vestigated in 6 patients. Two of these were studied during low calcium diet, 2 during high calcium intake, and 2 patients during low and high calcium intake. Addition of phosphorus to the diet led to a decrease in Sr^{85} absorption in 3 of the 4 patients each studied during low and high calcium intake, respectively. Urinary Sr^{85} excretion and urinary calcium excretion were decreased during high phosphorus intake in both the low and high calcium studies.

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Histamine and Mast Cells in Human Fetal Skin.* (29497)

HUGH ZACHARIAE (Introduced by G. Asboe-Hansen)

Departments of Skin and Venereal Diseases and Clinical Chemistry, Rigshospital, University of Copenhagen, Denmark

In 1879 Ehrlich(1) pointed out that mast cells appear in connective tissue during the later phase of fetal development. Lombardo (2) found mast cells in the subcutaneous connective tissue of the human embryo from the second fetal month. Holmgren(3) reported the first mast cells in skin in a 9.0 cm long human fetus. In the adult human, mast cells produce histamine(4). The human fetus produces histamine(5), and histamine-forming capacity has been demonstrated in a variety of human fetal tissues including skin(6).

The present investigation was undertaken because no studies seem to disclose the time of appearance of measurable amounts of histamine nor the relationship between histamine and mast cells in human fetal skin. Histamine determinations were made by the fluorometric assay method(7). The histologic identification of mast cells was carried out by metachromatic staining for acid mucopolysaccharides.

Methods. The material consisted of skin from 14 human fetuses, removed by legally approved induced abortion in gynecologic departments in Greater Copenhagen. The pregnancies were interrupted by hysterotomy through inferior median laparotomy. The skin specimens were obtained a few hours after the operation. If not determined immediately the skin specimens were frozen down at —20°C.

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TABLE I. Histamine and Mast Cells in Fetal Skin.

Case No.	Crown-rump length, mm	Age, wk	Sex	Wt of fetus, g	Ratio wet wt to dried defatted wt	Histamine, μg/g dried defatted wt	Mast cells
1	81	12	♀	30.6	20.0	1.3	None
2	82	12	♂	33.7	19.9	0	"
3	83	12	♂	32.5	18.1	0	"
4	84.5	12	♂	37.5	16.8	1.8	Very few, solitary
5	91	13	♂	41.9	15.6	1.4	None
6	92	13	♀	46.9	18.4	0	"
7	95	13	♀	55.5	15.2	0	"
8	100	14	♀	60.6	13.2	1.9	Very few, solitary
9	110	14	♂	72.2	10.5	4.0	Few, faintly granulated
10	112	14	♂	87.6	12.1	.4	None
11	158	18	♂	245.2	11.2	19.2	Considerable number, well granulated
12	168*	18	♀		9.3	9.3	Several, faintly granulated
13	185	20	♀	321.0	8.8	12.7	*Idem*
14	190	20	♂	340.0	10.3	16.1	"

* In case 12 the crown-rump length could not be measured accurately because of injury to head of fetus. An estimated crown-rump length is used, based upon foot length (34 mm) as described by Streeter(10).

Eight of the fetuses were male, and 6 were female. Fetal age was determined by the crown-rump length(9), measured on the fresh fetus lying supine. The crown-rump length, *i.e.* the distance from the vertex to the tip of the coccygeal bone, is a better indicator of fetal age than the length of the menostasis period. The material comprises fetuses of ages ranging from 12 to 20 weeks.

The skin area chosen for this study was the back. Skin specimens for histamine determination weighed from 114 to 405 mg (wet weight). Subcutaneous fat was mechanically removed by knife or scissors. Defatting was carried out by shaking the minced samples twice with 15 ml of ether for one hour. The defatted tissue was then lyophilized 48 hours at room temperature under a pressure of 2 mm Hg. The defatted and dried skin samples were homogenized in 5 ml of 0.4 N perchloric acid using a motor-driven glass homogenizer. The homogenate was allowed to stand for 10 minutes and then centrifuged. A 4 ml aliquot of the supernatant was analyzed for histamine by the spectrofluorometric method of assay according to the procedure previously described (8).

