XVII. Potassium Tolerance Test by Means of Sun-Bathing

The previous chapter dealt with the studies of the relationship between melanogenesis and pituitary-adrenal system, especially mineralcorticoids, in various pigmentary dermatoses. In this chapter will be studied the relationship between the same in normal persons by comparing the results of serum potassium tolerance test before and after sun-bathing, in a fair-complexioned and a dark-complexioned Japanese group.

Experiments and Results

The skin colors of normal Japanese were determined with reference to the color labels of the Japanese Color Research Institute or, in case of difficulty, with the help of the reflectance spectrophotometer, and indicated in terms of luminosity by CIE value (Y), dominant wavelength (λmμ) and purity (pe%). Then those subjects were allowed to bath in the sun at a beach in summer: i) 11 normal men and women on 31st of July, 1955; ii) 10 normals at 6th and 8th of August, 1956 (Tables XXXII, XXXIII). Prior to and after sun-bathing, examinations were performed of the changes in K and Na contents in the serum due to potassic salt administration as mentioned in the previous chapter.

1) Changes in Color Tone: To estimate the effects of sunbathing, the subjects were roughly divided into two, a fair group with luminosity over 38 and a dark group with luminosity below 38. In the former group the change in color tone, especially the lowering of luminosity was quick, the recovery tended to be also rapid, and the change of dominant wave length formed an acute angle, while in the latter group the lowering and the recovery of luminosity were slow and the process of dominant wave length formed an obtuse angle.

2) Changes of K and Na Contents in the Serum: Upon examination of the behavior of mineralcorticoids by measuring the change in the serum K and Na contents following oral administration of 6 g potassic salt, the increase of serum K two hours after administration on the day before sun-bathing was lower in the fair group (26.7%) than in the dark group (37.4%), a result in consonance with that of a similar examination of Whites and Negroes by Leschi. The measurement made on the day after sun-bathing, however, showed an inverted result, the rate of K increase having risen to 47.7% in the fair group as compared with the 40.8% of the other. That is, in the dark group a single sunbath caused hardly
Potassium Tolerance Test by Means of Sun-Bathing

TABLE XXXII
Results of Serum Potassium Tolerance Tests before and One Day after Sun-bathing Performed on July 31, 1955 at a Beach

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Skin color</th>
<th>Lumino-</th>
<th>Before Sun-bathing</th>
<th>After administration increase %</th>
<th>1 day After Sun-bathing</th>
<th>After administration increase %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark complexioned</td>
<td>61</td>
<td>M</td>
<td>38</td>
<td>3.6</td>
<td>36</td>
<td>3.7</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>M</td>
<td>25</td>
<td>3.6</td>
<td>39</td>
<td>3.7</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>M</td>
<td>35</td>
<td>4.1</td>
<td>22</td>
<td>3.9</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>M</td>
<td>35</td>
<td>3.7</td>
<td>40</td>
<td>3.5</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>F</td>
<td>36</td>
<td>3.9</td>
<td>40</td>
<td>4.5</td>
<td>40</td>
</tr>
<tr>
<td>Average</td>
<td>34</td>
<td>3.8</td>
<td>37.4</td>
<td>3.9</td>
<td>40.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair complexioned</td>
<td>28</td>
<td>M</td>
<td>45</td>
<td>4.0</td>
<td>20</td>
<td>3.6</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>M</td>
<td>45</td>
<td>3.7</td>
<td>35</td>
<td>3.7</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>M</td>
<td>40</td>
<td>4.1</td>
<td>58</td>
<td>3.7</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>M</td>
<td>38</td>
<td>5.0</td>
<td>13</td>
<td>4.9</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>F</td>
<td>44</td>
<td>4.6</td>
<td>24</td>
<td>4.6</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>F</td>
<td>45</td>
<td>4.8</td>
<td>10</td>
<td>4.5</td>
<td>40</td>
</tr>
<tr>
<td>Average</td>
<td>42.5</td>
<td>4.4</td>
<td>26.7</td>
<td>4.2</td>
<td>47.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Average value in both the cheek and extensor surface of the upper arm.

any fluctuation in the rate of K increase, whereas in the fair group it effected a remarkable change.

