taneous. Strains established as aureus, albus and roseus probably are variant forms of a common ancestor.

Granting an analogy of dissociative patterns, one may predict an R-white phase, a pink type as Pinner found, and perhaps others for *Staphylococcus*. Effort to educe them is under way. It would be of importance to know the significance of the mucinous substance of the M phase, whether the yellow and white staphylococci are type specific by serologic or 'phage methods and if both forms convert to different respective serologic yellow and white types.

Staphylococcus and *G. tetragena* seem to be much more closely related than generally thought. The resemblance in colonial appearance, and in coccal size, shape, staining and arrangement probably often leads to bacteriologic diagnostic error. It is impossible to differentiate the respective S-yellow or S-white forms of either on that basis. The biologic differences as listed(14) are minor and may vary even among identical strains; and they differ from some reported here. Officially, *St. albus* liquefies gelatin and ferments mannitol; my white forms did not. *G. tetragena* is said not to liquefy gelatin nor ferment mannitol, in agreement with my tests(1), but the myth of pathogenicity for mice is perpetuated. In my hands, growth of staphylococci and of tetragenas was inhibited by similar amounts of penicillin, the M cocci of both made a mucinous substance and the yellow forms grew more luxuriantly and resisted heat better than the white forms.

Summary. A partial pattern of dissociation into color-type and phase variation emerged after aging a strain of *Staphylococcus*. From the smooth yellow (aureus), a mucoid yellow and a rough yellow colony form were derived, and in addition a smooth white type (albus) and its mucoid white phase. Thus far the dissociative pattern is analogous with that of *G. tetragena* and *Pneumococcus* as regards type and phase variation and interconvertibility. It may apply to *Staphylococcus* in general.

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Increased Sensitivity to Estrogen in Uterine Hyperplasia in DBA x CE and Reciprocal Hybrid Mice.* (23495)

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At 6 to 7 months of age, virgin female DBA x CE and reciprocal hybrid mice spontaneously develop a progressively severe endocrine imbalance involving the ovaries, adrenal cortex and pituitary(1,2). One of the more prominent morphological features of this syndrome is marked enlargement of the uterus

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TABLE I. Uterine Response to Estrogen in Ovariectomized DBA × CE and Reciprocal Hybrid Mice in Relation to Age.

Age (mo)	No. of mice	Treatment	Body wt (g) ± S.E.	Uterine wt (mg) ± S.E.		Uterine wt/body wt (mg/g) ± S.E.	
4– 5	10		26.2 ± .5	29.1 ± 1.1	(340% incr.)	1.1 ± .0	(336% incr.)
	11	Est	26.5 ± .7	98.8 ± 6.7		3.7 ± .3	
9–12	11		29.3 ± .6	40.2 ± 2.7	(449% ")	1.3 ± .1	(469% ")
	10	Est	29.3 ± .7	180.5 ± 23.5		6.1 ± .3	
15–18	10		32.2 ± .4	72.1 ± 12.2	(498% ")	2.5 ± .1	(464% ")
	12	Est	31.1 ± .7	358.8 ± 11.2		11.6 ± .5	

accompanied by muscular and glandular hyperplasia, adenomyosis, generalized fibrosis and vascular congestion. Previous studies have demonstrated that these uterine lesions result, at least in part, from gradual prolongation of the estrogenic phases of the estrous cycle which culminates in a condition approaching "constant estrus" by 15 months of age(3,4). The question has arisen, however, whether the hyperplasia of the uterus might also be due in part to an increase in sensitivity of this organ to estrogen in addition to increased estrogenic stimulation previously demonstrated. The present experiment was designed to test this hypothesis.

