is that in three cases with prostatic cancer a typical alkaline phosphatase “kick” was obtained initially, but

FIG. 5.—In this patient aged 67 bone secondaries of unknown origin were observed radiographically, but the alkaline phosphatase value remained unaffected by stilboestrol therapy. This graph suggested a non-prostatic cause for the bone secondaries. Lung cancer was later proved.

FIG. 6.—The elevation of the acid and alkaline phosphatase by the third year of treatment with dienoeestrol in a patient aged 74 with prostatic cancer suggested the presence of malignant extension. This graph shows the response which followed a change from dienoeestrol to stilboeestrol therapy. There is a rapid fall in the acid phosphatase and an associated alkaline phosphatase rise to a peak followed by a gradual fall suggesting that bone metastases were degenerating.

no deposits could be seen on radiographs at that time. Stilboeestrol therapy was continued and three months later a further radiograph revealed typical osseous deposits in all these cases. I would suggest that the deposits were there all the time, but that due to the therapy used there was a change in their density rendering them radiographically visible.

Choice of a Therapeutic Agent.—When a case of cancer of the prostate with bone secondaries gives a satisfactory alkaline phosphatase response or “kick” it indicates not only that these metastases are degenerating but also that the therapy

used is beneficial. If no such “kick” occurs the therapy should be changed. If in spite of a change there is still no phosphatase “kick,” then the prognosis is less good. If while the patient is undergoing oestrogen therapy the graphical records show any decline in the overall picture, then the dose of oestrogen may be increased or a change made to another preparation. In addition orchidectomy may be advisable if not done at the onset. In either case a further alkaline phosphatase “kick” will be seen if the new therapy or procedure is causing the bone secondaries to recede. An example of the former, in this case changing from dienoeestrol

FIG. 7.—The falling haemoglobin and slightly rising acid phosphatase about the 12th to 14th month suggested an extension of the known malignant prostatic lesion in this patient aged 61. Orchidectomy at that stage was followed by a rapid increase in the haemoglobin and also a small but definite alkaline phosphatase response suggesting that bone secondary deposits were degenerating.

to stilboestrol, is shown in Fig. 6. The patient felt well for three and a half years on dienoestrol, when it was clear from the graphs that metastases were forming, but the warning was not heeded for another nine months, by which time the patient had started to feel ill. The dienoestrol was then stopped and stilboestrol given. A most satisfactory response resulted.

A point worthy of comment here is that it has been observed that evidence of relapse is to be seen in these graphical records weeks or months before it is observed clinically or even before the patient himself is aware of any change.

The results followed orchidectomy are shown in Fig. 7. In this case stilboestrol initially gave a characteristic response, but within the year there was evidence of a relapse. Following orchidectomy there was a further alkaline phosphatase "kick" showing that more bone metastases were degenerating.

In conclusion it is suggested that the alkaline phosphatase "kick" might be used as an indicator

FIG. 8.—The well-marked alkaline phosphatase response following adrenalectomy in a patient aged 47 with bone secondaries from a breast cancer suggests that these osseous deposits are rapidly degenerating. This was further supported by a rapid improvement in the patient's overall condition and the radiographic changes observed in the bone deposits during the months following operation.

to test the effectiveness of a therapeutic agent or surgical procedure against any bone-metastasizing malignant growth, whether prostatic or other cancer. The alkaline phosphatase response might well be one way of obtaining a finer end-point in these research projects. By using a selected series of those cases of cancer of the prostate with bone secondaries, the activity of various oestrogenic agents can be investigated and a result obtained within two or three months as compared with five years or longer needed for clinical observation. An example of this use in another type of cancer is to be seen in Fig. 8, which shows the alkaline phosphatase trend following adrenalectomy in a case of cancer of the breast with bone secondaries. In this case the operation was followed by a well-marked alkaline phosphatase "kick" which preceded a most dramatic clinical improvement.

To summarize, it is suggested that the results obtained in this investigation show, first, that the estimation of the formaldehyde stable fraction of the plasma acid phosphatase is a better indication of the presence of cancer of the prostate than is the more usual investigation of the total value; second, that urinary retention may itself cause a moderate elevation of the acid phosphatase level in the absence of any malignant process and that the results of this test are not significant until this retention has been relieved; and, third, that the pattern of response or "kick" in the blood alkaline phosphatase value when bone secondaries are degenerating can help in the diagnosis, prognosis, and treatment of cases of cancer of the prostate and may also be useful as an experimental end-point in other investigations.

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