PRESENT STATUS OF APLASTIC ANEMIA IN JAPAN

MITSUTO HASEGAWA

Department of Internal Medicine, School of Medicine
Keio University, Tokyo, Japan

(Received for publication October 2, 1967)

INTRODUCTION

The symposium on aplastic anemia was held at the 8th meeting of the Japanese Society of Clinical Hematology in September 1965 and the author was given an opportunity to be a chairman of the symposium. Considering it to be the chairman’s responsibility, the outline of the speeches and the comparative studies of the different results will be described and some comments also made from my own viewpoint in the present paper.

INCIDENCE

It has long been said that incidence of aplastic anemia in Japan is much higher than that in Europe and the United States. From my previous review of the literature, it was indicated in Europe and the United States that aplastic anemia was found only 3 cases a year on the average in the hospital where distinguished hematologist worked, whereas in Japan 5 to 6 cases a year on the average and that secondary aplastic anemia due to drugs was found more frequently than in Japan. In fact very few in-patients of aplastic anemia were able to be observed during my visiting trip at the various hospitals in Europe and the United States (1957-58). In the symposium, first of all, the incidence of aplastic anemia and leukemia for the last eleven years was studied with the cooperation of many hospitals. The results are shown in Fig. 1, and Table 1. As indicated in the chart, incidence of aplastic anemia is of about 44% of that of acute leukemia, 1.4 fold of chronic leukemia and approximately 33% of total number of leukemia and there is little difference in the ratio before and after 1960. Pediatric patients are excluded in this study, therefore, actual figure is
Fig. 1 Comparison of the incidence of aplastic anemia, acute and chronic leukemia during 11 years. (From 1954 to 1964)

Table 1

Types of Aplastic Anemia reported from 51 Hospitals in Japan

<table>
<thead>
<tr>
<th>APLASTIC ANEMIA</th>
<th>LEUKEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
</tr>
<tr>
<td>Years</td>
<td>Typical</td>
</tr>
<tr>
<td>1954-1959</td>
<td>511</td>
</tr>
<tr>
<td>1960-1964</td>
<td>611</td>
</tr>
<tr>
<td>Total</td>
<td>1122</td>
</tr>
</tbody>
</table>

* Atypical aplastic anemia indicated cases having more than two of following items. (1) More than 10% of reticulocytes. (2) More than 10% of monocytes. (3) No elevation of both serum iron and serum copper. (4) Splenomegaly.
supposed to be higher and continues to increase year after another. From this figure, the importance of the study of aplastic anemia should be emphasized and secondary aplastic anemia reveals approximately of 10%, although much less than Europe and the United States, and pure red cell anemia is by no means few.

CRITERIA OF DISEASE

Since Ehrlich first reported on “aplastic anemia” in 1888, resembling or similar diseases had been reported under various names. However, the criteria for establishing diagnosis seemed to be not always clear (For details, refer to my “Historical review of aplastic anemia”2).

Afterwards various authors have been suggested the various types of this anemia. For instance, Morita3 uses “Panmyelopathie” designating all types of this anemia with the following characters: a) “panmyelophthisis” or “are-generative anemia” for those with rapid progress and extremely reduced hematopoietic tissue in the bone marrow; b) “hypoplastic anemia” for those with slow progress and slight reduction of hematopoietic tissue; c) “chronic pan-myelopathy” for those with slow progress but repeating improvement and aggravation alternately and no exacerbation observed in hematologic findings in long course; and d) “panmyelopathy with pure maturation arrest.” Otherwise Kawakita,4 Hiraki5 and Hattori6 classified the disease mainly based upon the bone marrow findings.

