areas. Such infants may die if the cyanosis is attributed to congenital heart disease and treatment is not given.

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CUTANEOUS REACTIONS TO INJECTION OF PROGESTERONE SOLUTIONS INTO THE SKIN

BY

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It has been noticed that the intradermal injection of progesterone solution causes a complex reaction in the skin—an immediate and transitory “triple response” (Lewis, 1927), followed after about a week by a localized follicular eczema, which on subsiding leaves a pigmented patch. It is known that in different circumstances oestradiol or testosterone may increase skin pigmentation; and the present observations are perhaps mainly of interest in that they provide a further example of such an effect of a sex hormone.

Experimental Procedure and Results

Progesterone solutions were injected into the skin of 29 medical students, 10 being women, and into my own skin. Each received two intradermal injections at points a few centimetres apart on the anterior surface of the forearm; one was of “progestin,” containing 1 mg. of progesterone per ml. in ethyl oleate, the other of progestin, 25 mg. per ml. In each case 0.04 ml. was injected, but measurement showed that about half of the oily solution rapidly escaped through the track of the needle. The quantities of progesterone that remained in the skin were therefore about 0.02 and 0.5 mg., and of ethyl oleate 0.02 ml.

In every case a stinging sensation and a widespread flare developed within a minute or two. Wheal formation at this stage was minimal, and (as shown by subsequent tests on one subject) the size of this initial reaction depended on the volume of solution injected, of whichever strength, rather than on the amount of progesterone it contained.

This reaction subsided during the first day, and for the next week many of the subjects showed little evidence of the injection. Then from about the seventh day onwards a further reaction was seen in all but 5 of the 30 subjects. It looked like a small patch of follicular eczema, but it was only mildly irritating. Each “follicle” was the centre of a minute area of brown pigmentation; when the blood was pressed out of the distended minute vessels by means of a microscope slide the pigmentation was more obvious. The pigment was not identified, but throughout all stages of its development and fading it was indistinguishable in colour

from that of sun tan. During this period in the summer many of the subjects developed a moderate natural sun tan which overlapped the experimental areas.

When the experimental reaction was at its height, at about the fourteenth day, 13 subjects showed at the site of the injection of the larger amount of progesterone a patch of pigmentation which was judged to be equivalent to a marked sun tan and a further 8 showed one equal to a mild sun tan; the corresponding figures for the smaller concentration of progesterone were 2 and 16 respectively. Although these figures are the result of subjective judgment, there is no doubt that, at this stage, in many cases the pigmentary reaction to the more concentrated solution was greater than that to the less concentrated. Only 4 of the 30 subjects showed no pigmentation whatever.

The occurrence of pigmentation of any degree was distributed evenly among those with fair, medium, or dark hair and skins, but the densest was seen in dark (European) subjects. There was no preponderant incidence in either sex. The pigmentation persisted in most cases for some weeks, although the eczema-like reaction subsided during the next few days.

Then in nine subjects (four men and five women) an unexpected reaction occurred. During the third week after the injection the site, particularly that at which the more concentrated solution had been introduced, became first itchy and then “inflamed,” with eczematous follicles and wheals. The surface desquamated and the whole area of about 5-cm. diameter became apparently oedematous and pervaded by the brown pigment. Although half the women showed this more severe reaction, as compared with one-fifth of the men, there was no significant correlation with the phase of the menstrual cycle. The most severe reaction was in a woman. Some subjects had an intense irritation, and the application of adhesive tape to hold dressings in place caused subsidiary foci of reaction. Although the students had by now dispersed and the later stages of the reactions could not be watched personally, it seems that in no case did any infection of the areas occur.

Mepyramine hydrogen maleate (“anthisan”) cream gave some relief, but usually was not completely effective. The reactions subsided, in some cases with recrudescences, during the next week or month. The pigmentation tended to fade a little more slowly than the other manifestations.

Further similar injections of the oily medium alone (ethyl oleate) were made into my skin. It was apparent that the initial triple response could be caused by injection of the medium alone. The later eczematous reaction appeared, but in smaller degree, and it was very doubtful whether any pigmentation resulted. Slight pigmentation, however, followed intradermal injection of normal saline. I did not suffer any severe reaction to either the progestin or the ethyl oleate injections; but, inasmuch as the other reactions appeared to be due partly to the medium, and some of the other subjects had experienced unpleasant reactions, it was not felt justifiable to repeat the injections with the medium on the other subjects.

Repetition of pairs of injections, of progestin and ethyl oleate, in my skin during a period of several months gave gradually diminishing responses to both.

Discussion

The evidence suggests that the initial triple response and the eczematous reaction of the second week are non-specific responses to the injection of the oily medium, ethyl oleate. The greater intensity of pigmentation at the site of injection of the concentrated solution, and possibly the whole of the later severe reaction that occurred in 4 of the 20 men and in 5 of the 10 women, seem to depend on the presence of progesterone in the injected solution. Some examples are known of similar effects of sex hormones. The localized hyperpigmentation of pregnancy can be imitated by oral administration of oestrogens (Davis *et al.*, 1945), but the possible participation during pregnancy of other hormones such as progesterone does not seem to

have been excluded. Testosterone is necessary for the full development of pigmentation after ultra-violet irradiation (Edwards *et al.*, 1941). Of other steroid hormones, deoxycortone inhibits the development of melanophores in explanted chick embryo skin (Hamilton, 1940), but does not usually decrease the hyperpigmentation in Addison's disease. Cortisone inhibits pigmentation in black-hooded rats (Whitaker and Baker, 1948), but apparently not in human subjects (Järvinen, 1951). To this list may be added the effect of progesterone described here.

