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.

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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

on starting treatment has been noted. Of Zimmerman and Burgemeister's 109 patients, 9% experienced side-effects that were usually related to high dosage and were relieved by reduction of the dose. These symptoms included nausea, gastric discomfort, drowsiness, and dizziness. Skin rashes have not been observed and no significant haematological or urinary changes have been recorded in any patients treated.

PRESENT SERIES

No accounts of the use of ethosuximide have so far been published in this country, and the present communication deals with 50 hospital out-patients who have been treated with this drug. All of them suffered from petit mal and 19 had also had grand mal convulsions at some time. The petit mal was generally of the classical form, consisting simply of transient loss of awareness without falling, but it was sometimes associated with momentary jerking of the head or arms, or with a brief akinetic attack in which the subject fell limply to the ground and then quickly got up again. Routine electroencephalograms were not made, but classical 3-per-second wave-and-spike records were obtained in 22 cases. Sixteen patients gave a family history of epilepsy; 36 were under 20 years of age; and 40 had been subject to petit mal for more than one year before treatment with ethosuximide was begun. None had responded satisfactorily to other drugs. Almost all had already been treated with phenobarbitone and 27 of them had also had troxidone, aloxidone, phensuximide, or amphetamine. A few had had all these.

Ethosuximide was prescribed in addition to whatever antiepileptic drugs the patient was already taking, and the initial dose was generally one capsule (250 mg.) two or three times daily. Sometimes the dosage was gradually increased up to six capsules daily, but those who responded satisfactorily to the drug usually did so quickly with smaller doses of three or four capsules daily. When a satisfactory response was obtained, other drugs were gradually stopped, if feasible, and eventually in a few cases where control of attacks seemed complete the ethosuximide itself was gradually stopped. Results of treatment in our 50 cases were: 27 successfully controlled, 10 partially and inadequately controlled, and 13 unaffected.

Of the 27 cases described as "successfully controlled," 21 have remained completely free from attacks for an average period of 10 months. The distribution of these periods was: 3 to 12 months in 12 cases, 12 to 18 months in 4, and 18 to 24 months in 5. The other six patients have been almost completely free from petit mal attacks for an average of eight and a half months. They have had only occasional attacks (about once a month, usually after some special provocation such as omission of capsules, undue fatigue, or excitement) whereas previously they had usually had several daily.

Of the 27 successfully treated patients, 15 had been subject to petit mal for three years or longer before starting ethosuximide. The drug was not noted to have any provocative or therapeutic effect on grand mal in this series.

The effective daily dosage of ethosuximide in the successfully treated cases was: one capsule in 2 cases, two capsules in 2 cases, three in 15 cases, four in 4 cases, five in 1 case, and six in 3 cases.

In seven instances it has been possible to withdraw the ethosuximide gradually after about six months, without recurrence of petit mal. These patients have now been without any treatment for an average of 12 months, although previously they were having frequent attacks. In other cases, however, reducing or stopping ethosuximide has led to temporary recurrence of petit mal until the drug has been restored.

The following is an illustrative case history:

A boy born in 1946 and first seen in 1955 had had typical petit mal up to four or five times daily for one year and was treated unsuccessfully with phenobarbitone, amphetamine, and troxidone in turn. Troxidone had to be stopped because of leucopenia, and he was then given phensuximide. There was some temporary improvement, but after six months' treatment with phensuximide he was having six or more attacks daily. In July, 1959, when he started taking ethosuximide (three capsules daily), he was having about 16 petit mal attacks a day. These continued for the first three days of treatment, but since then he has remained completely free of them. As he felt sick and sleepy at the beginning of this treatment, the dose was reduced to two capsules daily. He became alert and remained well. In March, 1960, the drug was stopped and there has been no recurrence of this petit mal. Serial white counts showed a steady rise in the polymorph count to a normal level after beginning treatment with ethosuximide.

SIDE-EFFECTS

Although we have encountered no serious toxic reactions to ethosuximide, 17 of our patients showed some side-effects when they began to take the drug (14 of these received three capsules daily and three received two capsules daily). Apathy, depression, or drowsiness occurred in eight, nausea in five, vomiting in four, and dizziness and transient stammer each in one case. In five further cases apathy, nausea, or vomiting occurred later, when the dose was increased to four, five, or six capsules daily. These symptoms usually subsided rapidly when the dose of ethosuximide was reduced; treatment then continued normally. In four instances it was thought advisable to stop the drug permanently.

No urinary abnormalities or skin rashes were seen. Blood counts were done in some two-thirds of the patients at some time during treatment and considerable variation from time to time was noted. Occasional polymorph counts of between 2,000 and 3,000/c.mm. were observed, but these were unaccompanied by any clinical manifestations and were not regarded as an indication for reducing the dose. In two cases, although previous oxazolidine-dione therapy had resulted in polymorphonuclear leucopenia, the polymorph counts increased steadily after starting treatment with ethosuximide.

SUMMARY

Fifty patients with petit mal have been treated with ethosuximide and in 27 of these the attacks have been successfully controlled for periods of up to two years.

