SKIN PIGMENTATION AND THE MENSTRUAL CYCLE

BY

B. W. McGUINNESS,* M.D.

Formerly Holt Research Fellow, Liverpool University

Dermatologists have been aware of a facial pigmentation which develops in apparently normal girls at puberty, and which waxes and wanes with each menstrual period, since Brocq (1923) first described such a condition under the name of "erythrose péribuccale pigmentaire." Comments on this disorder are few outside the French literature (Ingram and Brain, 1957), although it is probably not an uncommon condition (*British Medical Journal*, 1952). Its characteristic features (Ingram and Brain, 1957) are the localization to the central part of the face of a relatively constant reddish or yellowish-brown pigmentation. A perioral ring of pale skin is sometimes seen, and it may be possible to blanch some of this coloration by diascopic pressure. This last feature suggests an element of vasomotor instability in the condition. There may, however, be a more diffuse mottling of discoloration noticeable, especially across the forehead (MacKenna, 1952).

Goldsmith and Hellier (1954), citing Edwards and Duntley (1949), mentioned that the skin of women is more sensitive to ultra-violet light and is more vascular during the premenstrual phase of the menstrual cycle. They also describe the occurrence of a chloasma in non-pregnant females and draw attention to a heredofamilial factor in the predisposition of patients to this condition. The condition was said to be an essentially normal phenomenon by Poor (1930), who described a macular seborrhoea in association with the brownish or blackish pigmentation. Poor noted that the pigmentation occurred in young girls at the time of the first menstrual period and that it was situated chiefly round the mouth but involved other parts of the face.

Ormsby and Montgomery (1954) made a distinction between Brocq's pigmentation and that variety described by Poor. They believed that Brocq's pigmentation may be pathological whereas Poor's pigmentation is a purely physiological phenomenon. They encountered facial pigmentation in patients with ovarian neoplasms, functional diseases of the uterus, and in cases of "disease of endocrine imbalance." Daily and even hourly fluctuation in the intensity of the pigmentation was described by these writers in their cases, and they attributed the changes to endocrine and nervous imbalance.

The physiological facial pigmentation described by Poor occurred in normal young females and was not a sign of disease. Poor called the condition "chloasma periorale virginium." His associate, Von Verde (1930), added a further series of similar cases which were characterized by pigmented macules about the mouth occasionally spreading to other parts of the face and appearing in young virgins. Von Verde believed that the pigmentation was related to ovarian function and found that, although the cases were resistant to all forms of treatment, he believed the condition usually disappeared spontaneously after some years.

A further series of cases was described shortly after this by Ormsby and Ebert (1930, 1931), who drew attention to the darkening of facial pigmentation immediately before the menstrual period began. Occasional case reports and comments on the condition have appeared in journals since then.

All writers mention the probable importance of the endocrine glands in the genesis of fluctuating facial pigmentation, and Brocq himself suspected this. However, hitherto no one appears to have related the pituitary melanocyte-stimulating hormone (M.S.H.) to this condition. This is readily understandable in view of the relatively recent advent of experimental work on the properties of M.S.H. and its secretion in health and disease. Final elucidation of the relationship between M.S.H. and changes in normal pigmentation can only be expected when methods of extraction, purification, and measurement of the hormone are reliable beyond doubt and easy to perform.

In a previously documented study I was unable to demonstrate consistent changes in the serum M.S.H. levels of normal women in relation to their menstrual cycles (McGuinness, 1959). This was probably because of difficulty with the methods of assay employed. It is believed that regular changes in pituitary M.S.H. production are likely to occur normally despite the present lack of convincing laboratory evidence in support of this.

Apologia for the Present Study

If these fluctuations in the secretion of M.S.H. do in fact occur and are effective in producing a regular pattern of changes in skin pigmentation, a critical survey of the day-to-day appearances of a number of normal persons might be expected to reveal evidence of this.

There are no references in the literature to such a survey ever having been conducted. Therefore, a small survey of female medical students and medical practitioners aged 19 to 30 years was carried out by questionary. The object of this was to find out whether pigmentary variations could be detected in normal females and whether changes in the intensity of the pigmentation were related to the phases of the menstrual cycle. The subjects, as a special group in the community, were chosen because their trained skill in observation and knowledge of the physiological background to the study made it likely that the results they recorded would be accurate and therefore of value in assessing the problem under investigation.

