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The Researches on the Korean Population Genetics

—Studies on the frequencies and distributions of some human enzyme deficient traits—

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韓國人의 遺傳學的 硏究

酵素缺乏에 의한 遺傳形質의 頻度와 分布

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적 요

한국인의 G-6-PD 결핍, acetylator phenotype, acatalasemia 및 hypocatalasemia의 출현빈도를 서울, 경기도 강화군 교동도, 강원도 원성군 문막면 및 강원도 양양군 양양읍에서 각각 조사했다. 한편 교동도 거주집단의 격리 상태를 보기 위해서 색감이상자 빈도도 아울러 조사했으며 그 결과는 다음과 같다.

1) G-6-PD 결핍의 평균 출현빈도는 1.33%로서, 서울에서 0.67%, 교동도 3.41%, 문막면 1.27%, 양양읍에서는 0%를 나타냈다.

2) 색감이상과 G-6-PD 결핍은 열성인자에 의한 반성유전형질이며 인류유전의 표식인자(gene marker)로 사용된다. 교동도 남자집단에서 색감이상 빈도는 5.76%로 서울의 빈도 보다 약간 높았고 색감이상과 G-6-PD 결핍을 동시에 나타내는 쌍둥은 1예 였었다.

3) acetylator phenotype의 출현빈도는 slow type이 서울, 교동도, 문막면에서 각각 10.36%, 12.96%, 11.05%로 나타났고 slow와 rapid 유전자 빈도는 0.335과 0.665로 나타났다.

4) acatalasemia는 총 3,004명 조사 중 1명도 없었고 hypocatalasemia가 10예 검출되어 0.33%를 나타냈다. 지역적분포는 서울에서 0.29%, 교동도 0.27%, 문막면 1.15%였다.

INTRODUCTION

In human beings, erythrocyte gluose-6-phosphate dehydrogenase (G-6-PD) is a polymorphic enzyme that serves as a good genetic marker, and the production of this enzyme in erythrocytes is contolled by genes on the X-chromosome (Childs *et al.*, 1958). G-6-PD deficiency is a well-known example of the interaction between the gene and the individual's environment (Allison, 1960, 1964 ; Allison and Clyde, 1961; Motulsky, 1960; Siniscalco *et al.*, 1961). This may be of particular importance from the point of view of geographic population genetics because the frequency of the enzyme deficiency is characterized by a restricted geographical and ethnic distribution and by population groups (WHO Tech. Rep., 1967). It was also shown that the enzymic defect is the primary factor producing haemolytic anemia in G-6-PD deficient subjects after the ingestion of broad beans, (*Vicia fava*), certain types of drugs such as sulfanilamide, and antimalarial drug, primaquine (WHO Tech. Rep., 1967; Kirkman, 1968). Some studies have established that there is a close linkage on the X-chromosome between the loci for color-blindness and G-6-PD deficiency (Adam, 1961; Porter *et al.*, 1962; Siniscalco, 1963; Siniscalco *et al.*, 1964).

Acetylation polymorphism was found by studying the metabolism of isoniazid in human populations (Evans *et al.*, 1960; Evans *et al.*, 1961; Sunahara *et al.*, 1963; Evans, 1964). The acetylation of sulfadimidine (sulfamethazine) and related substances have been found to be under the same genetic control as is isoniazid (Evans and White, 1964; Evans, 1964, 1968). The frequency distribution of the percentage of the conjugated isoniazid which is excreted in the urine has been known to be bimodal, suggesting that individuals should belong to one of two classes, rapid or slow inactivator. Genetic analysis by means of twin and family studies revealed that slow inactivation of the compound is a Mendelian autosomal recessive character, while rapid inactivation is an autosomal dominant character (Evans *et al.*, 1960). Furthermore, it has been reported that there are local and racial differences in the frequencies of "slow" and "rapid" alleles (Sunahara *et al.*, 1961, 1963; Dufour *et al.*, 1964). The distribution of these alleles is, therefore, of great interest in population genetics.