COMMENT

These results seem to suggest that the sun-light worked as a stronger stress on the adrenal cortex of the fair group because of the higher sensitivity to ultraviolet rays of their fair skin. As described in the previous chapter, most of acquired pigmented diseases showed abnormal results in Thorn’s tests and serum potassium tolerance tests. Considering these results and our present results by means of sun-bathing, an influence of adrenal insufficiency on melanogenesis seems to be very important.

In 1952, Leschi1), who could but anatomically admit—on the bases of the comparative studies by Pearl, Gooch and Freeman of the weight of the adrenal glands in Whites and Negroes and the comparative investigation by Swinyard into the ratios in volume of the whole adrenal glands to the cortex/medulla in both races—the observation that the ratios between the whole adrenal glands and the cortex/medulla are smaller in the black than in the white, but who considered that the determination
of the value of adrenal function naturally required to be endorsed by various physiological researches, tried to know even a part of adrenal function by biochemical procedures. That is, in consideration of the works on the changes of Cl\textsuperscript{−}, Na\textsuperscript{+} and K\textsuperscript{+} in the blood corresponding to the functional unbalance of the adrenal glands, Leschi determined such contents in the serum of Whites and Negroes, with the results that the medium, maximum and minimum values of the Cl and Na contents were all higher in Whites than in Negroes but that those of the K content was much higher in Negroes. The determination of the K content in the serum before and after the administration of potassic salt to individuals showing a normal K content revealed that more instances were among the Negroes in which the increase rate was higher. The measurement of the K content in the serum before and after administration of DOCA showed that more instances of increase were among the Negroes and more instances of decrease among the Whites. This experiment was undertaken on the basis that disoxycorticosterone, which is a mineralocorticoid compound found in adrenal hormones, influences electrolytic metabolism. An anomaly of electrolytic metabolism such as in Addison’s disease was observed in Negroes, and this was explained as showing that the physiological threshold of adrenal functions in Negroes was below that in Whites. This view was
supported by referring to the report by Conn and Mathews that their clinical and autopsy results showed four times as many incidences of Addison's disease in Negroes as in Whites and the observation by Gennes, as cited by Amado, that hardly any of the 300 cases of Addison's disease were blonde. Thus it was inferred by Leschi that the difference in physical constitution and adjustment or adaptability to circumstances between the two races has caused the difference in the threshold value of adrenal functions between them. One may also be referred to the latest (1951 and after) U.S. statistics of mortality showing that the percentage of deaths of adrenal diseases has become higher in the Negroes than in the white. We can not readily agree with the above view, but it seems to give an interesting suggestion on the physiological genetics of the racial difference in color of the skin.

On the high frequency of Mongolian spot and nevus fusco-caeruleus Ota among us of the Yellow race, we must study from this point.

Furthermore, pigmentation of the oral mucous membrane is already known to occur in Addison's disease, vagabond's melanosisis and ephelides inversae, but it has also been observed frequently in colored normal individuals (Manson, Reiche and Dummett), though it is very rarely found in the white race (Crouzon and Chateilin). In Japan, it has been studied by Okuguchi and Mine, the latter of whom found it in 458 or 32% of the 1,425. It gives almost the same histological findings as Addison's disease, which are mainly accumulations of melanin and positive dopa reactions (Mine and Becker).

Pigmented spots on the palm and the sole are not very uncommon in Japan (Toyama and Kawamura et al.—8.6%). Mori and Kawamura have noted that the pigmentation of the palm and sole in ephelides inversae is centered on the crista profunda intermedia, and comparing it with the description of Nakagawa and Adachi that the pigmentation of the monkey's palm is also centered on the crista intermedia, have aroused genealogical interest. Thus the frequency of pigment maculae in the oral cavity, on the lip, the palm and the sole corresponds with that of Mongolian spots in that they are in proportion to the darkness of skin color and are regarded as physiological characters showing an ethnological difference in frequency, though the Mongolian spot is a hyperpigmentation in the corium which fades away with age in contrast to the pigmented macula is a hyperpigmentation in the epidermis which appears at a later age. This is of deep interest if considered in the light of the results of Leschi's ethnological examinations of Cu and K contents in the blood and those of our Thorn's tests and potassium tolerance tests carried out in the examination of adrenal function according to the criteria of pathological and physiological skin-colors. The quantity of pigment distributed in
the skin and the oral cavity varies in somewhat ethnological order, and the threshold value of that part of adrenal function which is concerned with the mechanism of melanin formation appears to show a corresponding difference; in other words, it is inferred that the physiological threshold of adrenal function in the yellow races shows a value standing between those of the white and the Negro races. And the statistical facts that melanoma is aggravated very often in the white race and very rarely in the colored races are observed to make sharp contrasts due to racial differences.

