Panel Discussion on
"Problems Concerning Circulation Centered
Around the Liver"*

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Speaker : Prof. Yawara YOSHITOSHI

Prof. Kiyoo KOSAKA

Prof. Tosaku MAEDA

Prof. Toshio TORII

Dr. Hiroshi SASAMOTO

Prof. Soroku SAITO

Prof. Hajime IMANAGA

Special Speaker : Prof. Magojiro MAEKAWA

Prof. Toyozo AIZAWA

Prof. Tsuneo YOSHIDA

Em. Prof. Yoshio MIKAMO

CHAIRMAN: We will now open the panel discussion on the "Problems Concerning Circulation Centered Around the Liver". The participants are the 7 chairmen of the symposiums on the same topic which were held today, and professor K. KUSUI, the chairman of the symposium "Therapy of Cardiac Insufficiency" which we have just heard. I have asked him to join the group since there is an intimate relation between the therapy of cardiac insufficiency and the circulatory problems concerning the liver.

I have asked these participants to speak for about 8 minutes each on their presiding symposium. Since three symposiums were held at one time in the morning, there are here probably many who missed a symposium they wanted to hear, so I think the reports on the important points of the symposiums by the 8 chairmen are necessary not only for the discus-

sion which is to follow, but for the audience to understand the proceedings.

After the reports, guests, professor M. Maekawa of Kyoto University, professor T. Yoshida of Osaka University and Professor T. Aisawa of Keiō University will be asked to give a special lecture. However, professor Yoshida could not be here with us because of his responsibilities as the president on the Japanese Society of Internal Medicine and I in turn will read an abstract of his lecture. After this I will speak for a few minutes on several slides which will be shown.

After these reports and lectures, the participants will form 3 groups, and discuss for about 50 minutes. The first group moderated by professor Yoshitoshi will discuss the methods of determining hepatic circulation and the hepatic circulation in hepatic diseases. Professor Emeritus Y. Mikamo of the Tokyo University who is a pioneer in this field has agreed to join the

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* Among this panel discussion, several speeches were translated by Editorial Secretary (K. OGINO, M. D.). Dr. OGINO wishes to ask speakers their forgiveness for the misapprehension and mistranslation of their comments.

discussion.

The second group will discuss the topic centered around the hepatic circulation in cardiac insufficiency and will be moderated by professor Kusui, and we just heard professor H. Ueda of Tokyo University who spoke in the symposium on cardiac insufficiency has agreed to join this group as a guest.

The third group will discuss the problems of the general circulation and cardiac disturbances seen in hepatic diseases and will be moderated by professor S. Saito. Professor Maekawa will join this group as a guest.

The three groups will discuss in turn, but each discussion will not be so strictly limited to those in the particular group.

For the reports on their symposium. Then, I should like to ask to seven chairmen, Prof. Yoshotoshi, Kosaka, Maeada, Torii, Sasamoto, Saito and Imanaga.

PROF. Y. YOSHITOSHI: There are two approaches in order to investigate the problems of hepatic circulation. One is that in the whole liver. Another is that in the hepatic lobulus, which is a smaller functional unit of the liver. The former will be discussed in the Symposium 'A' moderated by Prof. Kosaka,

The latter, in other words hepatic microcirculation, is to be discussed here.

This subject is rather new, because our knowledge obtained in its work field, which has recently been progressed, had to be in need of much advanced methods to further investigations, therefore today's papers are mostly those made reference to its methodology.

In our country, it was only once discussed before, at the 51st annual meeting of the Japan Society of Pathology last year.

Dr. Nakata is a pioneer in Japan in this field and has determined the minute vessel pressure by means of micropuncture technique under biomicroscopic observation in the rat liver. His schema of its pressure gradient has already been referenced by several authors, which is that the blood pressure in the interlobular vein was reduced by half as compared with that in hylum and then in the course of passing through the sinusoid it was lowered by a quarter of that in

hylum, besides such a pressure gradient can be easily influenced by respiration.

Dr. Oka and Dr. Kanetaka also have observed the interlobular circulation at the edge of the rat liver, in particular, being devised a newly modified technique to measure the sinusoidal pressure, i. e. a thin and tiny polyethylene bag was inserted into the sinusoidal vessel and then its inside pressure was little by little elevated, until the sinusoidal blood flow was stopped.

Thus, the pressure was regarded as the sinusoidal pressure. According to these experimental observations or some other's, i. e. the influences of ligation of hepatic artery or portal vein, it was concluded that the blood supply through the hepatic artery in hepatic cirrhosis was much more than that in the normal liver.

Dr. Hosokawa has made an observation on the vascular tree of the liver by using plastic cast method and demonstrated that the hepatic artery in cirrhosis was changed into a basket like network.

Dr. Miyake, Dr. Saito and Dr. Okudaira have also done the similar work on the human cirrhotic liver and, in addition, a perfusion method too. Thus, it was demonstrated that the distance between the hepatic artery and the hepatic vein became shorter and contrariwise the distance between the portal vein and the hepatic vein became rather longer. Therefore, the arterio-portal shunt seemed to be dominant among those possible vessel shunts in the course of a completion of hepatic cirrhosis.

Dr. Magari has carried out some observations on the hepatic lymph circulation, which is very important one in microcirculation and found maculacribriforms in Glisson's capsula in co-operation with Dr. Kihara.

Dr. Kato and Dr. Tsuchiya also emphasized the role of lymph flow in the formation of ascites from their experimental studies.

It is quite sure that there are still remained more problems in these work field.

On the other hand, it will certainly be expected too that in the near future we will progress in our knowledge in this field, because of newly advanced techniques, i. e. biomicroscope, colloidin vascular tree, as well as demonstration of fine structure of lymphatic vessels.

PROF. K. KOSAKA: Our symposium was concerned with the problem of method for measuring the hepatic circulation.

Prof. Wakisaka made the comparative study on various tests with dyes (Bromsulphalein, Azorbin S) or galactose, Au¹⁹⁸ or Rosebengal. He illustrated the clearance of these materials which showed different clearances for various hepatic diseases for example, the parenchymal diseases or the diseases of reticulo-endothelial system respectively. He also emphasized the fluctuation in the ratio of clearance values between Au¹⁹⁸ and BSP, Au¹⁹⁸ and Rosebengal labelled with I¹³¹ with the course of liver disease, for example, with the process of acute, chronic stage of hepatitis and liver cirrhosis.

Dr. Kameda examined the extraction rate of Au colloid showing that Au colloid was very different in size and that there was the crude one under 50% in extraction rate.

He offered advice to select the appropriate substance in applying Au colloid for the measurement of hepatic circulation. To obviate the afore-mentioned inconvenience he also introduced the method with the denatured human albumin tagged with I¹³¹. This method was enough useful despite 50~60% in the extraction rate of this albumin. Dr. Kameda also illustrated the application of telemeter in measurement of hepatic blood flow, and the separate measurement of hepatic arterial and portal blood flow by extracorporeal calculation.

Dr. Nakamura mainly examined the method with galactose having 100% in extraction rate. With this method he determined the blood flow in the intrahepatic and extrahepatic shunts. He also found the anastomosis between the liver and lung and measured the blood flow through porto-pulmonary anastomosis. Moreover he talked about the hepatic venograph and splenoportograph.