Acatalasemia is the symptom of the inborn deficiency of producing catalase in human erythrocyte which was reported by Takahara *et al.*(1967) for the first time, and since then studies about the symptom have been carried out extensively in clinical, immunological, and biological view points, especially relating to human genetics. Catalase is the enzyme concerning oxidation-reduction metabolism neutralizing the toxicity of H_2O_2 in body by means of reducing it to H_2O and O_2.

The hypocatalasemia, an autosomal heterozygote of the acatalasemia is feasible to identify from the normal trait by applying a chemical method which has been developed for measurement of the catalase activity in blood. The frequency of acatalasemia and hypocatalasemia in Japanese and the South-East Asian populations has been investigated by Takahara and his associates (1967, 1969). Since the gene frequency of this trait has been know to be different in various population, studies on hypocatalasemia are significant for the genetic analysis of the human population.

Although some studies on frequencies of the biochemical traits such as acatalasemia (Takahara *et al.*, 1967) and acetylator phenotypes (Sunahara *et al.*, 1961) in the Korean dwellers in Japan have been reported, their data were not adequate to apply to the population genetic studies because of small size of the sample. Moreover, no study has been reported on the G-6-PD deficiency in Korean population.

The present study, therefore, has been conducted in order to investigate the frequencies and distributions of these enzyme defiencies in Korean population and to compare the results with those of other populations.

The areas studied were Kyodong island (Kyunggi Province), Moonmak Myeon and Yangyang Eup (both Kangwon Province), and Seoul.

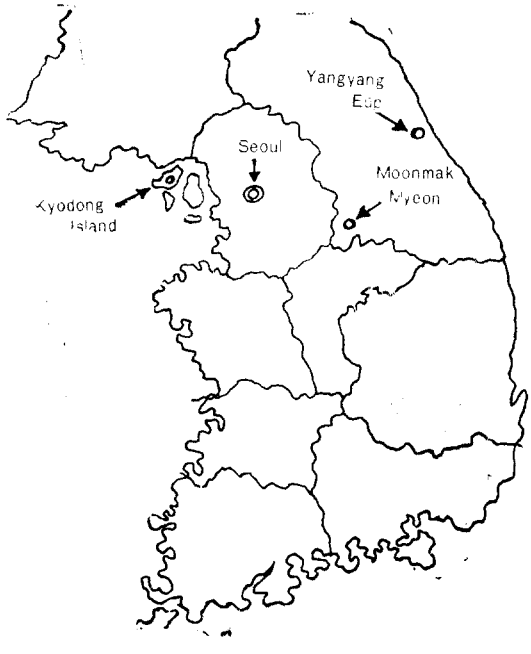

Fig. 1. The survey areas.

MATERIALS AND METHODS

1) Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency

The methemoglobin-reduction test (Brewer *et al.*, 1962) was used to determine the frequency of the erythrocyte G-6-PD deficiency in 765 boys of 10-16 years old in Kyodong island, Moonmak Myeon and Yangyang Eup, and in 891 males of 16-40 years old (614 subjects of 16-17 years old and 277 subjects of 30-40 years old) in Seoul area (Table. 1).

An aliquot amount of venous blood from each individual was collected and mixed in acid citrate dextrose solution. One sample tube and two standard tubes, positive and normal reference tubes for comparison of color differences, were prepared.

The sample tube contained 0.1 ml of the sodium nitrite (0.18 M)-glucose (0.28 M) solution and the same volume of methylene blue solution.

The positive reference tube contained 0.1 ml of the sodium nitrite-glucose solution, and the normal reference tube was remained empty. Each two ml of blood was poured into the three tubes. Then each tube was shaken several times for mixing, and incubated in a water bath at $37°\pm1°C$ for three hours. After then 0.1 ml of the mixture from each tube was added to each 10 ml of distilled water, and left stand for 2-10 minutes, and then finally the color produced in the sample tube was compared with those of two reference tubes.

If the color of the sample appeared red as in the normal reference tube, the sample was designated as normal. If the color of the sample turned to brown as in the positive reference tube, the sample was considered to be abnormal; G-6-PD deficiency.