In the symposium, Takaku defined the disease as the disorder in stem cell differentiation by citing Jandle’s Table7. He indicated the following three points as clinical criteria: 1) pancytopenia, 2) hypoplasia of the bone marrow and 3) no responsiveness to specific treatment. Of these, hypoplasia is proved as a rule by bone marrow puncture, however, he called an attention of erroneous diagnosis without studying various parts of the bone marrow and findings of bone marrow could not always be used as a clinical index, since hypoplasia would include, in addition to absolute hypoplasia, relative one advocated by Moor and others—hematopoietic tissue can not be responsive despite of anemia. For determination of hematopoietic function, he indicated 1) investigation of the bone marrow of entire body at autopsy, 2) 59Fe turnover, 3) measurement of total reticulocytes, and 4) excretion of urobilinogen in feces. According to the abovementioned criteria, anemia due to maturation disorder of the differentiated cell will not be included in aplastic anemia, therefore cases of refractory anemia reported by Björkman,8 Dacie et al9 and Vilter et al10 were excluded. This criteria is in fact interesting, however, Morita and Katsunuma offered an ar-
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gument that aplastic anemia with the maturation arrest in the bone marrow
would not be sufficiently explicable. In this regard Uzuka expressed his as-
sumption that such type of anemia would occur due to the lack of unknown
substance during the course of this anemia. Takaku considered the disturbance
in stem cell differentiation as basic cause and something more added to it.
There may be a criticism that stem cell which is not found morphologically yet,
is too imaginary concept. Aside from the adequacy of terminology, however,
broader interpretation of stem cell as erythroblast with mitotic activity will
possibly be more understandable, as Takaku previously pointed out. It seems,
on the other hand, that this definition fails to make clear distinction between
aplastic anemia and pancytopenia due to such as chronic nephritis and systemic
lupus erythematosus. And anemia due to infection or hypothyroidism is also
indistinguishable for which special treatment being available. Takaku mentioned
erthropoietin may use for the purpose of differaritation. The fore-mentioned
criteria, anyhow, may leave some problem to be discussed in future.

The other speaker's criteria were, as they were in the previous reports,
more or less based on the clinical findings. Arimori added siderogram and bone
marrow culture, and serum iron and copper values were added to the above
mentioned criteria by us and Ito stated the significance of result of radioiron
examination.

TYPES OF DISEASE

Takaku showed the number of cases by using Morita's criteria at first and
then divided into two groups according to ferrokinetics, i.e., one with satisfactory
function (\(^{59}\)Fe utilization more than 50% and \(^{59}\)Fe T 1/2 less than 180min.)
and the other with dissatisfactory function. This typing, he said, proved to be
compatible with prognosis in each case. He also, divided the cases into three
groups from the viewpoint of the course to death in each case; acute type (0-1/2
year), subacute type (1/2-3 years) and chronic (more than 3 years) and the
difference of statistical significance was observed in their bone marrow findings.
That is, more radical change in the bone marrow findings was observed in the
cases of acute type of aplastic anemia. Iwasaki referring to Hiraki's classifica-
tion based on the bone marrow findings, emphasized that prognosis would vary
by type and that the findings of bone marrow puncture alone would be sufficient
to determine the type of disease. Sawada mentioned Kawakita's classification
based on the bone marrow findings with emphasis on different prognosis observed
in each type. Uzuka pointed out a case of aplastic anemia whose ferrokinetics
was by no means different from that of normal person. Autopsy revealed partial hyperplasia in some cases but not total hyperplasia in the bone marrow. Ito classified into four types, namely idiopathic, secondary (due to drug and so on) congenital and special (pure red cell anemia and so on), and divided idiopathic type further into “acute” and “chronic.” In view of the bone marrow findings, he also made another typing, i.e., aplastic, hypoplastic, hyperplastic and normoplastic.

Reviewing the fore-described types, Takaku’s classification may have a criticism that it is hard to determine the type in the first examination of patients or upon hospitalization since the classification is based on observation of patients’ total course. The classification based on bone marrow findings will not escape the criticism of disregarding differences due to the site for puncture or the modification of bone marrow finding by modern treatment. Kawakita’s acute type is defined by the bone marrow findings and in addition septicemic symptom, while Ito’s acute type is necessary to have clinical finding such as hemorrhage fever in addition to bone marrow finding. Most of those cases, however, were improved and obtained delayed progress of disease by modern treatment. In common use of medical terms, “acute” and “chronic” immediately imply “short” and “long” course. Accordingly the author considers it more proper to use “severe” and “mild” instead. To be more specific, as Umehara previously proposed, degree of severity of the disease should be standardized using counting points. Some scholars, however, may have objections against Umehara’s method of counting points. My co-workers and I have used “idiopathic,” “secondary,” “congenital” and “special” types.

Furthermore, the standards described below had been used for the aid of classification.