Dr. Shimada calculated the portal pressure values from the spleen sinus pressure level obtained by peritoneo scopy which could be easily put into patients without bleeding. Gradients between the calculated portal pressure and hepatic venous pressure were varied according to the course or types of chronic liver diseases or liver cirrhosis. He also measured the diameters of

the intrahepatic branches of portal and hepatic veins by venographs.

Dr. Kuroyanagi introduced the Imanaga's (Prof. of Surgical Department, Nagoya University) classification of types in portal hypertension and emphasized the characteristic features in hemodynamics.

Dr. Hirose reported that Indocyanine Green is applied in determining not only the dye-extraction capacity but also the hepatic blood flow in liver diseases.

PROF. T. MAEDA: Hepatic abnormalities constitute common and important secondary effects of the congestive heart failure, because of a disturbed intrahepatic circulation, malnutrition as well as anoxia of the hepatic tissue.

This symposium deals with the hepatic circulation and metabolism in the cardiac insufficiency.

The first problem discussed by Dr. Inoue was about the hepatic circulation in the cardiac insufficiency. The factors which influence the liver are the ascent of the right cardiac and venous pressure, decrease of cardiac output or hepatic flow, decrease of blood oxygen, and malnutrition.

By means of a venous catheter the pressure of the pulmonal artery, the right auricle, V. cava inferior and hepatic vein were measured.

Compared with the ascent of the pressure of right auricle and V. cava inferior, elevation of the hepatic vein and wedge pressure, especially the latter, was more marked.

As the cardiac insufficiency progressed, cardiac output and also the hepatic flow decreased.

In a cardiac insufficiency, the oxygen content of arterial, mixed venous and hepatic venous blood decreased. The decrease in blood oxygen and hepatic flow indicates hypoxia of the liver. The relative increase of the difference in oxygen contents between the arterial and hepatic venous blood was considered to indicate a compensatory function which aims to keep the oxygen consumption of the internal organ normal.

Pressure of capillary of the rectum was measured to as an index of the portal pressure.

The second problem discussed by Dr. Yori-fuji also concerned the hepatic circulation in the cardiac insufficiency. He examined, in dogs and

rabbits, the hepatic flow and the relation between the hepatic artery flow and the portal flow, the ascites formation and its removal into the circulation. He examined the following 3 problems

- 1) Relation of hepatic arterial flow to portal flow in right heart failure.
- 2) Distributional change of the blood flow and ascites formation.
- 3) Evacuation of ascites into the systemic circulation.

His conclusions were as follows.

In the experimental right ventricular heart failure in dogs produced by the injection of lycopodium spores, total hepatic blood flow was shown to decrease with a distributional change, that is, relative increase of the hepatic arterial flow and, consequently, a relative decrease of the portal venous flow; such distributional change of hepatic blood flow as this may bring out an insufficient nutritional supply for the whole organism, though it compensates for the supposed anoxic conditions of the liver cells due to a decreased blood flow. This distributional change and other hemodynamic conditions are likely to accelerate the production of ascites, but even if it is produced, it can be rapidly evacuated into the systemic circulation in the experimental pulmonary hypertension. In the congestive heart failure of human being, ascites goes rapidly from the peritoneal cavity into systemic circulation and this rapid transit of ascites is thought to compensate for a decreased hepatic blood flow, though this compensatory mechanism is liable to fail if right ventricular failure advances in degree.

The third problem discussed by Dr. Same-shima concerned with clinical and experimental studies of liver function disturbances in congestive heart failure. The studies were made of hepatic disturbances in cases of congestive heart failure: in addition to routine liver function test, enzyme activities in patient's sera were determined. The results obtained were as follows.

The greater the severity of NYHA standards, the greater the increase in BSP, G6P, ALD and LDH and the greater the decrease in detoxication; cases of congestive heart failure showed marked abnormalities in BSP, detoxication capacity, Alk-P and LDH.

Rabbits with constrictive pericarditis showed a marked increase in the activities of G6P, PHI, ALD and LDH in the serum 1–2 weeks after the surgical intervention, followed by an approximate recovery to the preintervention stage in 4–5 weeks, eventually showing a slight increase again in about ten weeks. One to two weeks after the surgical intervention, rabbits showed an increase in the enzymatic activities in sera, accompanied by hemorrhage and necrosis in the peri-central area of lobules. About six weeks after the surgical intervention the enzyme activities in sera decreased: hemorrhage and the necrosis in the liver cleared up, leaving behind the vacuolization of the cytoplasm. Time-course curves of G6P, PHI, ALD and LDH in sera and liver tissue were found to be almost in a mirror-image relationship.

PROF. T. TORII: I presided over a symposium on Shock and Hepatic Circulation.

Dr. Tanabe et al. spoke about the hepatic circulatory changes induced by hemorrhagic and anaphylactic shock. In the cases with hemorrhagic shock, the hepatic circulatory alteration varied with the course or grade of bleeding. In the initial stage cardiac output and hepatic blood flow are not decreased much. However, in the moderate hemorrhage cardiac output are decreased and hepatic blood flow also does in parallel with decrease in cardiac output. These conditions are in the state of simple hypotension and can be recovered enough by the blood transfusion. In the more advanced stage, hepatic sphincter mechanism is so exerted as to elevate the portal blood pressure despite little increase in systemic blood pressure. Accordingly, hepatic blood flow decreases despite of increase in systemic blood volume. This condition is in the irreversible phase and runs gradually into the terminal stage. Contrary to the hemorrhagic shock, hepatic blood flow first decreases and then cardiac output diminishes in the anaphylactic shock. In this shock, portal blood pressure is so elevated as to induce the hepatic congestion. Such hepatic hemodynamics is followed by the increase in blood volume in liver and the marked extravasation of plasma.

Next speaker — Prof. Hemamoto — examined histologically the hepatic injuries induced by producing the antigen-antibody reaction in the

rabbits liver by bovine erythrocytes.

In the initial phase of this hepatic injury, it was revealed that Trypan blue intravenously injected flow out the adjacent parts of hepatic necrotic foci. This phenomenon seemed to be due to extravasal exsudation. In the latter stage, it was observed for Trypan blue not to enter into necrotic foci and for fibrin-thrombus to be found in the sinusoid. This morphological finding may partly support the occurrence of pooling of the blood indifferent to circulation in the terminal stage in shock.

Dr. Yamamoto studied on the hepatic hemodynamics in the use of plasmin—one of mediators in the shock mechanism. Injection of plasmin through portal vein was followed by the marked elevation in portal pressure. Histological change in this were as same as results in the Hamamoto's study.

DR. S. SASAMOTO: Respiratory insufficiency is referred to the condition of insufficiency in oxygenation or CO₂-elimination due to the abnormalities in lung or chest wall. It manifests itself clinically as anoxemia and/or hypercapnia acutely or chronically. Drs. Katagiri, Ohbayashi and Suemitsu spoke about the problem on hepatic circulation in respiratory insufficiency.

Dr. Katagiri stated on the hepatic circulation in the cases with chronic respiratory insufficiency, in the rabbits experimentally induced to chronic respiratory insufficiency and in the dogs with acute induced anoxia or hypercapnia. Low cardiac output and increased endo-diastolic pressure were observed in the patients with high pulmonary arterial pressure among the cases with respiratory insufficiency.