Methods.—The survey was begun in March, observations being made by the subjects from then onwards through the spring and summer months, the data being collected for analysis in October. Comments based on the results of this survey therefore depend on observations made over the course of about six months. Out of 120 subjects circularized, 63 replied. Each subject received a simple form which outlined the purpose of the inquiry, specified the observations required in the form of simple unambiguous questions, and explained by simple notes how the observations were to be recorded. The specimen form on the next page shows the exact arrangement and wording of the questionary.

*Now Medical Officer in Charge, Clinical Research Unit, Nicholas Institute for Medical and Veterinary Research, Slough, Bucks.

Specimen Form

SURVEY ON SKIN PIGMENTATION IN RELATION TO THE MENSTRUAL CYCLE

DEPARTMENT OF PATHOLOGY. LIVERPOOL UNIVERSITY.

Introduction

Relatively recently there has been described a pigmentation of the face developing in females at puberty and attributable to pituitary M.S.H. production.

To a critical observer skin pigmentation might be seen to vary with the menstrual cycle as pituitary function fluctuates.

No data have ever been assembled to investigate this possibility, and this inquiry is an attempt to assess the matter in normal women.

This is at present part of the work being undertaken in this department on pigment-producing hormones.

You are requested to fill in this form after observing your skin colour during the next six months.

Negative answers are just as important as positive ones.

The form should be returned to this department in the envelope provided.

Your name is not required, identification of subjects being by numbers only.

Questions

A
1. Age
2. Hair colour
3. Previous illnesses
4. Present health

B
1. Do you tan readily in the sun ?
2. How many hours' exposure to sun gives you minimal tanning ?
3. How long does pigmentation persist after your last exposure to strong sunlight ?
   (*a*) Minimal tanning
   (*b*) Marked tanning

Has your skin colour in the following regions changed in relation to the menstrual cycle ?

C
1. Forehead
2. Round the mouth
3. Round the eyes
4. Axilla
5. Areola of nipple
6. Abdomen, especially linea alba

D
1. Age of menarche
2. Is the menstrual cycle regular ?
3. Do you have any symptoms referable to changing hormone levels—e.g., premenstrual tension syndrome

Notes

In part A mention especially skin and endocrine conditions.

The questions in part B are to assess target-organ sensitivity. Minimal tanning is just sufficient to distinguish between adjacent exposed and non-exposed areas (e.g., above and below the collar). Marked tanning is sufficient to be obvious to the subject when exposed skin is examined without reference to unexposed skin.

Specimen answer to part C: "Forehead becomes noticeably darker 2 days before the M.P. is due, and this persists for about 10 days."

Results

Tables I–V summarize the results obtained. The findings are classified in relation to the occurrence or otherwise of varying skin pigmentations. It will be seen that about half the women questioned had some increase in skin pigmentation, which was noted in every case in the latter days of the menstrual cycle and in some cases during menstruation also. The others showed no skin changes whatsoever.

There was no correlation between hair colour and varying skin pigmentation, nor between this and the age of the menarche. The presence or absence of premenstrual symptoms was not related to skin shade. The sensitivity of the subjects' skin to ultra-violet light, as assessed by the speed of darkening in sunlight and the duration that tanning persisted, did appear to have a

TABLE I.—*Relationship of Hair Colour and Ultra-violet-light Skin Sensitivity to the Skin-pigment Changes of the Menstrual Cycle*

Indices of the Factor Under Consideration	Fluctuation in Skin Pigmentation in Relation to Menstrual Cycle		
	Changes Observed	No Changes Observed	Total
Total in series	29	34	63
Hair colour:			
Black (brunette)	2	5	7
Brown (light and dark)	24	25	49
Fair (blonde)	2	1	3
Red (auburn)	1	3	4
Skin sensitivity to ultra-violet radiation:			
(*a*) Speed of response measured by time of exposure required to produce minimum tanning:			
Rapid: <2 hours	5	3	8
Moderate: 2–12 hours	21	16	37
Slow: >12 hours	2	12	14
No response: Infinite	1	3	4
(*b*) Persistence of tanning after last exposure to direct strong sunlight:			
Minimum tanning:			
<1 week	6	11	17
1–3 weeks	6	12	18
1–3 months	17	11	28
4–6 ,,	0	0	0
>6 ,,	0	0	0
Marked tanning:			
<1 week	8	14	22
1–3 weeks	9	14	23
1–3 months	6	6	12
4–6 ,,	3	0	3
>6 ,,	3	0	3

Minimum tanning is pigmentation just sufficient to distinguish between adjacent exposed and non-exposed areas—for example, above and below the collar. Marked tanning is pigmentation sufficiently dark to be obvious to the subject when exposed skin is examined without reference to unexposed skin.