Procedure. Sixty-four virgin female mice, offspring of DBA x CE and reciprocally crossed parents, were used. The mice were born in the Jackson Laboratory colony and were maintained at a temperature of 70°F on a diet of Purina Laboratory Chow and water *ad libitum*. At the beginning of the experiment animals in 3 age groups were selected with reference to the development and progress of the hyperovarian syndrome: (1) 4 to 5 months of age—prior to appearance of symptoms, (2) 9 to 12 months—during most rapid progress of the syndrome, and (3) 15 to 18 months—after the syndrome is well advanced. Uterine sensitivity to estrogen was determined in the following manner. The mice were bilaterally ovariectomized. Fourteen days later approximately one-half of the animals in each age group were sacrificed without further treatment. The remaining animals were injected subcutaneously with 3 μg of crystalline estradiol diproprionate in 0.1 ml of sesame oil and were sacrificed 48 hours later. The uteri of both control and treated mice were removed by cutting across the cervix and trimming the cornua free of their attachment to the mesometria. The cornua were slit and blotted with filter paper to remove any fluid in the lumina. Uterine weights were then determined to the nearest 0.1 mg with a Roller-Smith torsion balance. The estrogen response was calculated as the percentage of mean weight increase of the uteri of injected animals compared with mean weight in untreated controls of the corresponding age group.

The *results* are summarized in Table I. The increment in uterine weight following injection of the standard test dose of estradiol diproprionate in mice ovariectomized at 4 to 5 months of age (*i.e.*, prior to the onset of uterine hyperplasia) was approximately 340%. In mice ovariectomized and tested after the appearance of uterine hyperplasia, on the other hand, the uterine weight response was 449% at 9 to 12 months and 498% at 15 to 18 months.

It can be seen from the Table that with increasing age there is a considerable increase both in body weight and in post-ovariectomy uterine weight in untreated controls as well as in injected animals. If the actual mean uterine weights are expressed in proportion to mean body weights of the animals in each group, the uterine response to estrogen is 336% in pre-syndromic mice and 469% and 464% respectively in the 2 groups exhibiting the syndrome. When calculations are made in this manner, the apparent difference in responsiveness between the 2 latter groups disappears.

Discussion. The present observations clearly demonstrate that in DBA x CE and

reciprocal hybrid mice a considerable increase in uterine sensitivity to estrogen develops in conjunction with the hyperovarian syndrome. The observed increment represents a minimal difference because of the experimental procedure followed. That is, whereas the body weights of mice in the 9 to 12 and 15 to 18-month-old groups were about 11% and 20% greater than in the youngest group of animals, the test dose of estrogen was the same in all instances. It is probable that if the amount of hormone given had been increased in proportion to gain in body weight, the increment in uterine responsiveness in the older mice would have been even greater than that actually measured. In view of the present findings, then, it seems reasonable to conclude that the uterine hyperplasia which develops in these hybrid mice after onset of the hyperovarian syndrome is due in part to increased responsiveness of the uterus to estrogen as well as to the hyperestrinism previously reported.

The present findings also have implications of general interest apart from their bearing on the pathogenesis of uterine lesions peculiar to these particular mice. In endocrine studies cognizance is seldom taken of possible effects of aging on hormone sensitivity of target organs due, no doubt, to the paucity of information on the subject. In so far as the reproductive tract is concerned, the only extensive studies have been those of Hooker(5) and Price and Ortiz(6) who have demonstrated a temporary increase of 500% or more in hormone sensitivity during puberty in the rat. Unfortunately their observations included but a relatively short period after puberty. In a small number of ovariectomized monkeys, on the other hand, Allen and his co-workers(7) found that only one-third to one-half as much estrone was needed to induce withdrawal bleeding from uteri of mature animals as compared with immature and puberal animals. The present observations and those cited above agree that age-related changes in hormone sensitivity of the reproductive tract occur. Due to different experimental conditions and species studied, however, no clear-cut pattern can be discerned. It is evident that further investigation of this phenomenon is imperative, especially for the proper evaluation of data based on bioassay technics and for elucidation of endocrine-related pathologic conditions of the uterus such as liomyomatosis and endometrial hyperplasia which occur in women with increasing frequency as the menopause is approached.

Summary. Virgin female DBA x CE and reciprocally crossed hybrid mice were ovariectomized at 4 to 5, 9 to 12, and 15 to 18 months of age. Two weeks later one-half of the animals in each group were injected with 3 μg of estradiol diproprionate and were sacrificed 48 hours later. The uterine response was calculated by comparing uterine weights (adjusted to mg/g body weight) after estrogen treatment with those in the untreated controls. In the 4 to 5-month-old animals the increment in uterine weight was 336%; in the 2 older groups, 469% and 464% respectively. These data indicate that the uterine hyperplasia which develops spontaneously in these mice after 7 to 8 months of age is due in part to increased uterine sensitivity to estrogen as well as to the hyperestrinism previously known to occur.

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