Summary

Serum potassium tolerance tests were made in normal persons before and after sun-bathing, and the results were compared between two groups, that is, a fair-complexioned and a dark-complexioned Japanese group. It was made clear that ultraviolet irradiation gave a stronger stress to fair-complexioned persons than to dark-complexioned persons.

Yellow races have many specific pigmenitary manifestations different from those in other races, for instances, Mongolian spot appears in almost one hundred per cent of new borns, nevus fuscaeruleus Ota is more often found here than in other races, and here again pigmented spots occur also more physiologically in the oral mucous membrane or on the palms and soles. These facts must be studied from the view point of physiological genetics.

References

1) Leschi, Races melanodermes et leucodermes pigmentation et fonctionnement cortico-surrénalien, 1952, Masson.
4) Okuguchi, Japan. J. Dermat., 1927, 27, 646.
5) Mine, ibid., 1928, 28, 325.
6) Becker, Arch. of Dermat., 1927, 16, 259.
7) Toyama, Japan. J. Dermat., 1932, 32, 1124; 1937, 41, 325.
8) Kawamura, ibid., 1956, 66, 75.
XVIII. 17-Ketosteroids and Sex-Hormones in the Urine

In a preceding chapter we have reported our studies of electrolyte metabolism in patients with various pigmentary diseases by means of Thorn’s tests and potassium tolerance tests performed to investigate into the possible relation of melanin formation to the pituitary-adrenal system. In this chapter we will describe the results obtained from our study of the changes in urinary 17-ketosteroids and sex hormones in pregnancy and various pigmentary diseases.

Measurement of Urinary 17-Ketosteroids

In 17-ketosteroids are included a rich variety of steroids, most of which have been pointed out by Selye and Soffer to originate in the adrenal cortex. They are utilized for estimating the extent of dysfunction of the adrenal glands.

Increased pigmentation follows bilateral adrenalectomy in man (Kepler, Hall et al.) and in other animals (Ralli and Graef, Spoor and Ralli, Butcher), whereas administration of desoxycorticosterone (Spoor and Ralli, Hamilton), cortisone (Whitaker and Baker, Hall et al., and many others) or aldosterone (Mack et al., Kekwick and Pawan) to cases of increased pigmentation due to adrenalectomy or adrenal dysfunction causes fading of the pigmentation. Consequently it is supposed that the decrease of adreno-cortical mineralo- and glucocorticoids will result in an increased pigmentation, and the increase, in a decreased pigmentation. We have made quantitative determinations of 17-ketosteroids (Drekter’s method) and the fractions (Suzuki-Adachi’s method) in the urine of pregnant and patients with pigmentary diseases of the skin.

Experiments and Results

a. Pregnancy, parturition and puerperium

Pregnancy is accompanied with increased pigmentation in the skin of the nipples, halos, linea fusca and external genitals, which is heightened with the months of pregnancy and begins to fade away gradually during puerperium. To estimate the total amount of 17-ketosteroids excreted in the urine, we measured a total of 52 samples including 6–8 each of the 8 groups of urine taken during the 2nd—10th month of normal pregnancy,
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in parturition and on the 3rd and 10th days of puerperium (Fig. 47). The total 17-ketosteroids value does not differ much in the early and the middle stage of pregnancy from that of the normal non-pregnant woman, begins to rise slowly from the 8th month, forms a steep peak at childbirth, and recovers the value of the normal nonpregnant on the 10th day of puerperium.

![Graph showing urinary 17-ketosteroids values](image)

Fig. 47. Values of total urinary 17-ketosteroids in normal pregnancy, parturition and puerperium. --- mean values of normal non-pregnant women.

Furthermore, the 17-ketosteroids extracted from the urine were analyzed into Fractions I-VIII by elution chromatography. The steroids contained in separate fractions and their amounts are shown in Table: Fractions IV and V are the products of androgen metabolism, and Fractions II, VI and VII are the metabolism products of glucocorticoid, adrenosterone, etc. which are the adreno-cortical hormones. The percentages in the fractions are to the values measured in the samples from 5 normal women and 4 normal men (Table XXXIV).