Decreases in total hepatic blood flow, in O₂ gradient between artery and vein and in hepatic O₂-uptake were also found in the cases with pulmonary hypertention. Same results were obtained in animals experimentally induced to respiratory insufficiency. He observed that the respiratory fluctuations in pulmonary artery pressure and intra-pleural pressure were markedly increased in the cases with respiratory insufficiency. Therefore he supposed that ventilatory movement was so remarkable in the cases with chronic pulmonary diseases as to influence on total hepatic blood flow. He also observed

the increase in total hepatic flow after 10% O₂ or high CO₂ inhalation. Moreover he examined the relationship between the ventilatory movement and portal blood flow; portal blood flow was decreased by the positive pressure breathing during inspiratory phase and decreased by respiratory arrest.

Dr. Ohbayashi examined in patients with pulmonary tuberculosis or liver disease the effect of the acute induced anoxia (10% O₂ inhalation) on the hepatic circulation. About 69% increase in hepatic blood flow and about 80% increase in hepatic O₂ consumption was observed in the normal subjects by low (10%) oxygen inhalation. However, in the patients, increase in hepatic blood flow and hepatic O₂ consumption were lesser than that of normal subjects. These findings in the patients are supposed to show the disturbances in regulation for O₂ deficiency.

Dr. Suemitsu examined the effect of acute induced anoxia on hepatic metabolism. He examined the difference of splanchnic oxygen consumption, the release of glucose and the C₃-acid metabolism in 10% oxygen loading between normal subject and cases with hepatic disease. In normal subjects, remarkable increases in hepatic O₂ consumption, release of glucose and normal equilibrium in C₃-acid metabolism were observed during acute induced anoxia. In the patients with hepatic dysfunction, it was observed that hepatic O₂ consumption was decreased or not altered, release of glucose was less than in the normal subjects and C₃-acid metabolism was negatively balanced. He proposed the following consideration from these findings. In the normal liver, aerobic metabolism is so well maintained and capacity of C₃-acid metabolism or albumin storage are so abundant that energy for anaerobic glycolysis is not so much needed in the acute induced anoxia. Glucose released by hepatic glycolysis is supplied to other organ, i. e. cerebrum.

Therefore normal liver plays such compensatory function that glucose released by hepatic glycolysis is supplied for other organ i. e. cerebrum to utilize in anaerobic glycolysis. On the other hand, in the damaged liver acute induced anoxia causes the decrease in hepatic blood flow, hepatic O₂ consumption and anoxic state of liver

cell. Such liver cell utilizes for glycolysis abundant energy which is supplied from glucose released by hepatic glycolysis in liver cell itself. Hepatic glucose is converted to C_3 -acid which is excreted from liver cell.

PROF. S. SAITO: Dr. Hayashi and Motoyoshi studied on the relationship between the decrease in blood pressure and the hepatic damages which were certified by hepatic biopsy. They found the significant relationship between the decrease in blood pressure and such changes as liver cell necrosis, eosinophil changes or swelling. However they concluded prudently that such relationship should be considered from the dysproteinemia of diseases other than liver diseases.

Dr. Mukaino examined the relationship between the myocardial damages and the metabolic disturbances with special reference to electrocardiographic changes in liver cirrhosis or hepatic cancer. ECG changes are rather more found in liver cirrhosis and liver cancer and in parallel with the severity of disease. Especially ECG changes are rather marked in the cases of old aged or with ascites, hepatic insufficiency. Depression in ST segment, flattening of T waves or prolongation of QT interval are fairly correlated with the grade of dysproteinemia. Regarding dyselectrolytemia, ECG changes are prominent in the cases with marked fluctuation in Na/K ratio. Moreover hypocalcemia aggravates the ECG changes such as frequent occurrence of flat T waves or prolonged QT intervals.

Dr. Nangu examined the influence of Levy's test on ECG of primary hepatic diseases. Positive Levy's test was found in 30% of total cases with liver diseases and in 28% among the patients with hepatic diseases showing normal ECG at rest. He considered these findings as the severe deficiency in myocardial O_2 uptake in comparison with the disturbances in cardiohepatic blood flow.

Dr. Inagaki studied patho-histologically on the myocardium of the typical Wuhrmann's myocardosis and Hegglin's 'Energetische Dynamische Herz Insuffizienz'. PAS substances were revealed to be scattered in myocardium and rather frequently in left ventricular wall.

Dr. Shozawa also found this PAS substances rather more in the myocardium of septum.

Drs. Shozawa, Terao and Ohtsu also agreed with the presence of Rinzbach's mantel edema. Moreover Dr. Terao emphasized the characteristic lesion as perivascular accumulation of collagen which were first found by Prof. Takizawa. However Drs. Shozawa and Ohtsu reserved their opinion to support this findings to state that the significance of this changes should be considered from the thorough examination on the liver cirrhosis or hepatic cancer.

PROF. H. IMANAGA: Since manifestations of portal hypertension may vary from patient to patient, and they can be affected in various ways by the types of operations employed, it seems wise to fit the operations to the individual, and hence it might be appropriate to classify portal hypertension according to the site of the obstructions at pre- and post-sinusoidal levels.

First, since portacaval anastomosis is not feasible for a patient with extrahepatic obstruction of the portal vein, splenorenal anastomosis is advisable. However the operation is quite often not successful because of small size of the opening at the site of the anastomosis. But Prof. Inokuchi has obtained the good results by splenorenal anastomosis using a new device of vessel suture instruments invented by himself. Another method, splenocaval anastomosis has been brought about by Dr. Itaya. However, a long term observation following such operations should be made and this may lead us to judge the final results.

Second, it is worth while to point out again that intrahepatic portal hypertension should be divided into two main groups; presinusoidal and postsinusoidal obstructions. Dr. Hidemura from my department reported 66 patients who belonged to a group of presinusoidal obstruction in which end-to-side portacaval anastomosis showed excellent results in a long term observation up to 8 years. Whereas 65 patients demonstrated the postsinusoidal obstruction in which nearly half of the patients died with hepatic coma within a few years. According to these results it is also well recommended that portal hypertension should be classified according to the differences in the altered hemodynamics of the liver; namely pre- and post-sinusoidal obstructions to the portal vein.

There are some controversial opinions reported concerning the types of shunt procedures. We believe that end-to-side portacaval anastomosis almost certainly is the most reliable for long term patency and depressing the elevated portal pressure. However we could not agree with Dr. Sugiura's presentation in which he prefers the side-to-side anastomosis to the end-to-side. Because we demonstrated virtually total diversion of portal blood flow through side-to-side shunt with minimal amounts of the blood entering the hepatic portion of the portal vein. Moreover the reverse blood from the hepatic artery bypassing the sinusoids is proved to have untoward effects on the hepatic cells.

Last, I congratulate Prof. Kimura on his splendid work for Budd-Chiari syndrome. In 1950, Dr. Bennet suggested that a patient with Budd-Chiari syndrome due to membranous obstruction of the inferior vena cava could be surgically treated in near future. Prof. Kimura will be honored as the first pioneer who had achieved such an operation with great success. He demonstrated an interesting experiment in a dog's embryo that a pendle movement in blood flowing is visualized by cinerentgenography at somewhere between the heart and the opening of the hepatic veins. This phenomenon has been considered to develop an abnormal membranous obstruction in the inferior vena cava.

CHAIRMAN: Then, I should like to ask to the special speaker—Prof. Maekawa—for his comment.