2) Acetylator Phenotypes (Acetylation of sulfa drugs)

773 students were tested as follows: (1) 162 school boys from Kyodong island, (2) 222 school girls from Seoul area, and (3) 389 school boys from Moonmak Myeon. The subjects had been fasted at least for 12 hours prior to the ingestion of the sulfa drugs. 500 mg of the sulfadiazine (Kyodong island), the same doses of the sulfamerazine (Seoul area) and the sulfamethazine (Moonmak Myeon) were given orally to them. A light meal of bread and milk was allowed to take two hours thereafter. Urine was collected after 6 hours from the drug ingestion, and was stored in the ice box with dry ice until the analysis was performed. The frozen samples were thawed by placing in a hot water bath for a few minutes before analysis.

The free (F) and total (T) sulfa drug concentrations were estimated with the procedure established by the Bratten and Marshall (Weiner and Lourie, 1969).

Free (unconjugated) sulfa drug: The urine specimen was diluted 100 folds in volume. 0.2 ml of distilled water and 0.5 ml of 25% trichloroacetic acid(TCA) were added to 2.0 ml of the diluted urine, mixed and stood for 3 minutes. To the mixed solutions were again added 0.2 ml of 0.1% sodium nitrite solution and then 0.2 ml of 0.5% ammonium sulfamate solution. Finally 1.0 ml of 0.1% N-(1-naphthyl)-ethylenediamine dihydrochloride solution was added, mixed and stood for 10 minutes. The optical density of this solution was read at 540 nm with a spectrophotometer (Shimadzu Type MPS-50L).

Total (conjugated+unconjugtaed) sulfa drug: Urine specimen was diluted 500 folds with distilled water. 0.2 ml of 4 N HCl was added to 2.0 ml of the diluted urine, and heated in a boiling water bath for 1 hour. Evaporation could be reduced by capping mouth of the test tube by aluminium foil. 0.5 ml of 25% TCA solution was then added to the test tubes, mixed and stood for 3 minutes. The next procedures of the test were the same as those for "free sulfa drug".

The percentage of the sulfa drug acetylated was calculated by the following formula:

$$\frac{T-F}{T}\times 100,$$

where T is the optical density of the total sulfa drug, and F is that of the free sulfa drug.

3) Acatalasemia and Hypocatalasemia

The investigation on acatalasemia and hypocatalasemia has been performed on adults aged over 25 years living in Seoul, on students aged between 10-12 in Mconmak Myeon, and on students aged between 10-16 in Kyodong island.

Blood samples were collected in heparinized capillary tube. 0.02 ml of anticoagulated blood was primarily used for the screening test. Among 3,004 samples, 262 samples chosen randomly and some samples in suspicious of acatalasemia or hypocatalasemia were tested to measure the activity of catalase by a quantitative method.

(1) Screening test

Five ml of catalase phosphate buffer solution (Catalase-PBS) prepared by adding 0.01 M PBS(pH 6.86) to H_2O_2 solution until the final concentration of H_2O_2 reached 0.005 M, was taken into a 15 ml test tube. 0.02 ml of blood was haemolysed with 20 ml of distilled water. 1 ml of the lysed solution was taken, then quickly delivered into the test tube containing catalase-PBS, and finally the tube was shaken 2 or 3 times. After allowing the reaction for exactly 60 seconds, 2.0 ml of 2 N H_2SO_4 was added and shaken 2 or 3 times so as to stop the reaction. And then 7 ml of 0.005 N $KMnO_4$ was added to the test tube and shaken vigorously.

If the color of $KMnO_4$ remains in the solution, the sample is considered as

normal. When the color disappears, the sample is considered as acatalasemia or hypocatalasemia. For the abnormal case, the catalase activity was measured by titration with $KMnO_4$ solution.