Fractions were measured of the samples taken from 4 cases in the 2nd–3rd months of pregnancy, 3 cases in the 4th–5th months, 3 cases in the 6th–7th months, 3 cases in the 8th–9th months and 4 cases in the 10th month, in 2 of the latter cases measurements being done throughout the whole processes of parturition and puerperium (Fig. 48). Fractions IV (androsterone) and V (etiocholanolone), both originating in androgen, decrease as compared with other fractions, and increase during puerperium. This result is in contradiction to the known fact that androgen acts in intensifying pigmentation of the skin, as do the female sex-hormones. Hence it is presumed that androgen does not participate in hyperpigmentation during pregnancy.
17-Ketosteroids and Sex-Hormones in the Urine

**Table XXXIV**

Distribution of the 17-Ketosteroids in the Fractions

Figures express percentages of the total 17-ketosteroid excreted in a day

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Female Excretion</th>
<th>Male Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.5-10.0 mg per day</td>
<td>5.0-18.0 mg per day</td>
</tr>
<tr>
<td>I</td>
<td>1-20%</td>
<td>2-18%</td>
</tr>
<tr>
<td>II and III</td>
<td>Artefacts of hydrolysis: (androst-2-en-17-one, androst-3:5-dien-17-one, 3-chloroandrost-5-en-17-one)</td>
<td>10-55%</td>
</tr>
<tr>
<td>IV and V</td>
<td>i-androstenol-6-one-17, the others</td>
<td>25-50%</td>
</tr>
<tr>
<td>VI and VII</td>
<td>androsterone and etiocholanolone</td>
<td>3-25%</td>
</tr>
<tr>
<td>VIII</td>
<td>11-hydroxy-17-ketosteroids</td>
<td>0-14%</td>
</tr>
</tbody>
</table>

![Graph](image)

Fig. 48. Changes in urinary 17-ketosteroid fractions in normal pregnancy, parturition and puerperium. △-II. fraction, ×-III., ●-IV. and V., O-VI. and VII.

b. Pigmentary skin diseases

Table XXXV shows the total amounts of 17-ketosteroids excreted in the urine of the patients during 24 hours.

In Addison’s disease, the decrease in the total value of 17-ketosteroids is generally accepted, and in our tests all of the 7 typical cases of the disease showed lowered values. In the measurement of fraction, some cases were without any great changes in any fragment, but others showed a marked decrease particularly in the 11-oxygenated 17-ketosteroids (Fig. 49). A mild case suspected of Addison’s disease showed a marked decrease of 11-oxygenated 17-ketosteroids in the determination of fractions, though the total amount of 17-ketosteroids were within the normal range (Fig. 50). Thus it was known that all cases of Addison’s disease show a decrease in the absolute quantity of 11-oxygenated 17-ketosteroids or corticoidal 17-ketosteroids.
### Table XXXV

Urinary 17 Ketosteroids

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Time from onset to examination</th>
<th>Total 17-KS (mg/24 hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>M</td>
<td>6 months</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>M</td>
<td>6 months</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>2 years</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>M</td>
<td>2 years</td>
<td>2.2</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>M</td>
<td>8 months</td>
<td>3.6</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>M</td>
<td>3 years</td>
<td>3.8</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>M</td>
<td>16 months</td>
<td>4.5</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>M</td>
<td>6 months</td>
<td>17.5</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>F</td>
<td>2 months</td>
<td>1.6</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>F</td>
<td>11 years</td>
<td>2.0</td>
</tr>
<tr>
<td>11</td>
<td>46</td>
<td>F</td>
<td>1 year</td>
<td>1.7</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>M</td>
<td>6 months</td>
<td>2.4</td>
</tr>
<tr>
<td>13</td>
<td>42</td>
<td>F</td>
<td>4 months</td>
<td>7.4</td>
</tr>
<tr>
<td>14</td>
<td>39</td>
<td>F</td>
<td>2 years</td>
<td>8.2</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
<td>F</td>
<td>6 months</td>
<td>9.6</td>
</tr>
<tr>
<td>16</td>
<td>21</td>
<td>F</td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>17</td>
<td>20</td>
<td>F</td>
<td></td>
<td>5.2</td>
</tr>
<tr>
<td>18</td>
<td>20</td>
<td>F</td>
<td></td>
<td>6.1</td>
</tr>
<tr>
<td>Normal controls</td>
<td>4 cases</td>
<td>M</td>
<td></td>
<td>5.0~18.0</td>
</tr>
<tr>
<td></td>
<td>5 cases</td>
<td>F</td>
<td></td>
<td>4.5~10.0</td>
</tr>
</tbody>
</table>

