Serum Iron Response to Pituitary Adrenal Agents in Normal and in Cancer Patients

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HYPOFERREMIA has been induced in dogs by a variety of agents, which include histamine, epinephrine, adrenal cortical extract, adrenocorticotropic hormone (ACTH) and turpentine.1-3 Sayers4 found no significant alteration in serum iron levels taken at six and seven hours following administration of 50 and 100 mg. of ACTH to 2 normal male medical students. A marked early effect of ACTH, cortisone, desoxycorticosterone acetate (DOCA) and epinephrine on serum vitamin A levels* suggests that a comparable early effect on serum iron might have been missed in the preceding observations. The purpose of this study was to observe the effects of similar agents on the serum iron levels in normal individuals and in patients convalescing from various diseases, and to compare them to the effects produced by these drugs in cancer patients.

Materials and Methods

Two groups of individuals were studied. The cancer group consisted of patients seen and treated at the George Washington University Cancer Clinic. Diagnosis had been made by histopathologic study or surgery in all cases. Except in one individual, the disease was widespread and far advanced. The non-cancer group consisted of normal individuals and a few patients who were convalescing from other diseases. All individuals were fasting when studied.

Hemoglobin determinations were made by the oxyhemoglobin method and read on a Coleman, Jr. spectrophotometer. Red blood counts were made in the usual manner. The method of Kitzes, Elvehjem and Schuette6 was employed for serum iron determinations. Total eosinophil counts were done by a modified Dunger method.*

Epinephrine was given subcutaneously in 1:1000 solution. The ACTH was obtained from Armour and Co. Laboratories. Cortisone acetate (Merck & Co.) was given as a saline suspension by the intramuscular route.

Observations

1. Changes in serum iron levels over a four-hour period in fasting individuals.

Blood serum specimens for iron determinations were obtained from 5 non-cancer individuals and from 5 cancer patients at zero time, one-half hour, one hour, two, three and four hours later. The changes in the serum iron levels during this period of time for these two groups are given in figure 1. The average for each group is likewise indicated.
FIG. 1.—See legend, facing page
Changes in serum iron were measured in absolute units. That is, if an individual had a serum iron reading of 110 at zero time and 115 at one-half hour later, the change was recorded as plus five. This was chosen in preference to recording per cent changes since the latter method appeared to overemphasize changes in individuals with low serum iron levels, and to understate the changes in those with high serum iron levels. The standard deviation of a single measurement at a specific time was found to be ±5.6.

Although the average serum iron curves obtained over a period of four hours in these two groups were similar, the cancer patients showed more fluctuation than did noncancer individuals.

2. Comparison of effects of epinephrine on serum iron levels in cancer and in noncancer patients.

Epinephrine (3 mg.) was administered subcutaneously to 6 noncancer and to 6 cancer patients, and to one patient with Addison's disease. Blood specimens were drawn before administration of the drug and at one-half hour, one hour, two, three and four hours thereafter. The group and average responses are shown in figure 1. In all noncancer individuals, hypoferremia of varying degrees developed; in 2 there was mild initial hyperferremia. In all 6 cases there was an upward swing at the end of four hours; 2 patients demonstrated definite hyperferremia at four hours. Response of serum iron to epinephrine administration in cancer patients was less consistent. Two individuals in the cancer group showed a hypoferremic response at two hours, followed by a return toward normal, resembling that seen in the noncancer group. These patients were: (1) the only individual studied with minimal cancer, and (2) a young woman with recurrent salivary gland tumor, but with a good nutritional background. The patient with Addison's disease showed a mild but progressive hyperferremia.

Over the time studied, the noncancer individuals manifested a greater response to the epinephrine than the cancer patients. The difference is shown in figure 1. However, because of the large individual variation, the difference is not significant. In addition, the noncancer individuals appeared to recover more rapidly than the cancer patients.

