orientation and drowsiness and in one patient a hemiparesis with aphasia. Retinal abnormalities attributable to the injury were not detected in either treatment groups.

Significant differences between the treatment groups were not found in the incidence of urinary fat droplets or in the level of PaO_2. No reason was found for the difference in the serum triglyceride levels on the first day before treatment was started. Such differences were not found on the other days. The levels of serum clofibrate in $\mu g/ml$ were: Day 2, 127 ± 88; Day 3, 149 ± 56; Day 6, 110 ± 68. There were no significant differences between the treatment groups in any of several detailed tests of respiratory or liver function which were performed and which will be reported elsewhere.

Discussion

Measurement of blood levels shows that the clofibrate administered was absorbed, and the lesser rise in serum triglycerides in the treated group indicated that it exerted one of its well-known effects. The indices commonly used to characterize fat embolism did not differ between the groups. Indeed one of the most commonly mentioned indices—skin petechiae—occurred more often in the colifibrate group. Significant differences were not found when the clinical and laboratory indices were grouped according to O'Driscoll and Powell's (1967) major and minor criteria of fat embolism. The possibility remains that fat embolism might have occurred before adequate blood levels of clofibrate were achieved by the oral preparation. Further studies with an intravenous preparation of clofibrate would be necessary to exclude this possibility. At present an intravenous preparation is not available.

A striking finding in this study was the frequency with which low levels of PaO_2 were found in patients in whom no clinical respiratory abnormality was detected despite careful and repeated examinations.

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Skin Collagen and Thickness in Simple Obesity

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Summary

The effects of stretching of the skin on its collagen content and thickness have been studied in a group of subjects with chronic obesity. Despite the increase in skin surface a normal skin thickness, collagen content, and density were maintained. It is concluded that the skin stretching induced by prolonged obesity led to hypertrophy of collagen and that this had maintained both skin thickness and collagen content. It is not known whether this is due to enhanced synthesis or decreased degradation.

Introduction

Skin collagen content is best expressed as a function of the surface area of the biopsy, and using this expression we have demonstrated changes in the normal with age, sex, site of biopsy, and in diseases of the endocrines, bones, and connective tissues (Shuster and Bottoms, 1963; Shuster *et al.*, 1967a, 1967b; Black *et al.*, 1970a, 1970b, 1970c; Stevenson *et al.*, 1970). The question which now arises is whether the idea of relating skin collagen to surface area remains valid when skin is abnormally stretched. We therefore measured forearm skin collagen in patients with obesity of long duration. We measured skin thickness at the same time, since we have also shown that skin thickness, as measured histologically or radiologically, and skin collagen are directly related (unpublished observations).

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Patients and Methods

Sixteen patients with "simple" obesity were studied. Six were males aged 19-36 years and 10 were females aged 15 to 57 years. None had diabetes mellitus, myxoedema, hypogonadism or Cushing's syndrome. All were considerably overweight; and none was less than 30% above the average weight predicted from the age and height (Metropolitan Life Insurance Company, 1959). The body surface area for each subject was estimated, height and weight nomogram (Dubois and Dubois, 1915) being used. The "ideal" surface area was then obtained for each subject, using their "ideal" body weight as obtained from their age, height and sex. Forearm circumference was measured at the mid-point of the arm both in the obese patients and in a group of normal subjects (13 male and 13 female) of the same age range as the obese patients.

Skin thickness was measured by the radiographic method of Meema *et al.* (1964) as modified by Black (1969). The results were age matched and compared with our data for 90 normal adult males and 107 females (unpublished observation).

Total skin collagen was measured by the method of Shuster and Bottoms (1963) as follows: skin biopsy specimens were taken from the mid-point of the extensor aspect of the forearm with a high speed rotary punch of 5 mm diameter. The specimens were defatted in acetone and then dried to constant weight. After hydrolysis the hydroxyproline content was measured by the method of Woessner (1961) and

skin collagen was calculated from this. The skin collagen content of the 16 obese subjects studied were age and sex matched and compared with the results from 74 normal adult males and 80 females (Shuster and Bottoms, 1963; Shuster *et al.*, 1967a, 1967b; Black *et al.*, 1970a, 1970b, 1970c; Stevenson *et al.*, 1970). Total skin collagen was expressed as a function of actual surface area of the biopsy specimen ($\mu g/mm^2$) and the calculated "ideal" surface area from which the skin would have stretched during weight gain ("corrected collagen," Fig. 2). This ideal surface area was calculated by using the ideal body weight in the surface area nomogram. Collagen density was calculated from the ratio of collagen content of the biopsy to its thickness as measured radiologically.