For histologic studies skin specimens were fixed in a 4% aqueous lead subacetate solution for 24 hours and stained with a 0.5% aqueous solution of toluidine blue, which rather selectively stains acid mucopolysaccharides metachromatically.

Results. Table I and Fig. 1 give the histamine content of human fetal body skin in relation to age. Skin histamine rises with increasing fetal age. Fig. 1 also reveals a simultaneous fall in the ratio of wet weight to dried defatted weight. The average histamine content of back skin from fetuses 18 to 20 weeks old was significantly higher than the average histamine content of back skin from fetuses 12 to 14 weeks old ($P<0.001$). Small amounts of histamine in the fetal skin appeared about the end of the third fetal month. Identifiable mast cells and larger amounts of histamine were found in the fifth fetal month.

Discussion. It has been known for some time that histaminase (diamine oxidase) rises during human pregnancy(11,12). The bulk of this histaminase originates from the maternal placenta(13,14). The function is believed to be a protection of the maternal organism against histaminic effects(15), possibly of fetal histamine(16). Fetal tissues 19 to 24 weeks old have been shown to possess a high histamine-forming capacity(5,6). The present investigation, however, shows that cell-bound histamine apparently does not appear in larger quantities in fetal skin till the fifth fetal month, and only sporadically at an earlier point. The appearance of identi-

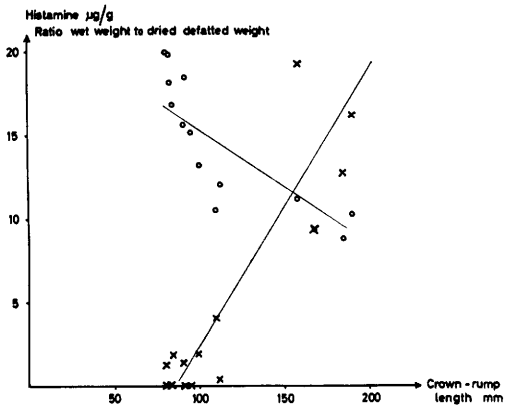

FIG. 1. Histamine values (×) and ratio wet weight to dried defatted weight (○) of human fetal skin in relation to fetal age. Histamine values are expressed in µg histamine base per g dried defatted skin. Crown-rump values from 81 to 190 mm correspond to fetal ages from 12 to 20 weeks.

fiable mast cells in fetal skin apparently coincides with the presence of larger amounts of bound histamine. This might suggest that the mast cell in the human fetus as well as in the human adult(4), provides the main part of cell-bound skin histamine. The amounts of skin histamine in the fifth fetal month are within the range of skin histamine values for normal adult human skin from a similar skin area(17).

Kahlson(16) associates the general processes of growth and repair with high histamine-forming capacity. From our results it seems likely that, in early fetal life characterized by rapid growth, the demand for histamine may be so great that storage can not take place simultaneously. The theories of Kahlson are in accordance with those of Asboe-Hansen and coworkers(18) that tissue edema initiates any process of growth, regeneration and repair of connective tissue. The observed high ratio of wet weight to dry defatted weight in human fetal skin, which declines with advancing age, is in accordance with the theory of Asboe-Hansen and coworkers (18).

Summary. Histamine and mast cells were studied in human fetal skin. Skin histamine rose with increasing fetal age. The appearance of identifiable mast cells coincided with the presence of larger amounts of cell-bound histamine in skin. The investigations also demonstrated a high ratio of wet weight to dry defatted weight, which declined with increasing fetal age. This is in agreement with the observation that tissue edema invariably initiates processes of connective-tissue growth, repair, and regeneration. It is proposed that, in early fetal life characterized by rapid growth, the demand for histamine is so considerable that storage of cell-bound histamine in skin cannot take place.

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