A reduction was noted in the total eosinophil count of from 59 per cent to 91 per cent at the end of the four hour period in the noncancer group, and of 42 to 100 per cent in the cancer patients. The patient with Addison's disease had an initial high total eosinophil count of 575 per cu. mm.; four hours after the subcutaneous injection of 3 mg. of epinephrine it was 589.

In an effort to obviate the individual response variation, serum iron studies were made on the same individual on two different days (fig. 2). No medication was given on the first occasion; the second series of blood levels was obtained following the subcutaneous administration of 3 mg. of epinephrine. After small early fluctuations the first curve was practically flat. Following epinephrine injection the serum iron rose slightly, then fell at the end of two hours to a point.
significantly below the starting level. Subsequently there was a trend upward. The total eosinophil count was 113 per cent of the control count at the end of the first study, but dropped to 28 per cent of the control count four hours after administration of the epinephrine.

3. Effects of ACTH on serum iron in 5 noncancer and in 6 cancer patients.

Eleven individuals were given 50 mg. of ACTH subcutaneously. Blood samples were taken before the administration of the drug and at one-half hour, one hour, two, three and four hours following the injection (fig. 1).

As with the other drugs, individuals given ACTH showed significantly different responses over the period of time studied. However, the differences between the cancer and noncancer groups were so pronounced that there was a significant difference (at the 5 per cent level) in response of the two groups. In general, the

![Graph showing serum iron response to ACTH](image)

Fig. 2.—Two serum iron curves on one healthy individual taken on separate days. The solid line connects the iron levels after no treatment, the broken line after the injection of 3 mg. of epinephrine. Peripheral eosinophil count changes are given.

noncancer individuals showed an early increase in serum iron level after the administration of ACTH, while cancer patients, on the average, showed a decline.

4. Effects of cortisone on serum iron in 6 noncancer patients and in 6 cancer patients.

The serum iron response to cortisone is indicated in figure 1. The results of this experiment are somewhat equivocal because the same amount of cortisone was not administered to all the individuals. All cancer patients were given 100 mg. of cortisone, but one of the noncancer patients received 25 mg. and one received 50 mg. Elimination of these two individuals from our calculations does not modify the findings substantially.

Although there was no consistent pattern of change in serum iron following cortisone administration, as can be seen, the drug produced marked individual changes. The cancer patients appeared to respond more slowly and to a lesser degree than did the noncancer individuals.

5. Effects of DOCA on 5 cancer patients and on 5 noncancer individuals.
Within the time period studied, there were no significant differences in the response between the averages of 5 noncancer individuals and 5 cancer patients who were given 7.5 mg. of DOCA in oil. The individual and average responses are shown on figure 1. However, in both the cancer and noncancer individuals, the drug increased the variability of serum iron to a significant degree during the time period of observation. The drug appeared to have some disrupting effect on the stability of the serum iron levels in the individuals studied.

6. Effect of HN₂ on serum iron and eosinophil count in 2 cancer patients.

Methyl bis (β-chloroethyl) amine hydrochloride was administered intravenously to 2 patients in doses of 0.1 mg. per kilogram. M. M., a 58 year old obese woman with multiple skin and bone lesions diagnosed histopathologically as fibrosarcoma, received a total dose of 9 mg. D. S., a debilitated 38 year old man with epidermoid carcinoma of the tonsil with metastases, received a total dose of 6 mg. Different patterns of response are exhibited in figure 3.

The serum iron curve in M. M. resembled roughly that produced by the injection of epinephrine in noncancer individuals. The serum iron response observed in B. S. was similar to the one seen following the administration of 3 mg. of epinephrine in a patient with Addison’s disease. Both patients exhibited an increase in the fasting serum iron levels obtained 24 hours later. Eosinophil counts dropped 25 per cent in B. S. and 32 per cent in M. M. four hours after administration of HN₂.