1) neutrocytosis or shift the left of neutrocytes
2) reticulocyte count in peripheral blood more than 10% and more than 5 erythroblasts per 100 of leukocytes
3) splenomegaly
4) maturation arrest of granulocyte in bone marrow smear, that is high percentage of myeloblast, promyelocyte and myelocyte
5) normal serum iron and copper values
6) more than 10% of monocyte or monocyte-like cells

The cases having more than two of those standards are designated as “atypical type.” These criteria however not applied the cases with the treatment of adrenocortical steroid or in remission. Reason for establishing definition is that first, aplastic anemia, being of unknown etiology, should be studied “typical” type
only, and secondly, many doubtful cases seem to have been included in the reports so far made, for instance, old review of Hirschfeld's cases (1911) and other reviews. Thompson (1034) supplemented with the word "so-called" and used "progressive hypocythemia" to describe some cases since they were different from Ehrlich's concept. In Japan, Hirafuku's report (1954) also included many "so-called" cases. Careful study of literature indicating development of acute leukemia for aplastic anemia reveals that such aplastic anemia is "atypical" type in the author's definition. Also those which are clinically diagnosed as aplastic anemia but are doubtful in autopsy often prove to be "atypical." The author assumes, therefore, that "atypical" type includes some other diseases. The author's classification of aplastic anemia was previously mentioned by Nakajima et al, however, seems not to have achieved general acception. Takaku, Kawakita and Uzuka agreed with the possibility of separating some cases from aplastic anemia to establish another independent anemia.

ETIOLOGY

There have been many theories as to the etiology of "idiopathic" aplastic anemia. In my previous paper these theories were once throughly studied with our clinical and laboratory findings. In the symposium, Arimori also made a comment using the results of the experiment conducted by his group. He pointed out the disorder in amino acid metabolism, particularly in amino acid formation of mitochondria, and also in biosynthesis of fatty acid. Electronmicroscopic study indicated, he continued, that erythrocytoblastic mitochondria was more polymorphic than usual. Some scholars considered, however, that it may be produced artificially. Whether these changes are the cause or the result of the disease remains as a problem for future studies, he assumed that virus or immune mechanism would be responsible for mitochondria disorder. Kawakita considered the significance of the spleen, and also emphasized the racial difference in the incidence of aplastic anemia which would be an important subject of study. Uzuka explained an assumption that antigen antibody reaction would be involved in the hypoplasia of the marrow, and that disturbance of cell maturation would be due to the lack of unknown factor(s). Considering of bone marrow capillaropathy due to allergy or virus, Ito proposed a new theory that disorder would by no means of erythron itself nor bone marrow cell. Umehara emphasized this theory in his speech. It is expected that detailed report supporting this theory will be published. Takaku, considering that unresponsiveness of stem cell to erythropoietin is essential in this anemia, attributed its etiology to
virus, auto-immunization and/or metabolic disorder. He also mentioned the change in free protoporphyrin in red cells, however, indicated that whether it be a cause or result had not been known. Itoga added that the disorder of fat metabolism in the bone marrow was observed in aplastic anemia, arguing that metabolic disorder was primary and hypoplasia was secondary subsequent to it. Its real cause, however, was not mentioned. Nakao stated in his speech that the disorder in fat metabolism was observed in the experimentally injured bone marrow and that some substance blocking fat metabolism was contained in serum of patients with aplastic anemia. However, nothing has been known of this serum factor.

The important factor in the cause of aplastic anemia, I assume, would be erythropoietin from the following findings in our laboratory. Erythropoietin in the cases of aplastic anemia is markedly high activity with Fried's method ($^{59}$Fe uptake in erythrocyte in rat) while low with Mattoth's method (using index of cell division in bone marrow culture in vitro) and with Krantz's method (using index of $^{59}$Fe uptake in heme in bone marrow culture in vitro). And the clinical study showed that the transfusion of anemic donor's plasma, professional donor, (high in erythropoietin value) would be effective in aplastic anemia, while plasma of healthy men proved to be ineffective. When the bone marrow of aplastic anemia patients were cultured in vitro, $^{59}$Fe uptake in heme was more significantly high in adding anemic plasma than in adding normal plasma. It seems to me, opposing American authors' concept that the bone marrow of aplastic anemia proved to be responsive to erythropoietin. The further study on these line should be emphasized. Although the search for etiology of idiopathic aplastic anemia seemed difficult, it was a great success that many interesting findings from various research groups were collected, and further studies on the subject were expected.

The causes of secondary aplastic anemia reported in the symposium included 11 cases of antituberculous agents such as Tibion, PAS and Streptomycin, 6 of Salvarsan, 6 of Benzol, 4 of antipyritic preparation, 3 of Chloramphenicol and one case of Aleviatin (anticonvulsions drug). Along with the advent of new drugs, similar cases will possibly be observed in future and clinicians always should be requested careful attention.