(2) Quantitative analysis

Reagents and facilities were the same as in screening test. Five test tubes containing 5 ml of catalase-PBS were prepared and the tubes were placed in a water bath at 37°C for 5-10 minutes. 1 ml of the haemolysed blood was delivered quickly into 4 tubes, left for a given time, and then reaction was stopped by adding 5 ml of 2 N H_2SO_4 into the tube. The reaction in solution of the 4 tubes was allowed for 15, 30, 45 and 60 seconds, and the last fifth tube was remained for the determination of the initial concentration of H_2O_2 by adding 5 ml of 2 N H_2SO_4 followed by mixing 1 ml of lysed blood sample. H_2O_2 concentration of each tube was determined by titration with 0.005 N $KMnO_4$ solution.

The catalase activity(K_1) was calculated from the formula:

$$K_1=\frac{1}{t}\log_{10}\frac{X_0}{X},$$

where X_0 represents initial amount of $KMnO_4$ and X the amount of $KMnO_4$ remaining after various reaction time, t.

The final activity was expressed as the following formula:

$$K_1\times\frac{14.0}{Va}\times 1,000,$$

where *Va* is value of sample haemoglobin content per 100 ml of the blood.

The haemoglobin level was measured with a haemoglobinometer.

4) Color-blindness

The survey was conducted with 813 students in Kyodong island, of whom 469 were boys and the others were girls. The examination procedures were described elsewhere (Kang *et al.*, 1965).

RESULTS

As mentioned above, G-6-PD deficiency is inherited as an X-linked trait (Giblett, 1969). Males who carry the gene show, therefore, full expression of either normal or deficient. Based upon this phenomenon, the studies on G-6-PD deficiency were carried out only on males.

The average frequency of G-6-PD deficiency in the male examined was 1.33%. The distribution of G-6-PD deficiency in four areas is shown in Table 1. Significantly lower frequency is observed in Seoul, Moonmak Myeon and Yangyang Eup populations in comparison with that of the Kyodong island.

Table 1. Frequencies of G-6-PD deficiency in four areas

Area	No. tested	No. deficient	% deficient	Age group
Kyodong island	381	13	3.41	12—16
Seoul	614	2	0.33	16—17
	277	4	1.44	30—40
	(891)	(6)	(0.67)	(16—40)
Moonmak Myeon	236	3	1.27	12—16
Yangyang Eup	148	0	0.00	10—12
Total	1,656	22	Average 1.33	

$X^2=19.405$, df=3, $P<0.005$. The X^2 value was calculated from the younger age groups of four areas. The figures in parenthesis represent total number of subjects of Seoul area.

Routine tests for color-blindness, using Ishihara and AO H-R-R pseudo-isochromatic plates, were performed on Kyodong island students. This test was done in order to find out relationship between G-6-PD deficiency and color-blindness because both characters inherit through X-chromosomes.

Among 469 boys, 27(5.76%) were found to be color-blind; 6 were protan, 18 were deutan and the remainders were doubtful(Table 2). No color-blinded subject was detected among 344 school girls tested.

Table 2. The frequencies of color-blindness in several areas in Korea

Areas	No. tested	Protan	Deutan	Doubtful	Total defects
Seoul*	1,231	1.06%(13)	4.14%(51)	0.32%(4)	5.52%(68)
Cheju island and other islands*	4,290	1.21%(52)	2.55%(109)	0.12%(5)	3.87%(166)
Kyodong island	469	1.28%(6)	3.84%(18)	0.64%(3)	5.76%(27)

The figures in parenthesis represent the number of color-blind individuals.
* Data from Kang *et al.*(1967).

Among 18 in deutan individuals 12 were tested for G-6-PD activity, one was found as a deficiency. Three of 6 protan individuals were tested, but no one was found to be deficient.

The frequency distribution of urinary sulfa drug acetylation in Korean population is shown in Fig. 2. The distributions are bimodal with the antimode at a figure of 50% in Seoul and 65% in Moonmak Myeon. Subjects who are included in lower than antimode are termed as slow acetylator, while those who are above the antimode are as rapid acetylator. The frequencies of slow acetylator phenotype are 12.96% in Kyodong island, 10.36% in Seoul and 11.05% in Moonmak Myeon (Table 3).

The occurrences of two phenotypes in the Seoul population were not significantly different from those in the Kyodong island population($X^2=0.653$, $P>0.5$).