PROF. M. MAEKAWA: Here, I want to additionally emphasize the significance of hypoproteinemia on the development of edema in congestive heart failure. In misinterpreting the edema due to hypoproteinemia as simple cardiac edema, diuretic syndrome is often induced by administration of potent diuretics in the cases with congestive heart failure. Especially, hypoproteinemic edema is mainly caused by hypoalbuminemia. Edema is easily occurred under 3g% of serum albumin concentration even when the venous pressure is maintained in normal level.

Hypoproteinemic edema has been often reported but has never been considered with refer-

ence to the dilution syndrome. Secondary aldosteronism is often found in the severe congestive heart failure. However aldosterone secretion is decreased in the intractable phase of congestive heart failure. Therefore when diuretics are administered in the course of congestive heart failure, increase or decrease in aldosterone secretion is alternately occurred. Such hormonal fluctuation in the severe congestive heart failure causes hyponatremia or normonatremia in lowest normal range. When aldosterone secretion can not be increased in response to the diuretic administration, terminal stage is drawing to a close after frequent repetition of the above-mentioned hormonal regulation. Naturally this hypoproteinemia should be considered from not only hepatic but also protein metabolism in whole body.

CHAIRMAN: Thank you very much. Then, Prof. Aizawa! would you please make your special speech?

PROF. T. AIZAWA: We measured cerebral circulation and metabolism in hepatic disease and coma by the nitrous oxide method. Though the mechanism of hepatic coma is unknown, measuring cerebral circulation and metabolism will be one step of the procedures this problem.

We studied cerebral circulation and metabolism in various states already, and found cerebral oxygen consumption ($CMRO_2$) were decreased in coma by what kind of origin would be induced.

In hepatic precoma, cerebral blood flow (CBF), $CMRO_2$ and cerebral glucose consumption ($CMRgl$) was slightly elevated. In hepatic coma, CBF, $CMRO_2$ and $CMRgl$ were decreased. These results were almost coincided with that of Bodechtel's and Scheinburg's. But Scheinburg reported $CMRgl$ decreased more than the decrease of $CMRO_2$ in hepatic coma. Bodechtel showed CBF and $CMRO_2$ were normal, only $CMRgl$ was decreased in hepatic precoma.

He added in coma, CBF, $CMRO_2$ and $CMRgl$ were decreased, especially $CMRgl$ was decreased markedly. The mechanism of decreased CBF was thought by being decreasing cerebral metabolism and arterial carbondioxide tension (PCO_2).

Meyer et al demonstrated that the depressed

cerebral metabolism accompanied the decreased CBF. On the other hand, the cerebral vasoconstrictive effect of respiratory alkalosis was generally accepted by many investigators.

Posner and Plum have reported that the degree of respiratory alkalosis paralleled with its encephalopathic degree.

Inhalation of 5% CO₂ produced no adverse effect on alert liver-cirrhosis, but clinical deterioration and significantly decreased CMRO₂ observed in patients having hepatic encephalopathy.

Acetazole-amide infusion produced no significant clinical or cerebral metabolic change in control subjects. Patients with hepatic encephalopathy showed no CMRO₂ change when given small doses of the drug. However, when patients with hepatic encephalopathy received large doses of acetazole-amide, they promptly deteriorated clinically and significantly decrease of CMRO₂.

Meyer, Gotoh and Tazaki have demonstrated experimentally the elevation of hydrogen ion concentration in brain tissue has accompanied by the EEG slowing. They also reported the decrease of pH in brain tissue after the administration of acetazole-amide.

From these results it is assumed the function of the brain in hepatic coma worsened by the elevation of hydrogen ion concentration in brain tissue. The chemical control of the cerebral vessels has already received by Tazaki and Gotoh.

They emphasized the important role of the hydrogen ion concentration in the target point of the cerebral vessels. The changes of the arterial carbon dioxide tension (PCO₂) was demonstrated as the most effective factor for the control of the tone of cerebral vessels.

In hepatic coma, the decrease of arterial PCO₂ was most important factor of the depressed CBF.

Bessman et al has reported the uptake of ammonia into brain was roughly proportional to the arterial ammonia concentration. Nakazato, one of our co-workers, presented the same results.

The ammonia intoxication should be one of the chemical factors in hepatic coma. The exact mechanism of the cerebral metabolic disturbance

in hepatic coma is unknown.

In this report, it is concluded that the decrease of cerebral circulation and metabolism were confirmed in hepatic coma, and it was also suggested that the elevated hydrogen ion concentration in brain tissue has undesirable effects on brain function and metabolism.

CHAIRMAN: Thank you. Then, I will read an abstract of Prof. Yoshida's comment.

PROF. T. YOSHIDA: The liver is unique in its circulatory system. About 70% of the total inflow is venous in nature via portal vein and the portal flow is often reduced considerably in hepatic disorders such as cirrhosis. Changes in hemodynamics are as important as derangements of cellular activity in hepatic dysfunction.

Therefore, the measurement of hepatic blood flow is important clinically as well as in understanding pathophysiology of liver diseases. Many methods using radioisotopes or special dyes have been proposed and being used.

In relation to the interpretation of the data, I would like to point out one thing that should be kept in mind: the most of the methods now being used can not separate hepatocellular dysfunction and reduction of hepatic blood flow.

We have tried a separate determination of the hepatic uptake of I¹³¹-Rose-Bengal and Au¹⁹⁸-colloid which were given simultaneously and found that the hepatocellular dysfunction was not always related to the degree of reduction of the hepatic blood flow especially in those who had cirrhosis.

Further development in this field is wanted by clinicians and researchers.

CHAIRMAN: Here, I will make my special lecture on "A Metabolic Compensative Function of the Liver in an Acute Induced Hypoxemia" showing some slides.

(1) This slide shows the percentage change in blood flow of important organs during induced hypoxemia. The blood flow increases in each case, especially that of the coronary increases the most followed by the liver, brain and kidney in this order.

(2) The oxygen consumption in healthy

subjects tends to increase slightly in the myocardium, or is nearly maintained in the brain and kidney, while it increases as much as 80% in the liver, despite a large drop in the systemic arterial oxygen saturation. This is a special reaction of the liver which is seen during induced hypoxemia and is worthy of special note.

(3) The next slide compares the hepatic circulation and metabolism of normal and diseased cases. From left to right, the graph shows normals, pulmonary tuberculosis, recovery period of acute hepatitis, chronic hepatitis and hepatic cirrhosis. The same hypoxemic condition, which in healthy subjects causes a 80% increase in hepatic oxygen consumption, was induced in each case, but the increase in hepatic oxygen consumption was very small in diseased cases, and in cirrhosis, even a moderate decrease was seen. It is felt that this difference in response by the condition concerned is a point should be kept in mind.

(4) The mechanism by which the oxygen consumption increases in the liver was considered. The hepatic blood flow increases in healthy subjects, but a more marked percentage increase of the coronary circulation is seen and a clear increase of the cerebral blood flow is also seen. However, the increase of myocardial oxygen consumption is small and the oxygen consumption of the brain is nearly maintained or even slightly decreases. Therefore, the high increase in oxygen consumption by the liver can not be due to the increase in blood flow alone.

More important factors seems to exist to clarify the mechanism of this increase of oxygen consumption.

