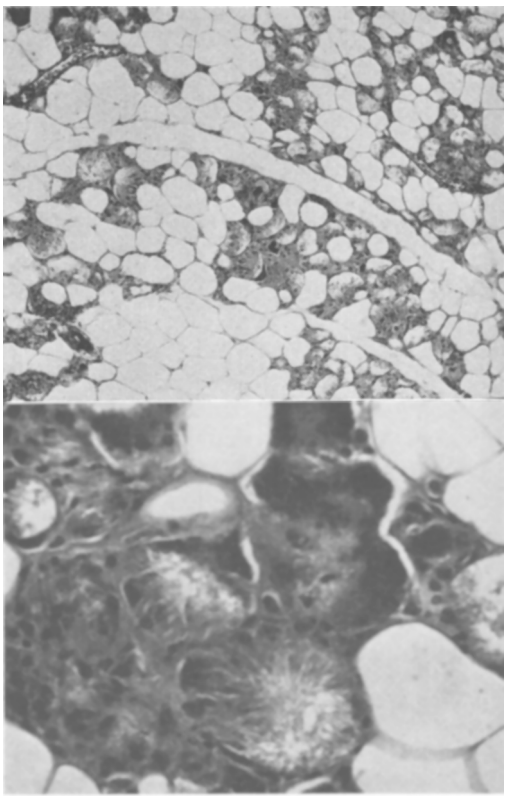

FIG. 1. *Top:* Periadrenal fat showing multiple islands of fat injury separated by normal fat. Hematoxylin and eosin, ×60. *Bottom:* Higher magnification showing variations of cellular reaction. Multinucleated giant cells are present at top of print. A fat cell containing radial slit-like spaces is seen near bottom of print. Hematoxylin and eosin, ×430.

This reaction in visceral and retroperitoneal fat of the rat bears some histologic resemblance to pathologic conditions of human fat such as fat necrosis of newborn(2), sclerema neonatorum(3), and traumatic fat necrosis of various types(4,5,6). Further studies are underway to determine the histochemical characteristics of the lesion.

Appearance of the foreign-body type reaction in all groups except that fed lard indicates that the reaction is a response to a relative or absolute excess of saturated long chain fatty acids. We are testing diets containing various proportions of saturated to unsaturated fatty acid to determine the critical ratio which produces this reaction.

Summary. A foreign-body type reaction has been observed in fat from rats fed diets containing high levels of saturated fat. The phenomenon and the dietary conditions under which it was produced, are described.

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Effect of Dilantin Sodium on Tensile Strength of Healing Wounds.* (24040)

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Hyperplasia of the oral gingiva is a common reaction among epileptics following systemic administration of sodium diphenylhydantoinate (Dilantin Sodium). The phenomenon does not occur in all patients and, in those affected, there is a wide range in severity of the lesion(1,2). The reason for this selective involvement of gingival tissues, other tissues throughout the body apparently being unaffected, is unknown nor is the mechanism of hyperplasia understood. Tissue reaction is basically a fibrous hyperplasia with formation of increased bulk of dense collagen fibers. This has suggested to Shapiro that the compound might favorably influence the healing of gingival wounds through enhancing collagenization(3). He reported that administration of dilantin to non-epileptic patients in-

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creased rate of healing of gingival wounds as judged histologically by accelerated epithelialization and increased connective tissue activity. In a related study by Forscher and Cecil, rats receiving varying doses of dilantin showed a significant decrease in acid-soluble phosphorus fraction of tissue from the palate in area that had been subjected to a radiofrequency current to induce acute inflammatory response(4). Of other chemical constituents studied, tyrosine, proline, hydroxyproline hexosamine, ribonucleic acid, desoxyribonucleic acid, inorganic phosphorus and residue phosphorus showed no significant differences from controls. Attempts have been made to produce this hyperplasia experimentally in small laboratory animals but these have been generally unsuccessful(5,6). King has reported its occurrence in the ferret(7). Many clinical observations of "dilantin gingival hyperplasia" and the report of Shapiro have indicated that further studies of the effect of this drug on connective tissue were important. For this reason, a controlled experimental investigation of the effect of dilantin sodium on tensile strength of healing wounds has been carried out.

