STUDIES ON THE MUCOPROTEINS OF HUMAN PLASMA. II. PLASMA MUCOPROTEIN LEVELS IN CANCER PATIENTS[1]

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A number of studies have indicated that there exist in blood, protein-like materials which are not readily precipitated by heat, by perchloric acid, by sulfosalicylic acid, or by high concentrations of trichloracetic acid. The concentration of such materials has been found to increase in the blood of patients afflicted with cancer as well as in patients with a number of other diseases.

In a program designed to elucidate the nature of this material and its possible significance in cancer, we have isolated the material from normal human plasma and have shown it to be a mixture of mucoproteins (1). Improved methods for the determination of plasma mucoproteins have also been studied (1).

This paper is concerned with an investigation into the plasma mucoprotein level in two conditions in which the concentrations have been found to be increased over the normal levels.

EXPERIMENTAL

Most of the determinations were carried out using the determination of perchloric acid soluble, phosphotungstic acid-insoluble tyrosine [2] of plasma as previously described (1). In certain experiments the carbohydrate content of this same fraction was determined in order to ascertain whether the carbohydrate-tyrosine ratio deviated significantly from normal in pathological sera.

Results on the determination of mucoprotein-tyrosine levels in the plasma of 337 normal individuals and 454 cancer patients are shown in Figure 1. The normals were largely taken from negative premarital Wassermann sera. All of the cancer cases included in Figure 1 have been diagnosed with certainty by biopsy or at autopsy. The disease in most cases was relatively far advanced. The extent of the work at the present time does not justify the grouping of the data as to type or extent of the malignancy. The results shown in Figure 1 show that the normal plasma mucoprotein levels are in the range of 1 to 4 mg. of tyrosine content per 100 ml. plasma and averaging 2.7 ± 0.05 mg.%, whereas the serum from cancer patients ranges between 2 and 12 mg.% averaging 6.1 ± 0.13 mg.%. There is considerable overlapping between the high normals and the low cancers, but the maximum frequencies are distinctly different in the two groups.

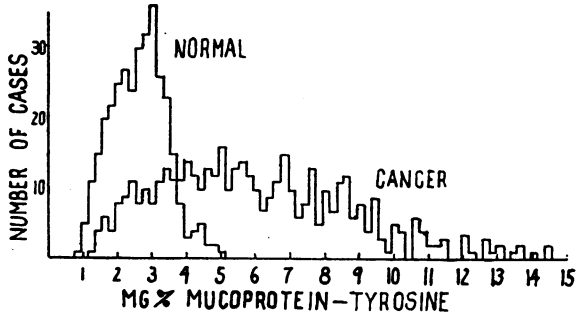

FIG. 1. PLASMA MUCOPROTEIN LEVELS IN NORMAL INDIVIDUALS AND IN CANCER PATIENTS

These results are in general accord with the work of previous investigators using polarographic determination of sulfosalicylic acid filtrates of denatured serum as well as with studies on the "index of polypeptidemia" (2 to 10).

Figure 2 shows the plasma mucoprotein level as a function of time in three pneumonia patients admitted to the hospital. It is seen that these patients had very high plasma mucoprotein levels initially when the body temperatures were at a maximum. These high levels fell to normal levels and paralleled the temperature and the recovery of the patient.

The observation that patients suffering from pyogenic infections have increased amounts of "protein split products" in the serum is in accord with the results of other investigators listed above. Crossley and his associates (11) have made an extensive investigation of changes in the

[1] This work was supported by a grant from the National Research Council Committee on Growth, acting for the American Cancer Society.

[2] Although the results are reported as "tyrosine" it is recognized that the Folin phenol reagent is not specific for tyrosine groups in proteins.