The effective dosage in the majority of patients was one capsule (250 mg.) three times daily.

No serious toxic reactions have been seen but transient side-effects may occur, especially at the start of treatment. The initial dosage should therefore not exceed one capsule daily for small children and two capsules daily for older children and adults.

We are grateful to Messrs. Parke, Davis and Co., who kindly supplied capsules of ethosuximide (zarontin) for this trial.

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Medical Memoranda

Aorto-duodenal Fistula after Surgery of Abdominal Aorta

The following case histories are presented to draw attention to the occurrence of aorto-enteric fistula as a sequel to reconstructive operations such as thrombo-endarterectomy or grafting of the abdominal aorta, for when such a complication occurs the patient may present with symptoms and signs of gastro-intestinal haemorrhage. The complication has occurred in approximately 2% of our cases.

CASE REPORTS

Case 1.—In April, 1958, a 58-year-old man presented with an aneurysm of the abdominal aorta which was treated by resection and insertion of a nylon prosthesis. His convalescence was complicated by the development of a small-bowel obstruction due to adhesions, wound sepsis, a pelvic abscess, and a deep-vein thrombosis in the left leg. He was discharged from hospital seven weeks after operation. In August he was admitted to another hospital and an operation was performed for a small-bowel obstruction due to adhesions. The post-operative course was apparently complicated by a staphylococcal septicaemia. In May, 1959, he developed sudden abdominal pain, collapsed, and died. Necropsy showed that the proximal graft anastomosis had ruptured into the posterior aspect of the third part of the duodenum, and the stomach and small gut were filled with blood. There was also extensive clot in the retro-peritoneal tissues and right psoas sheath.

Case 2.—A 57-year-old man developed intermittent claudication in the thighs and calves which stopped him walking after 50 yards. The common femoral pulses were reduced and no other pulses were palpable in the lower limbs; aortography confirmed the presence of an atherosclerotic occlusion of the aorta and common iliac arteries. In December, 1958, thrombo-endarterectomy of the lower aorta and common iliac arteries was carried out with complete relief of the claudication and restoration of popliteal and ankle pulses; the patient returned home on the 19th day after operation. A month later he started to complain of intermittent epigastric and para-umbilical pain; physical examination was negative and a barium-meal examination revealed nothing abnormal. In April, 1959, he had a haematemesis and was treated medically in hospital for six weeks. In July he was admitted to another hospital with a recurrence of the haematemesis; an emergency partial gastrectomy was carried out, but he died. Necropsy showed that the cause of the gastro-intestinal haemorrhage was a fistula between the right common iliac artery at the line of suture and the third part of the duodenum.

COMMENT

Reported cases of aorto-enteric fistula occurring after reconstruction operations on the abdominal aorta are few and relate mainly to the use of homografts. In an analysis of 120 consecutive cases of major arterial grafts Humphries *et al.* (1956) noted two instances in which freeze-dried homografts had ruptured into the duodenum and one case of rupture into the jejunum. DeWeese *et al.* (1959) also recorded two cases of aortic homograft failure with rupture into the jejunum. In the case described by Hagland *et al.* (1959) the patient was found to have a duodenal ulcer and was submitted to partial gastrectomy before it was realized that the cause of his gastro-intestinal haemorrhage was rupture of an aortic homograft into the ileum.

While the reports from the literature suggest graft failure as the cause of fistula formation, it seems probable that the friable nature and poor suturing qualities of the atherosclerotic aorta are of even greater importance, and it is perhaps surprising that the complication does not occur with greater frequency. The third part of the duodenum is at a much lower level than is generally realized and must often be reflected upwards to expose the aortic bifurcation. Where fistula formation takes place this part of the duodenum, which is unprotected by peritoneum, would appear to be especially vulnerable, irrespective of whether a grafting procedure or thrombo-endarterectomy has been carried out.

Aorto-enteric fistula should be regarded as a likely cause of gastro-intestinal bleeding in patients who have been submitted to reconstructive surgery of the abdominal aorta, for as survival rates for such operations improve it may be that this complication will be seen more often.

We are indebted to Dr. H. F. Barnard and Dr. J. Adler for the post-mortem reports.

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A revised British Standard—Methods for Determination of Air Pollution (B.S.1747: 1961), Part 1. Specifications for Deposit Gauges—has now been published. When it was first published in 1951 it was concerned solely with deposit gauges. Now it is being reissued in several parts to cover, in addition, apparatus and procedure for the measurement of (1) fine particles (smoke), and (2) gaseous impurities, as well as the solid material (such as grit) which is measured by the deposit gauges specified in Part 1 of the standard. Experience in the use of deposit gauges during the past ten years has enabled the British Standards Institution committee concerned to introduce a number of refinements into the standard, but the procedure outlined is substantially unchanged. The standard deals with the construction, installation, and use of deposit gauges. A standard report form and a statement of the analytical determinations to be made are included. Copies may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1, price 5s. each, postage extra to non-subscribers.