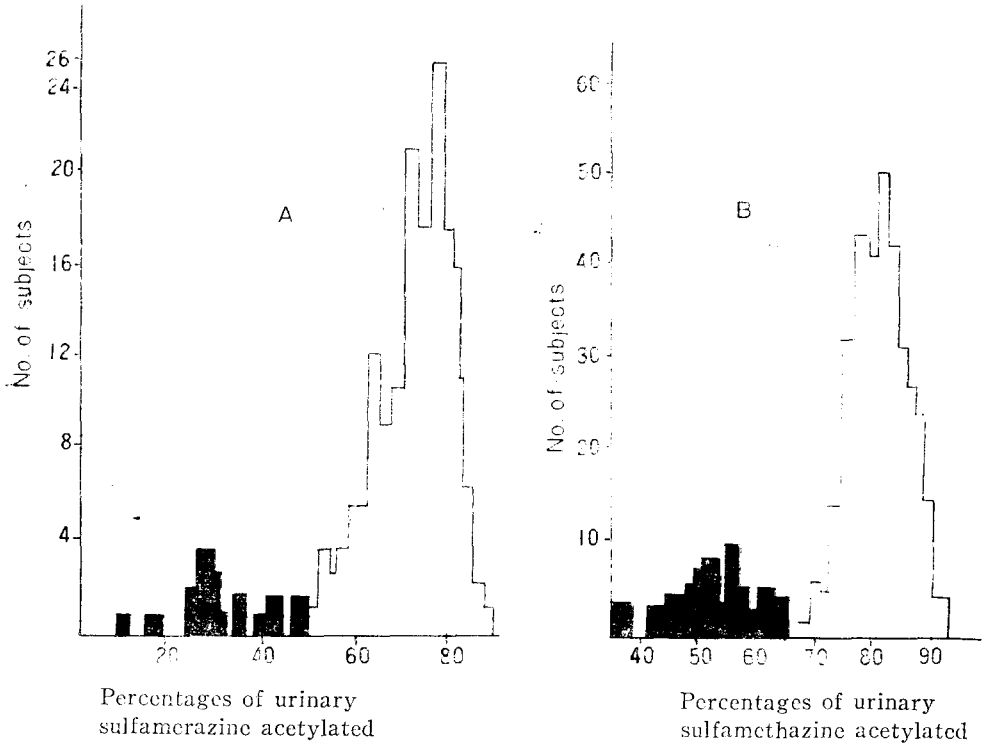

Fig. 2. Frequency of the acetylator phenotypes in Korean population. The dark and light parts show slow and rapid acetylating subjects, respectively. A; Seoul population, B; Moonmak Myeon population.

Table 3. The distribution of two acetylator phenotypes in Korean population

Area	No. tested	Rapid acetylator	Slow acetylator
Seoul	222	89.64% (199)*	10.36% (23)
Kyodong island	162	87.04% (141)	12.96% (21)
Moonmak Myeon	389	88.95% (346)	11.05% (43)
Total	773	(686)	(87)
Average		88.75%	11.25%

The figures in parenthesis represent the number of subjects.

The results were comparable with that of Sunahara *et al.* (1963). Consequently, it is predictable that the incidence of the slow acetylator in the Korean population may be about 11.25%. The gene frequency of the rapid calculated from data in Table 3 was 0.665

In the present investigation, 10 persons among 3,004 examined were discovered as being hypocatalasemia (Table 4). According to Table 4, frequency of the hypocatalasemia appears about 0.33%. The frequency was 0.29% in Seoul, 1.15% in Moonmak Myeon and 0.27% in Kyodong island, presenting a slight

geographical difference ($X^2=3.70$, $P>0.05$). The normal catalase activity of Korean population appeared to be between 4.45 and 4.73 and the frequencies were homogeneous through geographical constitutions.

Table 4. The frequencies of hypocatalasemia and catalase activity in Korean population

Area	No. of screening tests	No. of hypo-catalasemia	No. of quantitative tests	Mean activity of catalase
Seoul	2,076	6(0.29)*	139	4.45
Kyodong island	754	2(0.27)	96	4.73
Moonmak Myeon	174	2(1.15)	27	4.49
Total	3,004	10(0.33)	262	4.54

* Figures in parenthesis are %.