Methods. The present study was divided into 3 parts differing basically only in dosage and manner of administration of the drug. Sixty-day-old male albino rats of Sprague-Dawley strain were used, housed in wire bottom cages and maintained on stock laboratory diet and distilled water *ad libitum*. Series I consisted initially of 24 animals equally divided into control and experimental groups. Experimental animals differed from controls only in that each animal in former group received 50 mg of dilantin sodium/day by stomach tube. Series II consisted of 36 animals divided equally into control and experimental groups. In this case the dilantin sodium was administered at 25 mg/day/animal by dissolving in a special diluent† and injecting intramuscularly. Series III was identical with Series II except that 48 animals were used and duplicate determinations were recorded. This last series was repeated for confirmation of data. In all series, dilantin sodium was administered for 18 days before induction of experimental wound. The wound was inflicted after removing hair on abdomen by a depilatory with animals under Nembutal anesthesia. A longitudinal incision was made by scalpel approximately 30 mm long and 6 mm from midline. The incision was carried through the skin and down to the fascia overlying abdominal muscles. The wounds in Series I and II were not sutured, but in Series III were closed by 2 interrupted sutures of 4/0 black silk. Duration of wound in Series I, from time of incision to sacrifice of animal, was 3 days; in Series II and III 4 days. The tensile strength of wounds was tested similar to the method described by Enzinger and Warner(8) and many others and consisted of first removing a strip of tissue, approximately 40 mm long and 10 mm wide, at right angles to original incision. Only those animals whose wounds were healing by primary intention were utilized. One end of the tissue strip was attached to a small spring clamp while a small paper cup was suspended from the other end of the tissue strip by another clamp. Bromoform, used because of its relatively high specific gravity, was then added to the cup by burette until the strip separated at line of incision. This endpoint was definite in all cases. Values were recorded as ml of bromoform required to cause separation of the wound. Histologic studies were also carried out on sections taken through the wounds of 11 animals in control group and 10 animals in experimental group of Series III. Sections were prepared in usual manner and a trichrome stain was applied as well as routine H and E.

Results. Series I group was seriously depleted by deaths due to accidental aspiration of the drug during stomach tubing and by discarding of those animals whose wounds were not healing by primary intention. Only 5 control and 4 experimental animals remained and from these 8 and 7 tensile strength determinations respectively were completed.

The data (Table I) indicate a dramatic in-

† This diluent was furnished through the courtesy of Parke, Davis, & Co., Detroit, Mich. and consisted of 40% propylene glycol and 10% alcohol in water with sodium hydroxide to adjust to pH 12.

TABLE I. Tensile Strength of Wounds in Control and Dilantin Treated Rats.

	No. of animals	No. of determinations	ml bromoform	"t" value
		Series I		
Control	5	8	13.8 ± 2.1*	4.14
Dilantin	4	7	34.1 ±11.2	
		Series II		
Control	9	9	17.0 ± 9.3	5.48
Dilantin	12	12	38.5 ± 9.0	
		Series III		
Control	15	29	18.4 ± 7.8	4.30
Dilantin	11	21	32.4 ± 8.6	

* Mean and stand. dev.

crease in tensile strength of wounds in dilantin treated rats. The mean value, expressed as ml of bromoform is approximately 147% greater than that of control animals. While the number of animals and of determinations in this series is not large, this difference between control and experimental groups is statistically significant at the > 1% level of confidence.

Series II contained a larger number of animals at beginning of the study and of these, 9 control animals and 12 in experimental group were suitable for use. The data are very similar to those in Series I, the same dramatic difference between control and dilantin treated rats being found. Mean value in experimental group was significantly greater than the mean in control group at > 1% level and represents an increase of 127% in mean tensile strength of experimental wounds. Control studies with the diluent alone showed that it did not increase tensile strength of wounds.

The results of Series III are nearly identical with those of Series I and II. In this portion of the investigation, 15 control and 11 experimental animals remained at termination of study. The mean tensile strength of wounds in the experimental group showed a 76% increase which is significant at > 1% level.

It was not possible to differentiate between histologic sections of wounds from control and experimental animals. The trichrome stain enhanced visualization of the new collagen in the healing wounds but there was enough variation within each group to preclude using the sections as confirmatory evidence for the differences in tensile strength.

Discussion. Since tensile strength of a healing wound parallels and is dependent primarily upon collagenization of the wound, the finding of increased tensile strength of wounds in rats given dilantin sodium is consistent with the fibrous hyperplasia of the oral gingiva which is of common clinical occurrence. Although connective tissue overgrowth clinically involves only the gingiva, the drug is obviously not anatomically specific for this site. The common appearance of hyperplasia here can probably be related to the nearly universal occurrence of at least a mild chronic inflammation in tissues surrounding necks of teeth although the nature of this relationship is speculative.

Summary. Systemic administration of dilantin sodium produces a dramatic increase in tensile strength of healing wounds in rats. This is probably a function of increased collagenization, the same basic reaction which accounts for the undesirable side-reaction of gingival hyperplasia in epileptics receiving this drug, although the mechanism is unknown.

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