My thanks are due to the medical students who acted as subjects, and to Messrs. British Drug Houses Ltd., who supplied the progesterone solutions.

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Medical Memoranda

Milk Allergy

The following case is worthy of record because of the interesting way in which it presented itself.

CASE REPORT

The patient, a boy aged 4, developed slight eczema of the hands at the age of 2 months. He was breast-fed from birth, and at 7 months weaning was attempted. He showed an immediate distaste for cow's milk, and whenever given it a perioral urticarial rash developed, and his eczema became worse. Many different forms of milk were given, but to all he showed a reaction. Thus he continued being breast-fed until 15 months old, also taking solids and orange juice. He was not given cow's milk or any substitute. He was then seen by a dermatologist, who thought his eczema was due to proteins in the diet, so he was put on a relatively protein-free diet of vegetables, fruit, cereals, orange juice, and a little milk, which always caused a perioral urticarial rash. He was given a little meat, but, although it did not seem to cause a reaction, he did not like it very much. The mother discontinued her visits to the dermatologist after some months, but still kept the child on this diet.

The child was referred to us at the age of 4 years because a medical officer thought he looked undernourished, and found on questioning the mother that during the past few months he had been irritable and easily tired, played games very little, and had to have afternoon naps. Sometimes, though not often, his stools were pale and offensive.

On inquiry from his parents it was found that he was sensitive to the following food, and in addition showed various idiosyncrasies:—(1) Fish: extremely sensitive—even the smell of fish is said to cause a reaction. (2) Milk (goat's and cow's): perioral urticarial rash; eczema worse. (3) Eggs: appear to have a delayed action. (4) Meat: no reaction, but does not like it. (5) Cereals: does not like porridge; likes bread—no reaction. (6) Cheese: does not like it.

His family history showed allergies on the maternal side. His grandmother suffered from asthma, an aunt from eczema, and a cousin from urticaria. His mother herself has eczema and is highly nervous.

On physical examination the boy was very pale, with normal height and weight for his age. His lower eyelids were puffy, and small glands were palpable in his neck.

He showed marked eczema of the hands, but no lesions of the skin elsewhere except cracks at the corners of the mouth. No enlargement of liver or spleen was noted.

Blood count: Hb, 75% (10.5 g.) Sahli; R.B.C., 2,800,000 per c.mm. (P.C.V. 27%, M.C.V. 96.4 μ^3 , M.C.H.C. 38.8%); W.B.C., 4,800 per c.mm. (polymorphs 61%, lymphocytes 35%, monocytes 4%); reticulocytes, 0.5%; total plasma protein, 5.25 g.%. Stained blood film showed many well-haemoglobinized macrocytes.

Response to Milk.—Under surveillance the boy was given some fresh cow's milk to drink. Within five minutes he developed a well-marked perioral urticarial rash. Later he was given boiled milk, and only a very slight rash appeared. A skin-sensitivity test was carried out, using pieces of lint dipped in boiled and fresh milk. No reaction was observed with the boiled milk.

He was put on boiled milk instead of fresh milk, and was given proteolysed liver extract, folic acid, and "marmite," because of a suspicion that he might have an incipient B-avitaminosis. On this treatment he rapidly improved, and his last blood count, taken 10 weeks later, was as follows: Hb, 94% (12.8 g.) Sahli; R.B.C., 5,150,000 per c.mm. (P.C.V. 42%, M.C.V. 80 μ^3 , M.C.H.C. 30.5%); W.B.C., 9,500 per c.mm. (polymorphs 50%, lymphocytes 35%, monocytes 6%, eosinophils 8%, basophils 1%); total plasma proteins, 6.5 g.%. His parents stated that he was more active than they had ever known him.

COMMENT

This boy presented as a case of macrocytic anaemia associated with protein deficiency, having lived for about 2 years 7 months on a diet poor in proteins, especially in first-class proteins.

The most important factor was his allergy to milk, which normally provides the chief source of protein in a child's diet. Milk itself is one of the three commonest food allergens, being second in frequency to wheat, and equal in incidence to egg. For example, in a series of 175 cases of food allergy, Rowe (1931) found 57% due to wheat, 31% to milk, and 35% to egg, the overlapping figures being due to multiple sensitization in some of the patients. Alvarez (1937), in a group of 500 cases of abdominal distress due to food allergies, found 26% due to milk, cream, and ice-cream, and another 5% due to cheese.

In many cases of infants reacting to milk there is a history of milk incapacity in the parents, and, though this was not found in this case, there was a strong family history of eczema. The diagnosis of milk allergy in infants and children rests on the history and the therapeutic test of withdrawal of milk from the diet. Scratch skin tests have been used, but they are of small value as an aid to diagnosis.

In one series of 65 cases of milk eczema in which scratch skin tests were carried out, only 5 were positive to cow's milk (Kerley, 1936). Kerley has classified persons subject to milk reactions into (1) those who suffer from shock through ingestion; (2) those with gastro-intestinal symptoms; and (3) those with skin reactions—eczema and urticaria. At least two deaths have been reported in the shock-reaction group (Finkelstein—see Kerley, 1936). My case obviously falls into the third group.

Studies on milk allergy by Ratner (1935) have shown that the heat-labile elements in the milk (lactalbumin and lactoglobulin) are responsible for practically all cases, so that some form of heat-treated or chemically denatured milk can be safely used. Skimmed fresh cow's milk, cooked for several hours, is said to supply the best desensitized milk product for use in eczema of infants (Kerley, 1936). The skimming removes the fat, which either interferes with the desensitizing process or adds an element that bears on the production of the eczema. It is sometimes found, though it was not true in this case, that goat's milk does not give a reaction.