Fig. 49. Values of urinary 17-ketosteroid fractions in case 3, (man, 42 y.), of Addison’s disease. Total 17-ketosteroids : 1.5 mg/day (297 γ).
17-Ketosteroids and Sex-Hormones in the Urine

Fig. 50. Values of urinary 17-ketosteroid fractions in Case 8, (man, 34 y.), of slightly advanced Addison's disease. Total 17-ketosteroids: 17.5 mg/day (207 γ).

The amount of urinary 17-ketosteroids in Riehl's melanosis was estimated by Spira\textsuperscript{11)} to be decreased, and by Uno\textsuperscript{14)} to be approximately the physiological value in his 1 case. In our 2 cases, the total amount was decreased, but the rates of the fractions were almost normal (Fig. 51). In 2 cases of lichen pigmentosus, a decrease in 17-ketosteroids was observed as in Riehl's melanosis (Fig. 52). In chloasma, the total amount showed nearly normal values; but the glucocorticoidal 17-ketosteroids were found decreased in one of the 2 cases in which the fractions were measured (Figs. 53, 54).

Fig. 51. Values of urinary 17-ketosteroid fractions in Case 9, (woman, 30 y.), of Riehl's melanosis. Total 17-ketosteroids: 1.6 mg/day (280 γ).
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Fig. 52. Values of urinary 17-ketosteroid fractions in Case 11, (woman, 46 y.), of lichen pigmentosus. Total 17-ketosteroids: 1.7 mg/day (55.9 μg).

Fig. 53. Values of urinary 17-ketosteroid fractions in Case 13, (woman, 42 y.), of chloasma. Total 17-ketosteroids: 7.4 mg/day (158 μg).

Fig. 54. Values of urinary 17-ketosteroid fractions in Case 15, (woman, 34 y.), of chloasma. Total 17-ketosteroids: 9.6 mg/day (575 μg).

In 2 cases of vitiligo, however, the 17-ketosteroids showed normal values, and in 1 case of complete albinism all the steroid-hormones showed
17-Ketosteroids and Sex-Hormones in the Urine

Fig. 55. Values of urinary 17-ketosteroid fractions in Case 18, (woman, 20 y.), of albinism. Total 17-ketosteroids: 6.1 mg/day (475 μg).

normal values (Fig. 55), suggesting that these diseases are of an obviously different mechanism, probably tyrosinase inactivation or denaturalizations in the epidermis.

To compare pregnant women with cases of hyperpigmentation as regards chiefly 17-ketosteroids in the urine: in the former the androgenic fractions IV and V decrease with the progress of pregnancy and the corticoidal fractions VI and VII show a tendency to rise in the latter half period of pregnancy, but the total 17-ketosteroid content remains to be almost normal throughout the whole period as in chloasma; whereas in cases of hyperpigmentation, such as Addison’s disease, Riehl’s melanosis and lichen pigmentosus, the total 17-ketosteroid content is lowered in value, and the relative percentages of fractions IV and VII, being risen in no case, probably represent the actual decrease in their amount. Thus it seems that pregnant women and patients with hyperpigmentation are contrary to each other as regards the total urinary 17-ketosteroids, in particular, the quantities of Fractions VI and VII.

In short, the participation of the adrenocortical system in melanin formation can be partly conjectured from urinary 17-ketosteroids also.

Changes in Urinary Estrogen and Progesterone

As non-steroid hormones presumably related with skin pigmentation may be mentioned MSH, ACTH, gonadotropin, adrenalin and nor-adrenalin. ACTH expedites the secretion of glucocorticoids by acting upon the adrenocortex; besides, it has in itself a similar action as MSH, which is generally attributed to the probable coexistence of MSH[15,16,17]. Gonadotropin acts upon the secretion of sex-hormones, while adrenalin
and noradrenalin control the action of MSH\textsuperscript{16,18}. Of these hormones, MSH has the strongest action on skin pigmentation as reported by many workers. Its administration to human bodies is followed by marked pigmentation (Lerner \textit{et al.}\textsuperscript{19}, Shizume\textsuperscript{20}). MSH, which increases in pregnancy, is highly responsible for hyperpigmentation in pregnant; it also increases in Addison’s disease\textsuperscript{16,20,21,22,23,24}.