TABLE II.—*Relative Frequency of Pigmentation at Several Sites*

Site	No. Affected
Forehead	8
Perioral	10
Periocular	25
Axilla	5
Areola of nipple	17
Abdomen: linea alba	6
No. with multiple site changes	19

TABLE III.—*Frequency of Sites Involved in Combination*

Site Combinations	No.
Periocular and nipple	11
,, ,, forehead and perioral	6
Axilla and nipple	2
,, ,, ,, and abdomen	2
Other combinations	0

The sites most commonly affected by this pigmentation are the periocular skin and nipple areola. Other sites are affected in 35% or less of subjects. Involvement in more than one place is common.

TABLE IV.—*Age of Menarche in Relation to Variation of Skin Pigmentation with Menstrual Cycle*

Age of Menarche to Nearest Year Above	Pigment Changes Observed	No Pigment Changes Observed	Total
12 and under	1	1	2
13–15	19	26	45
16–18	8	7	15
19–21	1	0	1
Over 21	0	0	0

TABLE V.—*Premenstrual Symptoms, Referable to Changing Hormone Levels, in Relation to Facial Pigmentation that Varies with Menstrual Cycle*

Symptoms Referable to Changing Hormone Levels	Pigment Changes Observed	No Pigment Changes Observed	Total Cases
Primarily organic:			
Full premenstrual tension syndrome	5	4	9
Gastro-intestinal disturbance alone	0	1	1
Frequency of micturition alone	0	0	0
Exacerbation of acne	3	6	9
Primarily psychological:			
Irritability	0	0	0
Depression	5	7	12
Malaise	6	3	9
Headache	2	2	4
No symptoms	8	11	19

bearing on the problem. Thus those subjects showing changes in skin pigmentation related to the menstrual cycle tended to have skin that pigmented more readily and more persistently than those in the other group. But there were exceptions to this general tendency in both groups; a few "pigmenting" subjects tanned slowly in the sunlight and lost their tan relatively quickly; a few "non-pigmenting" subjects tanned quickly and retained their tan a long time.

The site most commonly showing pigmentation changes was the skin around the eyes. Next most frequently affected were the areola of the nipple and the perioral skin. The forehead, axilla, and abdomen were affected in less than one-third of the "positive" subjects. Nineteen out of 29 subjects showed changes in more than one place. The commonest combination of sites was that of periocular skin with nipple areola skin.

Discussion

This survey was carried out on a group of young female subjects selected for training in scientific observation and for their understanding of the background to the work. It demonstrated that pigmentation of the skin varied in relation to the menstrual cycle in about half the women assessed. The periocular and nipple areola skin was most commonly affected, skin darkening occurring during the week preceding menstruation, and in some cases during menstruation also. Skin sensitivity to ultra-violet light was of importance in determining the occurrence of this phenomenon, but none of the other factors examined had any influence upon it. Although this is a small series, the conclusions based upon it probably apply to women in the general population, thus indicating that skin pigmentation varying in intensity, in time with the menstrual cycle, may well be a common normal condition.

There is a certain amount of evidence from experimental work (Collin and Drouet, 1933; Cunningham Dax, 1938; Lambillon and Lejeune, 1938; Shizume and Lerner, 1954) that this phenomenon may be referable to variations in the secretion of M.S.H. by the pituitary. Since the pituitary produces several hormones in a cyclical fashion, thus, for example, governing the cyclical pattern of the menses, it is not unreasonable to postulate that cyclical variation in M.S.H. secretion, in keeping with general pituitary behaviour, may also occur. Thus this apparently common cyclical variation of skin pigmentation found in young women may well have its origin in the fundamental cyclical activity of the master endocrine gland.