This slide shows the percentage differences in A-V i. e. differences in arterial-venous contents of oxygen (in the horizontal axis) and oxygen saturation (in the vertical axis). The saturation decreases as higher the point is, ○ is the coronary, △ brain and ● liver. In the brain and heart, when the A drops, A-V also becomes small because of the small A. However, in the liver, many cases increase the A-V despite a drop in A. As seen in the following figure, when the consumption rate $\frac{A-V}{A}$ is considered, this decreases or is only maintained in the other

organs while in the liver there is no case in which this decreases can be found and contrarily a fairly large increase is noted in each case. This is one important point.

The next slide shows the relations with the blood flow. In organs other than the liver, when the blood flow increases, the A-V decreases in proportion. While with the liver, the A-V increases markedly in cases with no increase in blood flow, and some increases is seen even in cases with an increase in blood flow. This increase in A-V during hypoxemia is seen only in the liver. Comparison of $\frac{A-V}{A}$ also shows that

in the liver alone it increases markedly when there is little or a moderate increase in blood flow.

These facts indicate that in the liver, besides the increase in blood flow, the ability to consume oxygen increases markedly especially in healthy subjects during hypoxemia.

(5) Next is the change in enzyme reactions of mice organs due to induction of hypoxemia. Respiration of 5% O₂ causes the respiratory enzyme system of various organs to decrease its activity, but this decrease is relatively small in the liver. Furthermore, a mild hypoxia due to 10% O₂ respiration (the same concentration as in the human tests) causes a definite increase in the liver enzyme activity, such as is not seen in other organs. This fact appears to be related to the increase in hepatic oxygen consumption of healthy subjects which is seen during administration of 10% O₂.

These facts indicate, by the speaker's opinion, that the liver has a metabolic compensative function in an acute induced hypoxemia.

This slide is a case of 30 years old male with severe cyanosis, with clinical findings compatible with tetralogy of Fallot. He has severe clubbed fingers and polycythemia. The hemoglobin is also increased tremendously. The patient has no respiratory insufficiency in the ventilatory phase, but polycythemia due to a chronic decrease in the oxygen saturation of the systemic arterial blood. The renal blood flow is greatly decreased in this case, and the hepatic blood flow is also decreased. Generally speaking, in acute induced hypoxemia, the hepatic blood

flow increases remarkably in healthy subject, slightly in those with light liver damage, and decreases in those with severe liver damage. This patient does not have very severe hepatic dysfunction, therefore it appears that chronic hypoxemia might not cause an increase or chronic polycythemia might cause a decrease in the hepatic circulation. Our investigations are those of acute induced hypoxemia and there may be quite probably some difference from those of chronic respiratory insufficiency.

CHAIRMAN, PROF. K. HARA: Now we will begin the free discussion on the problems concerning circulation, with special reference to topics in each symposium and this panel discussion. The first group moderated by Prof. Yoshitoshi and participated by Prof. Kosaka and Imanaga, Em. Prof. Mikamo will discuss on the methods of determining hepatic circulation in normal subjects and the patients with hepatic diseases.

MODERATOR, PROF. Y. YOSHITOSHI: Among these problems to be discussed now with regard to hepatic circulation, the most important thing is just the interrelationship between its circulation aspected from the point of the whole liver, i.e. that obtained as a mean value of the intralobular circulation and each intralobular one itself, because each status of the intralobular one will be not the same, but rather much different here and there.

Therefore, we can easily assume that the changes of the intralobular circulation will be not paralleled with the mean value of the whole hepatic blood flow. In other words, when we could obtain its reduced hepatic blood flow in human at the clinic, what sort of changes would it occur in its intralobular blood flow?

Furthermore, as its basic problem, it is of much interest to make clear the behaviors of the substances or pigments in the lobulus in situ, which have been used as a routine method to estimate hepatic blood flow. Prof. Kosaka, please give us your lecture on this subject.

PROF. KOSAKA: As you know, current methods for determination of hepatic circulation are based

on the Fick's principle and very primitive ones. Recently several new methods are introduced into this field.

Generally speaking, substances for determination of hepatic circulation have an affinity for liver cells, either parenchymal or reticulo-endothelial cells. Galactose, Rosebengal or Bromsulphalein is mainly taken by parenchymal cells; radio-isotope gold is mainly used for the analysis of reticulo-endothelial system.

Indocyanin Green or Asorbin S is also seldom used. The rate of hepatic uptake or hepatic extraction for such dyes or substances is calculated by either determining their concentration in serum or blood samples or extracorporeally counting the radio-activities.

This calculated values are considered to show the hepatic circulation. Hepatic hemodynamics is assessed from the rate of hepatic uptake or extraction in the current methods. This assessment is accurate in the acute stage of hepatic disease but is not always correct in the chronic stage, in which the disturbances in parenchymal cell or reticulo-endothelial system are so complicated that the fluctuation in the calculated values is very problematical.

Although galactose is considered to have 100% of extraction rate, slight fluctuation of measured value in individual cases should be cautiously interpreted. Next problem is concerned to the intrahepatic shunt through which the blood flow out the liver without having influence to neither hepatic parenchymal nor reticulo-endothelial cell. The problem on intrahepatic shunt was anatomically discussed in the Symposium on hepatic micro-circulation.

However, on our Symposium the function of the intra-hepatic shunt was discussed. According to Prof. Nakamura, when galactose concentration in the serum of systemic circulation is low in the course of galactose tolerance test, the substance in hepatic vein is not found in normal subjects but found in the cases with intra-hepatic shunt.

MODERATOR, PROF. Y. YOSHITOSHI: Thank you for your comment. Each substance used to estimate hepatic blood flow has a different significance respectively, because of a difference in its clearance rate from the liver. If 100%

of the injected galactose will be cleared up from the liver, it must be true that the galactose taken into the Disse's space from the sinusoid is not to be leaked into lymph flow at all and all the galactose must be taken into the hepatic cell. However, it is not easy to be confirmed that by experimentation. In the present symposium "microcirculation", there were presented several techniques employed, i. e. biomicroscope, colloidin injection method, electronmicroscope, as well as method on lymphatic flow. It is, of course, difficult to apply them all to clinical use, however, there has recently been progressed the method to be applied clinically for lymphatic flow.

Would you present your opinion in this subject, Dr. Mikamo.

EM. PROF. MIKAMO: Just as pointed out by Dr. Yoshitoshi, so far as the blood circulation is concerned, the hepatic circulation in various liver diseases has been extensively studied from physiological as well as patho-anatomical points of view. It has been suggested, however, by some surgeons, that ascites in liver cirrhosis comes from the surface of the liver where lymph channels are apparently dilated, and therefore, lymphostasis rather than portal hypertension may play a more significant role upon the accumulation of ascites in cases of liver cirrhosis. Furthermore, recent studies on the pathogenesis of ascites have indicated that the pure type of portal hypertension, in the other words, presinusoidal portal hypertension may not lead to the production of ascites, but, on the contrary, impair the absorption of ascites. There are considerable technical difficulties in the study of lymph circulation from clinical aspects. Recently, however, a lymphographic technique was introduced and using the method modified in our clinic we were able to demonstrate deep-seated metastatic lymphadenopathies in patients with malignancies in the pelvis and abdomen. I think that this technique will give us a promising field for investigation of lymphatic flow in the abdomen including the liver. Lymph vessels have been illustrated in the preceding presentation. They are probably on the basis of animal experiments, aren't they?