DISCUSSION

Cartwright and his co-workers have demonstrated in dogs the hypoferremic action of many agents as well as abolition or reduction of this effect by ad-
renalectomy, or the injection of colloidal thorium dioxide. Even the mild stress of blood collection produced a significant decrease in serum iron in half the dogs studied. The more marked fluctuations in serum iron in untreated cancer patients, as compared to those in untreated noncancer patients, may have been due to greater lability or to the unsteady state of endocrine equilibrium secondary to prolonged disease and pain in the former group.

The great individual variability in response to all agents suggests that the action of any agent is modified by the basic make-up of a subject. Contributing to this makeup is not only the inherent endocrine pattern of an individual, but also modifications resulting from such factors as stress response, effect of pain, protracted illness. Presumably larger doses of hormones than employed might result in more uniform patterns of response. The difference in serum iron curves in dogs following 3 mg. per Kg. and 20 mg. per Kg. of dibenamine has been shown to be quite striking. The larger dose produced more consistent responses. The doses of hormone used in this study were relatively much smaller, for obvious reasons, than have been employed in animal experiments, which might partially explain some of the diverse responses obtained.

Maximum hypoferremia following epinephrine and histamine injection in dogs occurred in six to eight hours, as compared to 24 to 48 hours following turpentine injection. A longer period of study in human patients would be desirable, but maintenance of individuals, sick or well, at basal level for prolonged periods is usually impracticable. Presumably fatigue, irritation, hunger or pain might indirectly stimulate or modify endocrine response.

In spite of great individual variation in the serum iron curves of noncancer patients following injection of epinephrine, an appreciable hypoferremia usually resulted. A similar response in the cancer group occurred only in a well-nourished young individual and in a patient with minimal disease. At the termination of the study, these 2 patients and all the noncancer individuals showed an upswing in curve. Definite hypoferremia was manifest in 2 individuals and might have been demonstrated in others had the study been prolonged. Hypoferremia from epinephrine appeared later in dogs, which may be accounted for either by the difference in species or in the dose of the drug. Adrenalectomy in dogs largely, but not entirely, abolished the hypoferremic effect of epinephrine. Our single patient with Addison’s disease showed a slow developing hyperferremia which we cannot explain.

The noncancer patients in our study showed a hyperferremic response to the injection of ACTH. This is in contrast to the hypoferremia in dogs reported by Cartwright. Either an early hyperferremia may have been missed in the latter study because of the routine adopted for the specimens, or because the factors of species and dose were operating. Cancer patients did not show this early hyperferremia; 2 of 6 individuals, however, demonstrated hypoferremia at four hours.

Although cortisone and DOCA produced marked fluctuation in serum iron levels in most individuals, the direction of response was not consistent in either the cancer or the noncancer group. Lack of clear-cut responses to these agents was no doubt due to slow and variable absorption. A larger dose of the drug, a different route of administration and a longer period of observation might have added desirable information.
Apparently there is, in human subjects as in dogs, an effect on serum iron levels by certain hormonal agents. The effect appears to be somewhat slower and of smaller degree in far-advanced cancer patients. Whether this is due to exhaustion of the pituitary adrenal mechanism or to a change in the reticuloendothelial system is not clear. One might speculate that prolonged stimulation by disease of these processes may be a factor in the reduced serum iron levels commonly seen in cancer patients. It is not likely that this is a specific effect attributable to a neoplastic process, but one which might operate in any severe, chronic disease process.

CONCLUSIONS

1. Serial serum iron determinations on cancer patients made over a period of four hours showed a tendency for fluctuation not observed in a small group of noncancer individuals.

2. Epinephrine (3 mg.) produced a hypoferremia more regularly in noncancer patients than in cancer patients. Recovery was also more rapid in the former group.

3. Administration of 50 mg. of ACTH to noncancer patients was followed by an early hyperferremia which was not observed in cancer patients.

4. Cortisone and DOCA in the doses employed resulted in marked fluctuations of serum iron but no consistent trends in either group of patients.

5. It is suggested that serum iron response to adrenal cortical agents in doses herein employed are modified by the basic endocrine pattern of an individual.

REFERENCES


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