PROGNOSIS

In the textbooks in use, prognosis is described as "absolutely grave," however, it has not necessarily been so in recent years and the progress in treatment
seems to be responsible for it. The data on mortality in our patients dividing into three periods using Umehara's proposal (period prior to production of cortisone, ACTH (1950–53); subsequent period (1954–56); and the period of common use of adrenocortical hormone (1957–64) was showed in Table 2. Ito's figures are almost consistent with ours. Arimori, in similar way, gave figures of yearly mortality which revealed gradual lowering of mortality as a whole. These findings suggest that prognosis should be studied separately in each therapy. Because of small number of cases in my study, however, an investigation in the total cases as a whole was made. In 84 cases excluding "atypical" cases and cases with duration of treatment less than one year, 3 cases could not be followed up. Of 81 cases of known prognosis, 46 deaths (56.7%) were reported including one each of suicide, stomach cancer, cancer of the uterus and hepatitis respectively. Seven patients (8.6%) required one or 2 transfusions of blood (every 6 months or once a year); 13 patients (15.4%) were engaged in regular work for more than one year without any blood transfusion; and 15 patients (18.4%) achieved complete rehabilitation with discontinuation of the treatment completely. These 15 cases included 9 having normal hematological picture, 6 having erythrocyte count 3,500,000 hemoglobin around 70.0% and no sign of aggravation of anemia nor hemorrhage. In other words, 28 (34.5%) of 35 survivors (43.4%) could return to the normal life. Excluding death due to the causes other than aplastic anemia, survival rate of 45.4% and reinstate rate of 36.5% were obtained.

There is slight difference in the ideas of the research groups concerning the standard for determination of prognosis, i.e. period of observation, etc., it is difficult therefore to make any definite statement from comparative study. By the way, Kawakita reported reinstate rate of 38 out of 118 cases (32.2%), Ito

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of cases</th>
<th>Lost to follow-up</th>
<th>Death</th>
<th>Death of other diseases</th>
<th>Death rate</th>
<th>Death rate°</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950–1953</td>
<td>22</td>
<td>0</td>
<td>18</td>
<td>1*</td>
<td>17/21 = 80.9%</td>
<td>84.6%</td>
</tr>
<tr>
<td>1954–1956</td>
<td>14</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>10/14 = 71.4%</td>
<td>69.0%</td>
</tr>
<tr>
<td>1957–1964</td>
<td>48</td>
<td>3</td>
<td>14</td>
<td>3**</td>
<td>11/42 = 26.4%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>3</td>
<td>42</td>
<td>4</td>
<td>38/77 = 49.4%</td>
<td></td>
</tr>
</tbody>
</table>

* Liver disease.
** Stomach cancer, uterus cancer and suicide, respectively.
° From Ito's data, Tokyo Medical College.
37 out of 118 cases (31.4%), Arimori 24 cases (25.8%) and Uzuka 13 out of 47 cases (26.9%). Miura pointed out only 5 out of 104 cases had no sign and symptom and not required treatment at the time of reporting.

Fifty percent survival rate in our study showed at 2-year. Kawakita reported that 50.0% survival rate was observed at 0.8 month in acute type, 2 years in chronic type without splenectomy (83 cases) including 2.5 years in 27 cases administered with adrenocortical steroid hormone and a year and 9 month in those without administration, and 10 years in 35 cases with splenectomy. Since acute type was separated in Kawakita's study, our figure was adjusted by

![Graph](image)

**Fig. 2** Relation of corticosteroid therapy to the survival rate of aplastic anemia in Keio University Hospital.
excluding death within 3 months. As the result, those alive up to 2 years marked 61.8%, 3 years 45.5% and approximately 2.5 years 50% regardless using of adrenocortical hormone. In Miura’s report, death within one year and survival more than one year were 39 respectively. Concerning the use of adrenocortical hormone, it was indicated in our study that mortality after one year marked 57.5% in 42 cases without administration while only 20.0% in those with administration (Figure 2). Ito emphasized that survival varies depending upon seriousness of the disease, showing that degree I and II indicated more than 70.0% of survival 4 years later, degree III, 50.0% in 2 years and degree IV, less than 3 months. Compared with the Lewis’ report, the Japanese findings seemed to be almost the same.