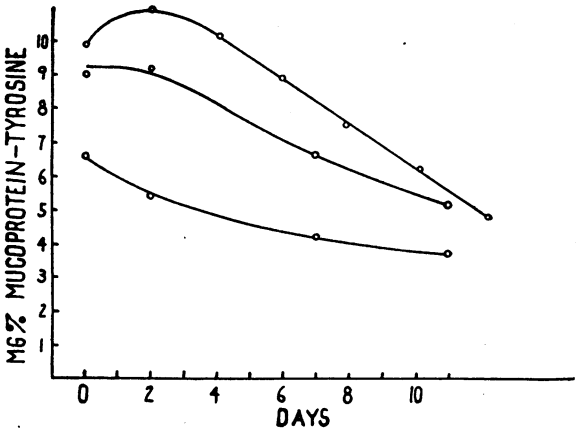

FIG. 2. THE PLASMA MUCOPROTEIN LEVELS OF PATIENTS WITH BRONCHIAL PNEUMONIA

plasma proteins including "peptone," of experimental pneumonia in dogs. Their work also shows a parallel relationship between serum "peptones" and the development of the pneumonia and subsequent recovery. In a recent paper, Vassel *et al.* (12) have isolated "proteose" from normal dog plasma and from that of dogs with pneumonia by fractionation with ammonium sulfate. They obtained increased amounts of this material in the infected dogs and showed that it contained about 25 per cent carbohydrate (expressed as mannose, galactose and glucosamine).

Although the method employed determines primarily mucoproteins in normal individuals, the possibility exists that the type of material determined may be altered in pathological states. This question is being investigated by direct isolation from larger quantities of blood. However, some indication as to the similarity of the material in normal plasma and from the patients with cancer or pneumonia is given in Table I which shows the tyrosine and carbohydrate content of the perchloric acid-soluble, phosphotungstic acid-insoluble material in plasma determined as previously described (1). The results show that the carbohydrate/tyrosine ratios of the materials in plasma which are soluble in 0.6 M perchloric acid but are precipitated by phosphotungstic acid, are contant in spite of the quite marked deviations in absolute levels of tyrosine. Thus it may be concluded that the materials responsible for the increased mucoprotein levels in pneumonia and cancer (and presumably other conditions) are chemically similar to the mucoprotein that has been previously isolated from normal human plasma (1).

TABLE I

Tyrosine and carbohydrate ratios of mucoproteins in normal and pathological blood

	Number of cases	Tyrosine*	Carbohydrate*	$\frac{CHO^*}{T}$
		mg. %	*mg. %*	
Normal	19	3.0±0.2	11.2±1.0	3.70±0.21
Cancer†	22	6.7±0.9	24.5±2.8	3.66±0.17
Pneumonia‡	15	7.2±0.8	26.9±2.2	3.74±0.20

* Including the standard error of the mean calculated from the relation

$$SE = \sqrt{d^2/n - 1}/\sqrt{n}$$

where "*d*" is the deviation from the mean and "*n*" is the number of observations.

† Relatively advanced cases.

‡ Blood taken from patients with lobar or bronchial pneumonia while the fever was at its height.

DISCUSSION

The data presented in this paper show that the plasma mucoproteins are increased over normal levels in a large percentage of patients with cancer. However, the increased levels are not constant or specific enough to be of great value as a diagnostic test for cancer. False positive tests are given in pneumonia and a number of other conditions. Likewise, false negative tests are given in many cancer patients, especially when the disease is not far advanced. However, levels of over 4 mg. of mucoprotein-tyrosine per 100 ml. of plasma are rarely found except under pathological conditions. A carefully controlled study of the possible use of the method for diagnosis of cancer of the upper gastrointestinal tract is currently in progress. The very fact that the plasma mucoproteins are elevated in diseases of such different etiology as cancer, pneumonia and myocardial infarctions (Simkin *et al.*, 13), suggests that some abnormality in protein metabolism may be common to all of these conditions. It will be of utmost importance to investigate the chemical composition and physicochemical properties of mucoprotein isolated from pathological plasma in order to determine whether they are similar to or different from those present in normal plasma. It will also be important to investigate the source of the plasma mucoproteins and to determine their physiological significance.

SUMMARY

An investigation has been made of the plasma mucoprotein levels in 337 normal individuals and 454 patients with cancer. The normal plasma mucoprotein-tyrosine levels averaged 2.7 ± 0.05 mg.% while the levels in cancer patients averaged 6.1 ± 0.13 mg.%. Patients with pneumonia also showed markedly increased plasma mucoprotein levels. The ratio of carbohydrate to tyrosine was about 3.7 in the plasma mucoprotein in both of these conditions as well as in the normals, suggesting the similarity of the plasma mucoproteins in all cases.

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