Results

The body weight, forearm girth, and calculated body surface areas are shown in Fig. 1. There was a good correlation between the calculated surface area and the actual limb girth. Despite the increase in surface area skin collagen as $\mu g/mm^2$ of the biopsy specimen was no different from normal subjects of the same age and sex (Fig. 2). Skin thickness and collagen density (collagen/thickness) were likewise normal. Since the skin surface area was increased *total* skin collagen was likewise increased. This is shown as "corrected collagen" for the individual biopsy specimen in Fig. 2 and for total skin collagen calculated for the whole body surface in Fig. 3.

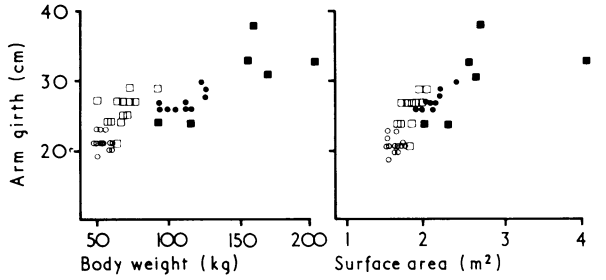

FIG. 1—Body weight, body surface areas, and forearm girth.

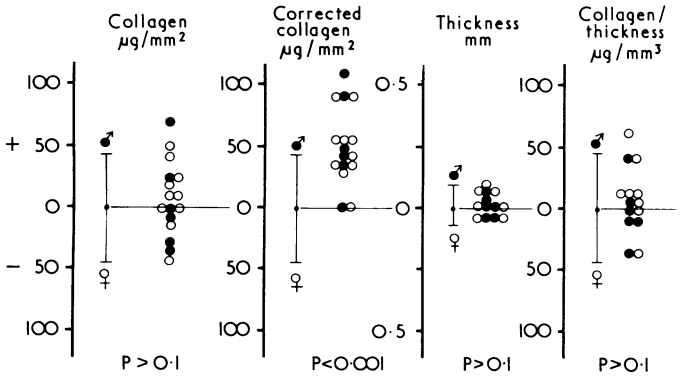

FIG. 2—Skin collagen, skin thickness, and skin density.

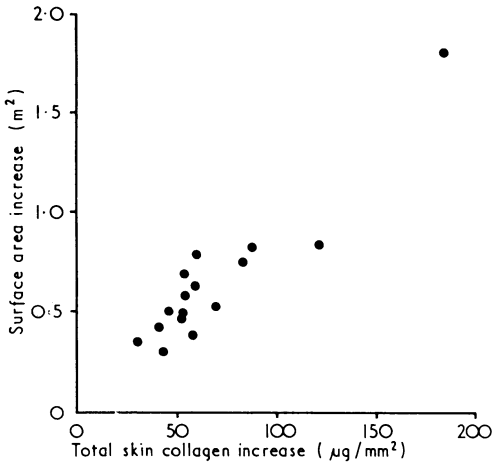

FIG. 3—Total skin collagen calculated for whole body surface.

Discussion

It might be expected that with an increase in arm girth stretching would decrease both skin thickness and the collagen content. We found to the contrary that the collagen content of 5 mm punch biopsy specimens taken from obese arms was no different from normal non-obese arms. This observation is strengthened by the parallel finding of a normal skin thickness and density of dermal collagen in obesity. This can only mean that total skin collagen had increased at the same time as the skin had stretched. These results suggest that with stretching or thinning of the skin there may be a compensatory mechanism which maintains its original collagen content and thickness.

Harkness and Harkness (1954) found that the collagen content of the rat uterus increases greatly in pregnancy, whereas the cervix showed a much smaller increase and the vagina none at all. Later they showed that the rat uterus subjected only to the hormonal stimuli of pregnancy formed relatively little collagen (Harkness *et al.*, 1957), suggesting the prime influence of stretching. Abercrombie and James (1957) found that collagen is deposited in large amounts in scar tissue long after wounding and after healing appeared to be complete. They also found that the scar tissue was under greater tension than the surrounding normal skin. It seems probable that in the course of achieving clinical obesity the skin is put under some degree of tension, and this may be the cause of the compensatory increase which maintains both skin thickness and its collagen content; such a mechanism would be biologically useful. However, both the skin regions involved and the rate of stretch may be of importance; thus the usual effect of a nine-month stretch on the abdominal wall is thinning and pregnancy striae. More studies therefore must be done before this response to obesity can be raised to a general principle. The mechanism whereby collagen synthesis is enhanced or its degredation delayed in forearm skin slowly stretched by fat could keep two research teams in contented competition.

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