To make a short mention of the recent literature on the relation of melanin formation to sex-hormones in particular: Davis \textit{et al.}\textsuperscript{25}, who administered estrogen to human subjects and guinea pigs, observed increased pigmentation on the nipples, halos and linea fusca but the absence of such pigmentation in menopausal women. According to Mighorst \textit{et al.}\textsuperscript{26} and Rothman\textsuperscript{27}, progesterone is said to expedite secretion of an MSH-like substance. Lerner \textit{et al.} state that a small dose of it causes pigmentation in the skin of frogs but that no such phenomenon is caused by any of steroid hormones. Wheeler \textit{et al.}\textsuperscript{28}, however, have reported that local application of estrogen, but not of progesterone, causes pigmentation on the nipples of guinea pigs. According to Pfeifer \textit{et al.}\textsuperscript{29}, local application of testosterone causes pigmentation on the beak of a sparrow; and similar pigmentation occurs on the scrotum of a squirrel (Well\textsuperscript{30}) and in the skin of a castrated man (Edward \textit{et al.}\textsuperscript{31}). According to Forbs\textsuperscript{32}, the pellets implanted into the skin of male and female rats cause pigmentation in the hair, while Hamilton\textsuperscript{7} has reported on the pigmentation caused in tissue-cultivated skin by estrogen and androgen. Lerner and Fitzpatrick\textsuperscript{16}, who have recognized no action of estrogen and androgen on melanin cells in the skin of frogs, have suggested that these hormones may have such an action in man.

As shown in these reports, estrogen and progesterone cause pigmentation in animal skin. But there have been hardly any reports dealing with the actual measurements of sex-hormone contents in patients with pigmentary skin diseases. For this reason we have made measurements of urinary estrogen and progesterone in pregnant and patients with chloasma, Richl’s melanosis, lichen pigmentosus and albinism, to study on what relationship there may be between these diseases and sex-hormones.

The experimental subjects were selected from among the patients treated at the Gynecology and Obstetrics Clinic and the Dermatology Clinic of Tohoku University Hospital, and 24 hour urinary excretion was used as samples.

Urinary estrogen was estimated by Suzuki and Mori’s method\textsuperscript{33}; and urinary pregnanediol, by Mack, Parks and McDonald’s method with the help of the spectrophotometer (Hitachi)\textsuperscript{34}. These methods are both for chemical determination of the quantity of sex-steroids. Pregnanediol, however, is a product of progesterone metabolism, and has neither hormone
activity of its own, nor any relation to skin pigmentation (Lerner), but was measured because an increase of this steroid in the urine is an index of increase of the progesterone in the body.

Experiments and Results

a. Pregnancy, parturition and puerperium

Fig. 56 shows the values of estrogen measured during normal pregnancy. Each point stands for the mean of values measured in 6-10 cases. The number of cases was 57 each for estrone, estradiol and estriol. In all cases, estrogen, in particular estriol, increased during pregnancy and decreased during puerperium.

Fig. 57 shows the results of 38 determinations of urinary pregnanediol. The values rise steeply with the course of pregnancy but fall suddenly on the 3rd day of puerperium, coming down to nearly nothing. The decrease of androgen and the increase of corticoids, as stated above in connection with the results of determinations of 17-ketosteroid fractions, are supposed to exert counteractions on increased pigmentation, but such actions seem to have been nullified by the marked increase of MSH, estrogen and progesterone during pregnancy.

b. Changes in estrual hormones in chloasma and Richl's melanosis

It has been pointed out by Crawford and Leeper, and others that urinary excretions of estrogen, progesterone and gonadotropin show definite changes according to the estrual stages. Fig. 58 shows the results
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Fig. 58. Values of urinary estrogen and pregnanediol contents in a healthy woman, 31 y., with normal sexual cycle. 

Menstruation; 
<estrone>, <estradiol>, <estriol>, <pregnanediol>. 

These marks will be applied also in following Figures (59-64).

of successive determinations in a normal adult woman of 31 years with the normal menstrual cycle, to serve as controls. Her basal temperature was of the double-phased type, and the estrone and estradiol values each showed a peak around the time of ovulation and the mid-stadium of luteal formation, respectively, each dropping to the lowest level at the time of menstruation. Pregnanediol amounts to little over zero in the follicular stage, increases in the yellow-body stage, and drops to zero in the menstrual stage.