CAUSE OF DEATH:

Hemorrhage was the cause of death in majority. In our study, 22 cases of death without administration of adrenocortical hormone were consisted as follows: cerebral hemorrhage 12, other hemorrhage 2, pneumonia 3, septicemia 1, and others 4. Eight cases administered with adrenocortical hormone included one cerebral hemorrhage, one intestinal hemorrhage, 2 pulmonary hemorrhage, one septicemia and 3 others. Ito, Arimori and Miura all generally agreed with, despite of some difference in figures, that hemorrhage was the cause of death in majority followed by infection. Slight increase of infection associated with use of adrenocortical hormone was reported by Uzuka and Ito. My co-workers and I, however, observed no change, although number of cases studied was small. Miura also stated no correlation between use of adrenocortical hormone and cause of death.

AGE:

In our study, patients were divided into two groups, patients under 50 year-old and patients of 51 year-old or more, mortality rate was high in the former at the end of one year after the first examination, while in the cases administered adrenocortical hormones no statistically significant difference was observed (Figure 3). Miura made a comparative study on 2 groups, the patients of 30 years old and more and under 30 years old, finding more survival in the younger patients. Arimori also referred to poor prognosis in the patients of advanced age. In the previously mentioned Lewis’ report, prognosis was poor in the patients of older than 40 years and relatively good in those in puberty.

SEX:

No difference by sex in prognosis was observed in our study, however,
Arimori and others reported more survivals in female. On the other hand, Uzuka indicated poor prognosis in female. Miura found no sexual difference, comparing the number of death within one year with the survival of longer than one year. The fact that no comment was made by Ito and Kawakita seemed no significant difference. It should be remembered, however, the cases used in Uzuka's study consisted of only 11 each of male and female and besides all cases received adrenocortical hormone.
SYMPTOM AND PROGNOSIS:

On this subject, my report was previously made in 1959. In the present study, however, poor prognosis of significant difference was observed in those with body temperature higher than 37.5°C and bleeding time longer than 20 minutes. No noticeable difference of prognosis was indicated in erythrocytes, leukocytes, granulocytes, blood platelets, reticulocytes (absolute number), erythrocyte sedimentation rate and serum iron and copper. These results slightly differed from those in the previous report. The reason may have been that the cases treated with adrenocortical hormone were included in this study.

Prognosis was studied with the bone marrow findings, that is the percentage of granulocytes, erythroblasts, lymphocytes and megakaryocytes (average of one or more in one smear of bone marrow), no significant finding was obtained. However, some difference of prognosis was indicated in megakaryocytes in the cases without administration of adrenocortical hormone. Reduced plasma fibrin lysis time (Ratnoff's method), that is, accelerated plasmin activity, had strong relation to poor prognosis. Arimori asserted that prognosis would vary in each type defined by its bone marrow findings. In my study, however, no significant difference was indicated by either peripheral blood or bone marrow findings.

According to the Lewis report prognosis was poor in such extreme cases with neutrophiles under 500 and blood platelet under 20,000, however, neutrophiles or blood platelets alone would not be indicative of prognosis and the bone marrow findings were hardly associated with prognosis. Accordingly, the conclusion may be reached that collective judgement based on combination of various findings such as Umehara's degree of seriousness of disease would be important in determining prognosis.

TREATMENT

No satisfactory treatment of this disease has ever been found and there are considerable different opinion in the treatment which each group considers most effective. The present symposium gave a good opportunity to make comparative studies on these different therapies.

SPLENECTOMY:

Sawada reported on the result of splenectomy in 35 cases performed by Kawakita group, indicating 22 effective cases (62.8%). No other report had been made using such large number of cases, therefore, it was hard to make a comparative study. In my study, all of 4 splenectomized patients died, 4 out of
5 in Ito's report, 2 out of 5 patients with known prognosis in Miura's, and 3 of 9 patients in Iwasaki's. Recent literature on splenectomy in this disease shows both pros and cons. For instance, Heaton et al. (1957) reported 6 successful cases out of 12. In the British Society of Clinical Pathologist (1965), out of 8 cases one case with satisfactory effect and the other fair effect were reported. Diversity in the effectiveness of splenectomy seems to result from the selection of indication and postsplenectomy treatment. Kawakita pointed out that splenectomy was successful in chronic type, specifying the conditions as being: 1) no responsive cases to medical treatment with bone marrow hyperplasia; 2) no satisfactory result obtained by treatments other than blood transfusion; and 3) reduced erythrocyte survival. In successful cases, Kawakita further stated, leukocyte and platelet increased after splenectomy. Ito and Arimori obtained the similar result. Arimori called the attention to his finding that 5 patients who were given sufficient presplenectomy treatment with adrenocortical hormone or ACTH all have survived. Morita emphasized in his comment that weight of the spleen should also be considered in determining effectiveness of splenectomy. In Kawakita's study, however, the spleen varied in size and weight in both successful and unsuccessful cases. Also in other reports, no significant difference was observed.