DISCUSSION

It has been recognized that erythrocyte G-6-PD deficiency is one of the most well known hereditary enzymic defects in man that the deficiency is found over 100 million individuals throughout the world (WHO Tech. Rep. Ser., 1967). The present studies on the G-6-PD deficiency in the Korean male population reveals an average frequency of 1.33%. It has been generally accepted that the frequency of the deficiency varies from one race to another(Table 5). For example, Mongoloids, Caucasians in northern Europe and North Americans have a relatively lower frequency of the G-6-PD deficiency than Negroes or Mediterranean Caucasians. The enzyme deficiency in Japanese has been found to be zero. In China, the frequency is about 3 to 5%, which is higher than the present data for the Korean population. It may be said, therefore, that G-6-PD deficiency is rather an uncommon trait for Mongoloid populations, but is certainly common for a Mediterranean population.

Motulsky(1960) pointed out that the distribution of G-6-PD deficiency parallels that of *Plasmodium falciparum* malaria. The interpretation is that the subjects who are deficient in G-6-PD in erythrocytes are of advantage to malarious environments, thus preserving in the malarial areas (Allison, 1960; Allison and Clyde, 1961). Unfortunately, accurate data about the frequency of malaria in the areas where present survey was made are not available. However, it has been known that the malaria endemicity in these areas is expected to be small, and there might be no difference in frequencies of malaria between the areas (H.I. Lee, personal communication). Therefore, the different frequencies between Kyodong island and other areas seems to be rather related to other environmental factor in the areas than to the malaria.

A great variation in the frequency of G-6-PD deficiency with age was shown in a malarious area such as Eastern region of Nigeria (Harris and Gilles, 1961; Harris, 1970). They observed the frequency is high in the male population between the ages of 5 and 10, and falls between the ages of 10 and 15 years, and again rises slightly in older age-groups.

Table 5. Frequency of G-6-PD defiency among various populations

Population	Percentage of G-6-PD deficiency*
Negroes	
Western Africans, Nigerians	10—27
Central Africans, Congolese	6—23
Eastern Africans, Tanganyikans	15—30
Southern Africans, Bantu	2
Northern Africans, Egyptian	26.4
American Negroes	7—17
Caucasians, northern	0.1
Caucasians, southern	
Northern and Southern Italians	2—3
Sardinians	3—30
Greeks	1—32
Jews	
European	0.2
Iraqi	25
Turkish	5
Kurdish	60
Asiatics	
Chines (in Taiwan)	2.9—5.0
Japanese	0
Korean (Present data)	0—3.41
Filipinoes	5—12.7
Thailander	7—33
Indian	0.6—19

* Data from Prankerd(1964) and WHO Tech. Rep.(1967).

A recent report showed that though Motulsky observed no correlation between ages and G-6-PD deficiency in American and Congolese Negroes, the frequency of the deficiency in populations in San Francisco Bay area was closely related with age (Petrakis *et al.*, 1970). That is, G-6-PD deficiency occurs more often among younger than older males. They suggested that the clinical and subclinical effects of environmental factors are more significant in distribution of G-6-PD deficiencies than had hitherto been realized.

But the present result is not accorded with that of Petrakis *et al.*(1970). In Seoul population the percent of G-6-PD deficiency in younger and older groups was shown to be 0.33% and 1.44% respectively, and its difference is non-significant($X^2=3.545$, $P>0.05$).

The reason for the lack of the correlation between age and G-6-PD deficiency in the present study is assumed to be that the older age group of Seoul population includes many persons immigrated from the rural area; therefore the population is not homogeneous in its constituents, while most young boys studied in this report were born in Seoul.

The cause of the change in the frequency of G-6-PD deficiency with age gives an interesting problem to be solved with regard to the relationship between gene expression and environmental factors.

The reason why the Kyodong island population seems to be higher incidence in G-6-PD deficiency as well as in color-blindness may be explanable if the inbreeding coefficient in that island is proved, because the incidence of these characters might be increased by more frequent consanguinity.

