The analysis of changes in serum protein in malignancy is in itself a means of studying abnormality in the protein metabolism in this condition. The present study was conducted in order to elucidate the mechanism of hypoproteinemia in cancer by analyzing the clinical statistics, by studying the changes of albumin metabolism, and the rôle of the liver in the evolution of hypoproteinemia. Studies were also directed to the changes of globulin fractions from the patho-physiological standpoint, and changes of serum globulin fractions associated with the phenomenon of hypoproteinemia in cancer were analyzed.

Materials and Methods

Materials : Clinical materials consisted of 646 cases with various types of malignancy (611 carcinoma cases, of which 346 were male and 265 female, and 35 sarcoma or leukemia cases, of which 25 were male and 10 female) and 310 control cases. For the animal experiments, Donryu rats weighing 150 to 200 g. were used to which Yoshida sarcoma was transplanted subcutaneously.

Clinical Statistics : The criteria for hypoproteinemia was defined as serum protein concentration below 6.5 g./dl., by referring to the distribution of normal values ($\pm 2\sigma$). The incidences of hypoproteinemia in cancer patients classified according to the types of cancer, age and sex were analyzed, and factors related to the evolution of hypoproteinemia were investigated referring to the patho-physiological findings of the cases.

Clinical and Experimental Studies : As for the clinical cases, the metabolic kinetics of albumin was studied using RISA (Sterling), and concentrations of fibrinogen, seromucoid (Otani), haptoglobin (Anisidine method), $\beta_2$-component (Takahashi), and of the three classes of immunoglobulins (Anzai) were determined. As for the animal experiments, the distribution of albumin in the body was determined daily, by assays of specific radioactivities after RISA injection, and also by the immunochemical albumin assays of the blood, liver, gastrointestinal tract and other organs and malignant tissues.

The ultrastructures of the liver tissues of patients obtained by surgical or needle biopsies were compared with the status of hypoproteinemia. The in vitro albumin net synthesis by liver slices was assayed according to the method of Higashi, using rat livers in the stage of hypoproteinemia, and compared with the controls.
Results and Discussion

1. On Clinical Statistics
   Approximately one half of patients with malignancy (49.6% of carcinoma cases and 60% of sarcoma and leukemia cases) were hypoproteinemiac, although the incidences were different according to the types of cancers. Among cancers having high incidences of hypoproteinemia, rectal and colonic (69.6%), lingual (62.5%), esophageal (61.1%) and gastric (59.0%) cancers can be enumerated, together with pancreatic, bronchogenic, biliary, maxillar, hepatic and prostatic cancers. On the other hand, renal (22.4%), thyroid (35.0%), breast (38.1%), bladder and female genital carcinomata had lower incidences of hypoproteinemia, suggesting the participations of disturbances of food intake, hemorrhage, and gastro-intestinal protein-losing phenomenon, in addition to the grade of malignity of the disease per se in the evolution of hypoproteinemia.

   There was a significant correlation between the extent of stomach carcinoma and the degree of hypoproteinemia. On the other hand, statistical survey of cancer cases on the whole disclosed no apparent factor among patho-physiological findings responsible to the formation of hypoproteinemia, although results suggested the participations of hemorrhage in cases of stomach carcinoma, of protein-losing phenomenon in cases of intestinal cancer and of age in cases of prostatic and breast cancers.

2. On the Mechanism of the Evolution of Hypoproteinemia, with Reference to Findings Related to the Liver
   (a) Clinical Studies
      The main role in the evolution of hypoproteinemia was played by albumin, while α-globulins and fibrinogen were generally rather increased in this condition, and changes of β- and γ-globulin levels were relatively slight.

      Regardless of the types of cancer, studies on the albumin metabolism revealed that hypoproteinemic cases were characterized by a reduction of $T^{1/2}$, decrease of intra- and extravascular albumin pools, a marked decrease of exchangeable albumin pool and a prolongation of the turnover rate. All of these were statistically significant when compared with the control cases (P<0.01). The ultrastructures of the biopsy livers taken at this stage were characterized with a remarkable decrease of rough endoplasmic reticulum and an increase of smooth endoplasmic reticulum together with deformation and dissimilarity of mitochondria with condensation of cristae and with nuclear atrophy. Even in the relatively early stage of cancer, the albumin metabolism was often characterized with an already reduced $T^{1/2}$.

   (b) Animal Experiments and In Vitro Studies
      Changes of albumin distribution in tumor-bearing animals were characterized by an increase in the tumor tissue parallel to the decrease of serum albumin, and albumin concentrations in other organs and tissues were lower than those of the control animals. However, the albumin concentrations in the liver showed a temporary increase in the tumor-bearing rats than in the controls.

      The in vitro synthesis of albumin by the liver was accordingly studied. Results
indicated that the decrease of serum albumin was accompanied by an inversely increased albumin net production (Fig. 1-a). Electron microscopic examination of the liver showed a remarkable increase of rough endoplasmic reticulum in coincidence with the augmentation of albumin synthesis (Fig. 1-b).

These results indicate that hypoproteinemia in cancer is an expression of cachexy representing the so-called homeostatic derangement in which the utilization and destruction of albumin by the tumor cannot be compensated by the organism, especially by the liver. The results also indicate that the utilization of albumin by the tumor is strongly exaggerated from the initial stage, and that the liver sharply responds to the exaggeration of albumin catabolism.

3. On the Patho-Physiology of Globulin Fractions

The previously reported suggestion\(^6\) that the increase of seromucoid was responsible to the increase of \(\alpha\)-globulins in cancer hosts was reinforced, and moreover, one feature of haptoglobin metabolism was studied using \(^{131}\)I-labelled haptoglobin. It was found that increased serum haptoglobin levels in hypoproteinemic cancer patients were accompanied by a prolongation of its \(T_1/2\). Also, an increased incidence of \(\beta_2\)-component, an "abnormal" protein isolated from hepatoma tissue, in the blood was confirmed, and decreases of the three classes of immunoglobulins with related depression of immune responsiveness in hypoproteinemic cancer patients were disclosed.

**Conclusion**

The incidence of hypoproteinemia in cancer hosts and the mechanism of its evolution were studied by clinical statistical surveys and by experiments focused upon the role of the liver. Findings of the changes in globulin fractions were also discussed in relation to the patho-physiological aspects of hypoproteinemia in cancer hosts.
References