Some groups consider that splenectomy is effective in some cases but efficacy is not so highly evaluated because of the standard of determining effectiveness. For instance, in a case of delayed improvement it is hard to determine whether or not splenectomy is responsible. It may be due to the adequacy of pre- or post-splenectomy medicine or treatment. Particularly nowadays when adrenocortical hormone proves to be as effective as splenectomy, some even consider that splenectomy is not necessarily required. Kawakita also stated that he would perform splenectomy only after adrenocortical hormone turned out to be ineffective.

ADRENOCORTICAL STEROID:

Reviewing literatures on the use of adrenocortical steroid in the treatment of aplastic anemia, the discrepancy of opinions was previously pointed out and discussed with my own experiences. Literature thereafter published also expressed different views. Uzuka claimed 3 mg of Dexamethasone to be most effective of all adrenocortical steroids, referring to cure or improvement obtained in 8 of 11 cases and to 24.0% effectiveness in symptomatic treatment. With 4 mg the effectiveness was reduced due to infection, he pointed out, and the drug proved to little effective in the type of maturation arrest and chronic panmye-
lopathy. He further added that efficacy of adrenocortical steroid would not necessarily be low in the case with unsatisfactory ferrokinetics and that erythroblasts of bone marrow increased in approximately 2 months after treatment and even the hyperplasia of the marrow was obtained in about 4 months. In Umehara's previous report, the hyperplasia of erythroblast after treatment was described in detail.

Ito stressed the reduction of mortality and the increase of longer survival, indicating 44.2% of mortality of 77 cases 5 years after administration of adrenocortical steroid and 50.0% of untreated control cases within 3 months. Effectiveness against pyrexia was of 64.4%, 70.6% of cases could extend interval of blood transfusion and against hemorrhage of 67.5%. Dose was considerably large at the early stage of the treatment in hospital when hemorrhage and pyrexia were accompanied, however, maintenance dose was reduced to 15-20 mg in Prednisolone. Miura reported improvement in ferrokinetics was not obtained immediately after administration of Prednisolone but later in several months. This finding was consistent with my previous assumption based on the hematological findings of aplastic anemia that adrenocortical steroid had no direct action of accelerating bone marrow activity. Miura furthermore admitted the fact that survival of longer than one year was significantly more in number in the drug-administered group, however, he avoided making definite statement on the immediate effect of the drug. The dose in his study was Prednisolone 15-30 mg and ACTH 10-20 unit. Iwasaki expressed the preference of concomitant use of adrenocortical steroid and ACTH to use of the former alone, indicating that one died out of 4 patients to whom Prednisolone alone was administered while 8 in 22 patients of concomitant administration. He also added that autopsy of the cases of concomitant use revealed no atrophy of the adrenal gland. Initial dose in his report was 20-30 mg of Prednisolone, which was reduced to the maintenance dose of 10 mg with temporary increase up to 60-100 mg at the time of pyrexia, and ACTH 10 unit per day.

As previously mentioned in the chapter on prognosis, the survival curve in our study showed considerable variation in cases with or without adrenocortical steroid. With increase of erythrocytes more than 500,000 in peripheral blood as an index for improvement, steroid therapy proved to be effective in 7 out of 15 courses in the cases without blood transfusion. In 26 cases in which blood transfusion was given, on the other hand, discontinuation of blood transfusion could be achieved in 13 courses, reduction of blood transfusion in 10 courses and no change in 13 courses, thus obtaining effectiveness in 19 (59.4%) of 32 courses. As a whole, 26 (55.3%) of total 47 courses in 35 cases proved to be effective.
Dose was as a rule 10–15 mg of Prednisolone in the cases with blood transfusion and 5–10 mg in those without blood transfusion and was increased in cases with hemorrhage. Sawada obtained in his experience with 27 cases of chronic type 50.0% survival of 2.5 years in adrenocortical steroid administered group while that of 1.9 year in the cases without administration, and effective cases marked 9 out of 20. It is indicated in some literature that after splenectomy adrenocortical steroid produced unfavorable effect on the bone marrow. However, Kawakita stated that adrenocortical steroid was equally effective in both splenectomized group and group without it. This dosage used in this study in the treatment was 20–30 mg of Prednisolone.