Summary

A pigmentation of the skin varying in intensity in a constant relationship with the phases of the menstrual cycle has been recognized by clinicians for many years. The pattern of this variation and its occurrence in normal young women has been demonstrated by a simple survey technique. The occurrence of the skin condition appears to be related to the sensitivity of the skin to ultra-violet light, darkening of the skin always occurring in the premenstrual week. Although the explanation of this phenomenon is not clear it seems likely that changes in the secretion of the melanocyte-stimulating hormone by the pituitary are responsible for this interesting and probably common condition.

I am indebted to Professor H. L. Sheehan, of the department of pathology at Liverpool University, for permission to publish this article. Thanks are also due to the female house officers at Liverpool Royal Infirmary and the David Lewis Northern Hospital, Liverpool, and to the many female medical students of the Medical Faculty at Liverpool University for their ready co-operation in this study.

REFERENCES

British Medical Journal (1952). In *Any Questions?* Second Series, p. 56. British Medical Association, London.
Brocq, L. A. J. (1923). *Presse méd.*, **13**, 627.
Collin, R., and Drouet, P. L. (1933). *Bull. Acad. Méd. (Paris)*, **109**, 794.
Dax, E. C. (1938). *Brit. J. Ophthal.*, **22**, 345.
Edwards, E. A., and Duntley, S. Q. (1949). *Amer. J. Obstet. Gynec.*, **57**, 501.
Goldsmith, W. N., and Hellier, F. F. (1954). In *Recent Advances in Dermatology*, 2nd ed., p. 181. Churchill, London.
Ingram, J. T., and Brain, R. T. (1957). In J. H. Sequeira's *Diseases of the Skin*, 6th ed., p. 273. Churchill, London.
Lambillon, F. W., and Lejeune, A. (1938). *C.R. Soc. Biol. (Paris)*, **128**, 1158.
MacKenna, R. M. B. (1952). *Diseases of the Skin*, 5th ed., p. 530. Baillière, Tindall and Cox, London.
McGuinness, B. W. (1959). Melanocyte Stimulating Hormone, M.D. Thesis, Liverpool University.
Ormsby, O. S., and Ebert, M. H. (1930). *Arch. Derm. Syph. (Chicago)*, **22**, 170.
—— —— (1931). Ibid., **23**, 429.
—— and Montgomery, H. (1954). *Diseases of the Skin*, 8th ed., p. 720. Kimpton, London.
Poor, F. (1930). *Textbook of Dermatology*, cited by Ormsby and Ebert (1931).
Shizume, K., and Lerner, A. B. (1954). *J. clin. Endocr.*, **14**, 1491.
Von Verde, K. (1930). *Arch. Derm. Syph. (Berl.)*, **159**, 506.

Preliminary Communications

Treatment of Petit Mal with Ethosuximide

Recent years have seen the search for an effective drug to control petit mal. The oxazolidine-dione compounds (troxidone and its allies) have given encouraging results in many cases but they have the disadvantage of being apt to produce unpleasant side-effects and occasionally severe damage to the bone-marrow with consequent agranulocytosis. Derivatives of the basic succinimide molecule have subsequently been investigated. The first was phensuximide ("milontin"), but, although apparently without any serious side-effects, its therapeutic effect in petit mal has on the whole been disappointing. The same applies to its successor, methsuximide ("celontin"). The most recently synthesized drug in this series is α-ethyl-α-methylsuccinimide, which has the approved name of ethosuximide. It is marketed in this country as "zarontin" and "emeside" in soluble gelatin capsules, each containing 250 mg. of ethosuximide.

Preliminary investigations in the U.S.A. showed that ethosuximide was without toxic effect when given by mouth to animals for 12 months. Zimmerman and Burgemeister (1958) produced the first clinical report of the use of ethosuximide in epilepsy. They regarded it as "essentially a petit mal drug" and were able to control the attacks completely or almost completely in two-thirds of their cases. Vossen (1958) next reported good results in some 39% of the 56 patients with petit mal, his observation period ranging from 3 to 18 months. Lorentz de Haas and Stoel (1960) obtained good results in about 47% of 60 patients. Gordon (1961) reported favourably on the value of ethosuximide in the treatment of pure petit mal (in the absence of brain damage) in a small group of cases.

No serious toxic effects have been reported by any of these workers, though occasional nausea or vomiting