Figs. 59–61 show the results of successive determinations throughout the menstrual cycle in 3 patients with chloasma. Two of them were adult women with the normal menstrual cycle, but the other had received uterectomy 2 years before and was amenorrheal, but her basal temperature was obviously of the double-phased type, lowering in the period before the ostensible ovulation time and rising after it, so that it was inferred that the endocrine function of sex-hormones was being performed quite normally in her. Thus, in all the 3 cases, estrone, estradiol and estriol each showed one peak in the ovulation stage and another in the middle of the luteal stage, while pregnanediol was found to fall almost to nothing before the ovulation but to rise after it. That is to say, the tendency of changes in
Fig. 59. Fluctuations of urinary estrogen and pregnanediol contents during a sexual cycle in a woman, 30 y., with chloasma.

Fig. 60. Fluctuations of urinary estrogen and pregnanediol contents during a sexual cycle in a woman, 25 y., with chloasma.
the estrual hormones in those cases was nearly the same as that in the control normal woman. The quantity, however, of these estrual female hormones, in particular of estrone, estradiol and pregnanediol was demonstrated to show markedly higher values in cases of chloasma than in the normal control.

Figs. 62, 63 show the similar changes of sex-hormones found in cases of Riehl's melanosis. The marked increase in estrone and estradiol observed in a woman (57 years) is a finding contradicting the observation by Davis cited above that no pigmentation followed estsogen administration to women in menopause and is to be noticed in studying the pathogenesis of Riehl's melanosis. We have also experienced a lowered basal metabolism and decrease of 17-ketosteroids in spite of normal menstruation in a female patient (Fig. 64) of 35 years suffering for 10 years from diffuse gray-brown pigmentation in her face somewhat resembling the pigmentation in Addison's disease or Riehl's melanosis, and surmised that it may be a pigmentary disease different from those alluded to in this case.

In short, we should not overlook the fact that in the comparative study of the estrual cyclic fluctuations of the urinary excretion of sex-hormones, a distinct increase was observed in the quantity of excreted
hormones in cases of chloasma and Riehl's melanosis than in a normal woman.

Besides, as shown in the preceding chapter, the chloasma cases showed normal values of urinary 17-ketosteroids, while in the cases of Riehl's melanosis the value was lowered, indicating a difference in the function of the adrenocortical system between the two diseases. This might give a hint on the pathogenesis of hyperpigmentation on the face in the two diseases.

Furthermore, the merely temporary increase in urinary 17-ketosteroid values at the time of parturition, and the gradual increase of estrogen and pregnanediol during pregnancy despite the decrease of Fractions IV and V of 17-ketosteroids originating in androgen, in combination with the increase of MSH during pregnancy, as reported in literature, seem to be the cause of pigmentation during pregnancy and give an interpretation of clinical observations of the localities of pigmentation different from those in pigmentary diseases. These relationships may be illustrated in the following Table XXXVI which will show the different tendencies there are between them.

**SUMMARY**

We have made measurements of steroid hormones in urine sampled...
from subjects showing increase of skin pigmentation, including women in pregnancy, parturition, and puerperium and patients with pigmentary skin diseases, by chemical methods and arrived at the following results:

1. The values of 11-oxygenated 17-ketosteroids were lowered in cases of Addison's disease, chloasma, Riehl's melanosis and lichen pigmentosus.

2. Estrogen and pregnanediol were found to be increased in preg-
nants and in patients with chloasma and Riehl’s melanosis, the increment being much higher in the former than in the two latter diseases. The increases of contents of these hormones at the menstrual cycles tended to be higher in female patients of chloasma and Riehl’s melanosis than in a normal non-pregnant woman.

3. Consequently, these hormones are presumed to participate in melanin formation during pregnancy and in the diseases alluded to in

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<td>Pigmented Sites</td>
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<tr>
<td>Pregnancy</td>
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<td>Total 17-KS Fractions</td>
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<tr>
<td>Estrogen</td>
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<td>Increased (espec. estriol)</td>
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<td>Pregnanediol</td>
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<td>Normal rates</td>
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<td>Increased by menstrual cycle</td>
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Conclusions 1 and 2.

4. No anomaly was observed in the urinary contents of these hormones in cases of complete albinism.

References

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