Studies by Siniscalco(1963) on Sardinian, by Adam *et al.*(1963) on Jewish, and by Porter *et al.*(1962) on American Negro families suggested that the color-blindness was positively correlated with G-6-PD deficiency. In the present survey, only one was identified as a carrier of both abnormal genes. If the family studies would have been carried out, more cases linked with two genes might have been detected.

In regarding to the acetylator polymorphism, two alternative hypotheses have been put forth in the literature, one is from the studies of Knight *et al.*(1959) and Evans *et al.*(1960), and the other is from Sunahara *et al.*(1961, 1963) and Dufour *et al.*(1964). Knight *et al.* assumed that slow inactivator is probably due to an autosomal recessive gene. Evans *et al.* added to this assumption their thought that the slow inactivator of isoniazid is also due to autosomal recessive gene after their thorough examination on family studies with Caucasoid which showed a bimodal pattern in frequency distribution of plasma isoniazid concentration.

On the other hand, Sunahara *et al.* and Dufour *et al.* found that the frequency distribution of the acetylator phenotypes is trimodal after examination using a microbiological method, and they postulated that rapid and slow inactivators are of homozygous, that intermediate inactivators are of heterozygous, and that neither allele is dominant. In the present studies, however, it was clear that the acetylator phenotypes showed apparently a bimodality as shown in Fig. 2.

Racial and geographical distributions of acetylator phenotypes were studied by several workers. By studying several races along the coast of the Far East and on the islands of Japan, Sunahara *et al.*(1963) has reported a cline of increasing frequency of the slow alleles from the Ainu in the North to the Thai in the South. Dufour *et al.*(1964) reported that the frequencies of rapid and slow alleles among Negro and Caucasian populations were similar, but a marked difference was existed in the frequency of the alleles between the above and

Japanese populations. Actually in the former populations the frequency of slow allele is approximately three times that of the rapid allele, but in the Japanese the proportion is reversed. In the present studies, the frequency of the rapid allele of the Korean population was found to be about 0.665 which is very close to that found in Japan.

Studies on acatalasemia were firstly done by Takahara who found quick change of the blood color to black when hydrogen peroxide was applied to the patient in an inflammation of maxillary bone. Takahara *et al.*(1967, 1969) reported that the frequency of acatalasemia in the Japanese population might be estimated to one per million, while the frequency of hypocatalasemia was different in different areas. That is, in Okayama of Japan the frequency is 0.12% which is around the mean frequency of the Japanese population, while in Ryukyuan, it is lowered to 0.01%. But the frequency of the Koreans living in Okayama is much higher(1.11%) than that of Japanese (Takahare *et al.*, 1967). In and around Hiroshima city of Japan, the frequency of Korean dwellers appears to be 0.33%, which is quite similar to that of the present investigation. Similar frequency was reported in the people of Tsushima island located on the sea between Korea and Japan. The Chineses in Formosa have nearly the same frequency of hypocatalasemia(0.29%) as Koreans do.

SUMMARY

The present paper is concerned with the frequencies of G-6-PD deficiency, acetylator phenotypes, hypocatalasemia and acatalasemia among Korean populations. The examination was carried out in the rural (Kyodong island, Moonmak Myeon and Yangyang Eup) and urban (Seoul) areas.

The average frequency of G-6-PD deficiency in the total male population was 1.33%. A significant difference was observed among four areas.

Tests on the color-blindness were performed in order to compare the two populations (Kyodong island and Seoul) and to obtain relationship between the color-blindness and G-6-PD deficiency. The frequency of color-blindness was 5.76% in the male rural population, and this rate was nearly consistant with that of the urban.

The frequencies of the slow acetylator phenotype were 12.96% in Kyodong island, 10.36% in Seoul and 11.05% in Moonmak Myeon.

Of the 3,004 persons investigated, no one has acatalasemia, but 10 cases of hypocatalasemia were found. The overall frequency was 0.33% which is slightly different from one area to another; 0.29% in Seoul, 0.27% in Kyodong island, and 1.15% in Moonmak Myeon.

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