MODERATOR: Yes.

EM. PROF. MIKAMO: Well, certainly they are experimental studies. It is possible to visualize lymph channels by a dye injection but the dynamic aspects of lymph circulation cannot be properly evaluated. It is extremely difficult to insert a very fine needle into the lymph channel and keep it fixed in an adequate position. The details of the technique will not be given here.

Utilizing the lymphographic method it will be possible to obtain some lymphodynamic informations. To my regret, our own data are not available as yet, but I hope I would be able to show you some data on the next occasion.

MODERATOR, PROF. YOSHITOSHI: There were a few reports on the techniques of lymphography at the last Meeting of Japanese Angiology. Several lymphograms have been demonstrated there. But I heard the technique was rather difficult.

EM. PROF. M. MIKAMO: The lymphography technique is said to be available currently in a few university clinic in Japan. The roentgenographic demonstration itself is not difficult if an adequate amount of the opaque media, ethiodol in oil, is injected correctly into the lymph channels.

MODERATOR, PROF. Y. YOSHITOSHI: However, are there the accuracy in the current method to measure the radius of lymph vessels?

EM. PROF. MIKAMO: Well, I think, it would be safely stated that the "lymphangiographic" diameters of the channels beyond the first lymph node from the site of injection may represent their almost "in vivo" diameters, because an influence of the injection pressure will not reach the channels beyond the first lymph node.

May I ask Dr. Imanaga? Don't you frequently observe during the surgical procedure the lymph dripping from the liver surface?

PROF. H. IMANAGA: In answering to Dr. Mikamo, ascites can be produced in animals by constriction of the hepatic veins, and be observed in patients who showed elevated wedged hepatic vein pressure, suggesting that obstruction to hepatic vein outflow (postsinusoidal obstruction) is the primary factor in the pathogenesis of ascites. In such cases the lymphatics at the hilum of the liver were extremely dilated, sometimes as large as the hepatic artery in diameter.

EM. PROF. Y. MIKAMO: Can you see by your eyes?

PROF. H. IMANAGA: Yes, we can see it. In ascitic patients and dogs the thoracic duct is usually dilated due to increased lymph flow resulting from postsinusoidal obstruction in the liver. Consequently it is clear that the thoracic duct may play an important role in the drainage of the lymph from the liver. Indeed, in our experiments, continuous draining of the thoracic duct lymph in the neck causes the disappearance of ascites. However on such clinical methods were found so far.

Interestingly enough, it was confirmed that end-to-side portocaval anastomosis was followed by successful dissipation of ascites due to the decompression of the liver itself by diverting a portion of the inflow blood volume, and the acceleration in absorption of fluid and electrolyte via the peritoneum. Therefore, it can be said that elevated portal pressure has a minor role in producing ascites but is of great significance in absorbing the ascites.

PROF. M. MAEKAWA: There is an opinion that the ascites is not transudated from splanchnics but from the surface of liver. This opinion is supported by the following experimental results on analyzing the thoracic lymph flowed out the liver. This analytical data indicate also the possibility that the ascites is rather absorbed from splanchnics.

MODERATOR, PROF. Y. YOSHITOSHI: Prof. Maekawa offered the difficult problem. Prof. Ueda! have you any comment as a specialist for hepatic diseases?

PROF. H. UEDA: The problem on lymph is one of obscure field on the occurrence of ascites. Our internist should consider about the findings as Prof. Imanaga pointed out. However, dripping of the lymph from the surface of liver is so slight and slowly that massive ascites can not be ascribed to this mechanism alone. Meanwhile we must treat the ascitic patients is considering this findings.

EM. PROF. M. MIKAMO: Still, lymph is often exsudated on the surface of liver in rapidly stripping out the hepatic capsule.

PROF. H. UEDA: I think there are the threshold for exsudation in such cases that lymph drips

and out from the liver surface. But, amounts of lymph exsudation is not so much as to have influence on the measurement of various amounts in circulation. In this case such lymph is supposed to be ready to make the ascites.

PROF. H. IMANAGA: We observed that fluid transdates from the capsule of the liver, and this capsular fluid contains as much protein as in serum. While retained in the peritoneal cavity, the concentration of protein gradually decreases, possibly due to the absorption of protein via the lymphatics and the thoracic duct.

MODERATOR, PROF. Y. YOSHITOSHI: Prof. Kosaka! may I ask you any comment?

PROF. K. KOSAKA: We observed often in the cases with chronic hepatic diseases or liver cirrhosis, the lymph accumulation, sometimes simulating to a cyste and the dilatation of lymph vessels in the liver margin. From these findings I think the micro-circulation must be considered in the abnormal condition of liver.

MODERATOR, PROF. Y. YOSHITOSHI: I thank to speakers for their earnest discussions on the problem about the lymph. I think also this problem is one of the most obscure field in the pathogenesis of hepatic diseases or circulatory disorders. Thank you very much again.

CHAIRMAN, PROF. K. HARA: The second group moderated by Prof. Kusui and participated with Prof. Maekawa, Ueda, Aizawa, Maeda and Hirosawa will discuss on the congestive heart failure.

MODERATOR, PROF. K. KUSUI: We have no enough time to discuss in detail, because it is too late. Professor Aizawa, you spoke about the cerebral circulation in the liver damage and concluded that the final important factor of the hepatic coma may be due to the fall of pH in the brain. Then, what plan do you take at the treatment of hepatic coma?

PROF. T. AIZAWA: Already the data in hepatic coma showed the decreased cerebral blood flow and metabolism. At the same time, it was also suggested any procedure which elevates hydrogen ion concentration in brain tissue had undesirable effects on brain function and metabo-

lism. It is very hard to say that the hydrogenation of brain tissue in hepatic coma should be acidosis or not. The decrease of cerebral blood flow is caused by the respiratory alkalosis, and the mechanism of respiratory alkalosis in hepatic coma is unknown. So how to improve effectively the cerebral circulatory disturbance in hepatic coma is unknown. The elevation of arterial Ammonia in hepatic coma was suggested as an important factor of this disturbance. So some methods to decrease the blood Ammonia concentration are the first choice of this disease.

PROF. T. MAEDA: May I ask Dr. Aizawa about the difference of the following two types of hepatic coma in view of cerebral circulation? That is my understanding reveal that there are types, one in which convulsion starts followed by hepatic coma, and the other in which hepatic coma starts from the very beginning.

PROF. T. AIZAWA: I am sorry to say that we have no data about it.

MODERATOR, PROF. K. KUSUI: Professor Ueda classified the refractory cardiac failure into four groups and showed the pathological findings of lung, liver, kidney and supra-renal gland body. And Professor Maekawa noted marked hypoproteinemia in the refractory cardiac failure. According to these data, it seems to me that the liver is not only the secondary factor, but also some what important element in the cardiac failure. About this problem, Professor Maekawa and Ueda, please show us your opinions.