Taking a general review of the fore-mentioned results, Uzuka was in favor of administration of large doses while Arimori insisted on concomitant use with ACTH. There was more or less difference in the opinions as to the dosage of the drug, however, all seemed to agree on the effectiveness in extending survival and improving prognosis. Discrepancy in efficacy was supposed to result from the lack of uniform standard for determining effectiveness as well as varied dosage of drug. Umehara indicated, in his report on efficacy of adrenocortical steroid, that it would first bring out "bulldozer" in the bone marrow to prepare for hematopoiesis, then, hyperplasia of the bone marrow. Similarly in our study, effectiveness was not obtained in the early stage of the treatment and hyperplasia was observed after 3 to 6 months.

ANABOLIC STEROID:

Androgen was used first in the treatment of congenital aplastic anemia, then in primary aplastic anemia and proved to be effective in both cases. In this symposium, Ito reported that effectiveness was observed to some extent when used concomitantly with adrenocortical steroid and in 3 cases administered androgen alone. Miura, on the other hand, argued that no improvement in hematological findings was obtained with administration of anabolic steroid. Maekawa further added that testosterone, 25 mg daily for 2-month administration, was not effective in improving erythrokinetics. Iwasaki explained his experience in use of the anabolic steroid for the purpose of preventing the side effect of adrenocortical steroid, obtaining one case of good result. In our study, the good result was observed in 2 of 10 cases when administered it alone and 12 of 38 courses (36.6%) when used concomitantly with adrenocortical steroid. (Index for efficacy was increase of number of erythrocyte more than 500,000). The bone marrow findings of the effective cases in our study showed increased erythroblastes. On the other hand, not a few cases resumed the pretreatment
condition after discontinuation of the treatment. Therefore, many problems were left unsolved as to the mechanism of action and whether or not anabolic steroid was responsible for improvement. In Kawakita's study, satisfactory clinical response was observed in 3 of 14 cases. Lewis reported that androgen, administered alone or concomitantly with steroid, proved to be almost ineffective except in the patients in adolescence. In short, it seems that effectiveness of the drug cannot be expected in short duration of administration but to some extent in certain cases after long-term administration. However, further studies on dosage are required.

As the other treatments, Arimori referred to concomitant use of Ceruloplasmin and folic acid and my co-workers and I plasma of anemic donors (high erythropoietin). Table 3 represents the summary of the results reported by the research groups in the symposium. Since various factors are involved as previously described, careful consideration should be given in discussing the comparative merits of those treatments.

<table>
<thead>
<tr>
<th>Keio Univ.</th>
<th>Tokyo Med. College</th>
<th>Okayama Univ. (Hiraki)</th>
<th>Tohoku Univ. (Yamagata)</th>
<th>Kumamoto Univ. (Kawakita)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate</td>
<td>56.7%</td>
<td>59.3%</td>
<td>53.8%</td>
<td>54.0%</td>
</tr>
<tr>
<td>Survival rate</td>
<td>43.3%</td>
<td>40.7%</td>
<td>46.2%</td>
<td>45.0%</td>
</tr>
<tr>
<td>Reinstatement rate</td>
<td>34.5%</td>
<td>31.4%</td>
<td>25.8%</td>
<td>26.9%</td>
</tr>
<tr>
<td>Number of cases</td>
<td>88</td>
<td>118</td>
<td>93</td>
<td>47</td>
</tr>
</tbody>
</table>

With the adrenocortical steroid therapy, many severe cases of aplastic anemia may be improved to some extent, however it is sure, there are some cases still hard to be cured. The long-term administration of adrenocortical steroid in moderate cases seemed to result in hyperplasia of the bone marrow as well as remarkably reduced mortality. However, it was extremely difficult that peripheral blood and bone marrow findings turned to completely normal. Accordingly, further efforts are expected in studying and developing the treatments.

CONCLUSION

Some problems in the study on aplastic anemia in Japan were outlined with emphasis on what was discussed in the symposium as well as the author's own view.
REFERENCES