PROF. H. UEDA: Several years ago, Prof. Maekawa showed the excellent results of the study on the relationship between the congestive heart failure and the hepatic function but then he did not draw the conclusion. He concluded clearly in his yesterday's lecture. Cardiac diseases are often followed by the hepatic disturbances. Especially chronic heart failure is frequently complicated with hepatic congestion showing sometimes slight jaundice. Such liver dysfunction will be followed by the abnormality in serum protein, especially the hypo-albuminaemia. Moderate or severe deteriorations are revealed histologically and functionally in the liver so the cases with congestive heart failure, of pulmonary edema type or of general dropsy type among four types which I classified in my lec-

ture. Hepatic disorders and digitalis administration will take away the patient's appetite and induce the hypoproteinemia. Moreover digitalis exerts no beneficial effect in the hypoproteinemia. This nutritional abnormality will have an influence to the function of adrenal gland or kidney. Therefore I think the problem on hypoproteinemia is very important to treat the patient with congestive heart failure.

I wish to notice that the process in the amelioration of congestive heart failure by means of adequate treatment is very interesting. By the appropriate therapy, edema decreases, circulatory blood volume increases; on the other hand the hypoproteinemia rather increases. However such hypoproteinemia is easily diminished by the improvement of circulatory efficiency, then body weight rather rapidly decreases; After total complete recovery from congestive heart failure body weight sometimes increases again due to not the edema accumulation but the increment in body protein.

PROF. M. MAEKAWA: I would like to add a few comments. I emphasized the importance of hypoproteinemia in the pathogenesis on congestive heart failure. However, hypoproteinemia would play only the secondary part on the occurrence of decompensation.

It is yet true that the primary cause of congestive heart failure consists of the 'back-ward' congestion due to the disturbance of 'Starling's Law' in the heart. Several years ago I assumed that the edema would be caused by the decrease in renal blood flow due to the back-ward congestion. This time I noticed the importance of hypoproteinemia induced by the hepatic disturbances and presented my opinion on the pathogenesis of edema in the congestive heart failure.

MODERATOR, PROF. K. KUSUI: Prof. Ueda talked about the cardiac cirrhosis. Prof. Maeda! would you please talk about the problem on prophylaxis for cardiac cirrhosis?

PROF. T. MAEDA: It seems that enzymatic activities reflect symptomatic manifestations. Those cases of congestive heart failure which leave pain increase in enzymatic activities of the serum especially an increase in LDH in the presence of improvement in routine hepatic func-

tion tests may be frequently subjected to aggravation of cardiac insufficiency.

MODERATOR, PROF. K. KUSUI: Each speaker stated the importance of causal therapy in the cardiac failure. I think it is more important to prevent and to remove the inducement to decompensation of the cardiac function, especially various infections in the patients with compensated heart diseases. Doctors, may I look for your answers?

PROF. M. MAEKAWA: It is sure. Yet, the prognosis of mitral stenosis is very poor, same is about myocardial fibrosis. The therapy on these diseases is very difficult without the complete understanding of the collagen.

MODERATOR, PROF. K. KUSUI: Prof. K. Hirosawa! Have you any comment on mitral stenosis.

PROF. M. MAEKAWA: Successful treatment can not be expected on mitral stenosis with the medical procedure. Pulmonary capillary pressure is about 30mmHg being near the oncotic pressure even when adequate treatment is put upon the case with mitral stenosis. Surgical treatment must be performed. I think the decompensation in the mitral stenosis should be referred rather to "mechanical obstruction".

PROF. K. HIROZAWA: I have same opinion as Prof. Maekawa.

MODERATOR, PROF. K. KUSUI: I thank to speakers for their fruitful discussion.

CHAIRMAN PROF. K. HARA: I should like to ask next moderator, Prof. Saito to begin the discussion. Prof. Torii, Sasamoto and Yoshitoshi will be participated in this discussion.

MODERATOR, PROF. S. SAITO: I should like to ask Prof. Torii.

Would you please summarize on the problem about the hepatic circulation in hemorrhagic and anaphylactic shock among speeches in your symposium? I beg you, in particular, to comment on the differences in hepatic circulation between anaphylactic and hemorrhagic shock and the reversibility and irreversibility of these shocks.

PROF. T. TORII: We have done the experimental studies on the hemodynamics in anaphyl-

actic and hemorrhagic shock in the dog. Therefore, we can not assert whether our results are applicable on the human beings or not.

The following hemodynamic disturbances were observed in the hemorrhagic shock of the dog. In the initial stage, blood reservoir in the liver is discharged into systemic circulation to maintain the circulatory blood volume. When bleeding became more markedly, hepatic blood flow diminished in parallel with the decrease in cardiac output.

Hemodynamic disorders in this stage is yet reversible and can be ameliorated by blood transfusion. However, in the severe hemorrhage, hepatic blood flow decreased despite the invariable cardiac output, so, hepatic congestion occurred and oxygen consumption in the liver was also markedly diminished. This hepatic circulatory disturbances may be caused by the sphincter mechanism peculiar to the dog liver. Catecholamine excretion gradually increased to death.

Concerning the anaphylactic shock, features are very varied according to the species of animals. The guinea pig in anaphylactic shock succumbs to the emphysema asphyxia due to bronchial spasm. On the other hand, in the anaphylactic shock of dog, the sphincter mechanism in the animal's liver play a great part to cause the decreases in venous return, cardiac output and blood flow. In this case albumin extravasation is also the most characteristic feature and intimately related to the animal's death. Pre-treatment with cortico-steroid hormones or antihistaminics can prevent this albumin extravasation and make the critical state improve.

However I think the hemodynamics in the terminal stage would be disturbed in anaphylactic shock in same feature as hemorrhagic shock. I can not now elucidate whether the anaphylaxis in human beings is of dog's type or guinea pig's type or of combined form. However, considering from clinical findings in anaphylactic shocks in patients, abrupt hypotension indicates the decrease in peripheral vascular resistance, in venous return and in cardiac output. On the other hand, human anaphylactic shock is associated also with albumin extravasation as

manifested in the glottis, pulmonary, hepatic or cerebral edema on autopsies. Therefore I suppose that vital response in terminal stage in shocks would be same though the hemodynamics in the initial phase is different between the anaphylaxis and hemorrhage.

MODERATOR, PROF. S. SAITO: I thank you for your comment about the academic illustration and the suggestion for treatment on shocks. Dr. Sasamoto! It seemed to me that, in your symposium, there was an important problem concerning the method or the interpretation of assessments in the studies on respiratory insufficiency; that is the difference between the chronic respiratory insufficiency and the acute induced anoxia. May I ask your comment on this problem?

DR. H. SASAMATO: From clinical pulmonary physiology, I have considered the respiratory insufficiency as the acute or chronic oxygenation insufficiency or CO₂ elimination insufficiency due to the disorders in a broad sense including lung, chest or trachea. Clinical evidences of respiratory insufficiency can be disclosed by the changes in arterial blood i. e. anoxemia and/or hypercapnia. However, studies on hepatic circulation in respiratory insufficiency are very difficult in practice. Studies are made on the patient with respiratory insufficiency or by experimentally ligating the pulmonary arteries or the bronchus or by abnormally infusing the pleural cavity.

As the above mentioned experiments are very troublesome, acute induced anoxemia or hypercapnia are often tried.

But I think the acute induced anoxia or hypercapnia essentially don't simulate respiratory insufficiency, but is acute induced anoxia or hypercapnia itself. Especially, in the case of acute induced anoxia, interpretation of assessment should be made considering the influence of hyperventilation necessarily accompanied with the procedure.

It is because hepatic circulation i. e. portal blood flow or hepatic blood flow is influenced by the ventilatory movement. Study on hepatic circulation is made by loading the acute induced anoxia on the patient under previous hypercapnia i. e. under anoxia plus hypercapnia. Con-

dition under anoxia plus hypercapnia is pulmonary-physiologically "asphyxia", and is followed by hyperventilation. Respiratory alkalosis should be considered in hyperventilation under asphyxia. As Prof. Aizawa point out, respiratory alkalosis has an influence to the cerebral respiratory center which indirectly affect the hepatic hemodynamics. Acidosis or alkalosis causes constriction or dilatation of the blood vessels.

MODERATOR, PROF. S. SAITO: Thank you Dr. Sasamoto. Now I wish to state my impression on the symposium which I presided. This impression is same as the thought which has born in my mind through my doctor's life as a clinician. On the patient's death, I have always obliged to meditate whether the cause of his death could be ascribed to the autopsical findings alone or not. In the to-day's symposium, various pathological findings such as the appearance of PAS positive substances, basophil granula or cresyl-violet substances in myocardium of the aged and the cases with myocardial fibrosis due to coronary insufficiency were demonstrated. On the other hand, senile lipochrome pigments are often found in the apparently normal region in myocardium of the case with myocardial fibrosis owing to not myocarditis or coronary sclerosis. It is difficult in the latter case to differentiate the lesion resulted from the myocardiodis from the myocardial fibrosis due to coronary insufficiency.

Then I should like to ask Prof. Yoshitoshi to comment on the following problems. Do you apply on the risk of serum hepatitis the blood transfusion on the patient with dysproteinemia? What digitalis derivatives do you prescribe to the patients with hypoalbuminemia? What procedure should be applied to the dyselectrolytemia? Have you experienced the successful treatment on the dyselectrolytemic patient with spironolactone?

PROF. Y. YOSHITOSHI: I already reported some aspects on serum protein patterns in heart failure, with reference to those in patients with edema, at the 17th Annual Meeting of the Japanese Heart Association in 1953.

When an intense edema exists, we find, in general, hypoproteinemia, much or less, how-

ever, its degree is usually lesser than it found in nephrotics or cirrhotics. Therefore, it is so doubtful that all such changes are to be called dysproteinemia, because there have been seen some cases having sera only diluted and normal A/G ratio.

Cardiac glycoside, in fact, has rather little influence on heart failure with hypoproteinemia and also the same with diuretica. If so, it should be supposed that such conditions are due to secondary lesions produced by the precended heart failure, such as some nutritional disorders, accordingly no symptoms are improved by an enhancement of heart muscle efficiency only.

In all the heart failure, no dyselectrolytemia has always been found, but sometimes it is true, i. e. hypokalemia which will be related to malnutrition or the function of the adrenal cortex, and hyponatremia which is usually found in serious cases and probably connected with an intake of too much water. Accordingly, it may be so good to control water intake in the heart failure patients.

Spirolactone has only a little effect on those having hyponatremia or hypoproteinemia also. Hypoproteinemia found in heart failure is mostly resistant to any treatments and in addition I have had no experiences before that human albumin showed a dramatic effect on such cases. However, it is to be tried once, I think.

MODERATOR, PROF. S. SAITO: I have not considered the cardiac involvement in hepatic diseases as decompensation but as the disturbance in energy production and the energy utilization. As well known, deficiency in energy production is caused by the disturbance in Krebs's cycle system; defect in energy utilization consists in the disturbance in myosin-actomyosin system in myocardium. Therefore all matters of decompensation are with the myocardium itself. I agree with Prof. Maekawa in this point. While we have only scanty knowledge about the glycogen, fat, protein and other cell elements on the process of energy production. Cardiac involvement due to the deficiency of these energy source is referred to "Substrat Herz Insuffizienz" by German school or "Energetische Dynamische Herz Insuffizienz" by Prof. Hegglin.

CHAIRMAN, PROF. K. HARA: Thank you very much. I would like to say a few words. Dr. Sasamoto has just spoken about a strict criteria of respiratory insufficiency. As you all know, he is an authority in the field of respiratory function and he had expressed his wishes that he wanted to follow a definite criteria in order to carry out his studies.

I think that it is very important to know what the influence of respiratory insufficiency is on the circulation and for metabolism of the liver and what relation it has on the regulatory functions of the whole body. Studies on chronic respiratory insufficiency are of course important but from a clinical point of view, those on acute respiratory insufficiency per se are also quite important. For instance, in cases of disturbances due to respiratory tract infections or smog disease, acute respiratory insufficiency becomes an important problem. However, it is almost impossible to study the hepatic circulation and metabolism of patients with acute respiratory insufficiency. But, we can not just stand by because it is difficult, we must make progress. Of course, we must not make misjudgments in the course of the study, and we should be careful about this point as we carry on our study.

I express my respects and gratitude to Dr. Sasamoto, who agreed to and undertook the task of acting as chairman of the symposium on the problem of hepatic circulation and metabolism in respiratory insufficiency which is a field that has just gotten its start.

I was unable to listen to the discussion on myocardiosis, but I was most interested in the patho-histological problems. According to the abstract by Prof. Saito and Dr. Ōtsu, edema of interstitial tissue of the myocardium and edema or degeneration of the cells per se were the main findings. They did not mention the coronary artery, and probably, there was no change worth noting there. I compared these changes with the Kokusan disease in Manchuria which I studied previously. We have also studied the myocardial patho-histology of some cases of hepatic cirrhosis, but I feel that this study should be done by authorities like Dr. Ōtsu and Prof. Saito who have been engaged for many years in the study of myocardial

changes due to coronary disease for comparison. That is why I asked them to take up the problem. I understood that the interstitial and cellular changes of the myocardium were the main changes in hepatic cirrhosis, —am I right?

MODERATOR, PROF. S. SAITO: I wish to add a few words about Dr. Nangu's speech on the oxygen uptake of myocardium in our symposium. We have no proper method for morphologically determining the myocardial O_2 uptake. As Dr. Ohtsu said in his concluding remark, Dr. Nangu's speech gives encouraging suggestion to pathologists. It seems to me—as a clinician—that there are much to solve in the morphological changes. I wish to close this free discussion to emphasize the necessity of the mutual communication between the clinical and pathological studies.

CHAIRMAN, PROF. K. HARA: Thank you very much. Many of you probably still have much to say, but I would like to close the panel discussion at this time.

First I would like to thank the chairmen of the various symposiums and guests.

I mentioned this before at the opening address this morning, but the reasons I thought of taking up this topic "Problems Concerning Circulation Centered Around the Liver" were,

that this 16th General Assembly of the Japan Medical Congress has very few special lectures and symposiums concerning the liver. Also almost no topic concerning hepatic circulation can be found. On the other hand, those engaged in studying the liver have investigated its circulation to quite some degree during the last few years. Therefore, it was my hopes, to fulfil this defect and to have those engaged in circulation research, surgery and pathology to make public their studies together with those engaged in liver research and discuss together this common topic for the progress of investigations in this field.

I expressed my apologies this morning on the fact that there were some delay in the information of this symposium widely, but the chairmen of the symposiums gave their undivided attention throughout the day and spoke at the panel without reserve and gave us a most worthwhile discussion. I thank them all very much. I also, wish to thank the many speakers who participated in the symposiums. Also, I together with the chairmen and those concerned with the symposiums would like to thank large audience who listened with deep interests here today.

Thank you.