

## AQUEOUS VITAMIN A IN ACNE VULGARIS\*

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The early observations of Frazier and Hu (1A) and the more recent studies indicate the importance of large doses of vitamin A in the treatment of acne vulgaris (1B to 4). The results obtained by Straumfjord (1) are noteworthy. He administered 100,000 units of vitamin A in oily solution daily, with no local therapy, and reported improvement in all but 3 cases out of 100. However, definite improvement was not obtained in less than 3 months and often more than 6 months were required. A period of 3 to 6 months or more is a sufficiently long period to allow for fluctuations and involution in the course of acne vulgaris. With these considerations in mind we subjected to test a preparation of vitamin A which has been shown to be more readily absorbed and utilized (5-9) than those preparations of vitamin A in oil hitherto employed in the treatment of acne vulgaris. We postulated that, if vitamin A is a factor, earlier results might be observed with such a preparation.

It had been reported in 1946 (5) from this laboratory that vitamin A when administered in aqueous media is absorbed more readily than vitamin A administered in oil, as shown by vitamin A tolerance tests in newborns, older children, adults (5, 6, 8, 9) and by vitamin A storage tests in rats (7). This difference of absorbability was especially important in conditions where diminished intestinal absorption of fats exists as in the celiac syndrome in prematures, in the newborn, in biliary block and in liver disease (5, 6, 8, 9, 10, 11, 12).

Vitamin A tolerance tests were performed on subjects with acne vulgaris to determine whether there is a similar improvement in absorption when the vitamin A is given in aqueous media. The aqueous dispersion used (13) contained, in addition to vitamin A, members of the B complex, vitamins C and D. Oleum percomorph was used as the oily solution of vitamin A. 3500 USP units of vitamin A were administered per pound of body weight to compare the results to similar studies done on normal adults and those with dermatologic disorders by Ruch et al. (14). The serum vitamin A was determined on venous blood by the method of Kramer et al. (6). The results are shown in Table 1 and in Fig. 1. Here again there is a definitely better absorption with the aqueous dispersion as measured by vitamin A tolerance tests. The average maximum rise in serum vitamin A was 245  $\mu\text{g}\%$  with oil and 596  $\mu\text{g}\%$  with the same amount of vitamin A in water. The maximum rise was not only higher with the aqueous medium but took place earlier. The rise three hours after the test dose was 39  $\mu\text{g}\%$  with oleum percomorph and 587  $\mu\text{g}\%$  with the aqueous dispersion 1. There seems to be evidence of impaired absorption when one compares these vitamin A tolerances with the oil to those obtained under comparable condi-

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tions by Ruch et al. (14) on normal adults. They also observed lower vitamin A tolerances in many of their subjects with dermatologic disorders.

It thus became apparent, from the above results, that if vitamin A is a factor in acne vulgaris, there would be a better chance of improving this condition with vitamin A in aqueous media than with vitamin A in oily media. Since we were not interested at this stage of our studies in separating the influence of the other vitamins which had been used in the past for acne vulgaris (15 to 20),

TABLE 1

*A comparison of the vitamin A tolerances in subjects with acne vulgaris using oleum percomorph and aqueous dispersion 1*

Vitamin A expressed in micrograms per 100 ml. serum\*

CASE	PREPARATION	FASTING	3†	6†	9†	MAXIMUM RISE
R. M.	Oleum perc.	41	42	306	130	265
	Aqueous disp. 1	59	825	588	170	766
S. S.	Oleum perc.	40	49	62	479	439
	Aqueous disp. 1	47	729	424	182	682
K. M.	Oleum perc.	59	56	94	246	187
	Aqueous disp. 1	56	595	182	154	539
R. B.	Oleum perc.	53	231	130	112	178
	Aqueous disp. 1	43	818	311	169	775
L. H.	Oleum perc.	48	58	303	250	255
	Aqueous disp. 1	52	655	250	128	603
A. H.	Oleum perc.	36	101	392	238	356
	Aqueous disp. 1	48	415	178	111	367
V. J.	Oleum perc.	44	47	64	81	37
	Aqueous disp. 1	36	387	477	249	441
Mean	Oleum perc.	46	85	179	219	245
	Aqueous disp. 1	49	632	344	165	596

\* 1 microgram of vitamin A = 3.57 U.S.P. units.

† Hours after test dose of 3500 U.S.P. units per pound of body weight.

we used a readily available preparation of vitamin A in aqueous medium, supplemented with the water soluble vitamins and vitamin D.

Aqueous Dispersion 1 (13) was given to a group of 30 patients, 20 of whom received therapy for over 2 months. The ages ranged from 14 to 26 and the duration of the eruption ranged from 1 to 10 years. All cases except 3 were moderately severe or severe. Under moderately severe, we classified cases exhibiting comedones, papules, many papulopustules and scars; under severe cases we classified those that exhibited also very deep nodules and/or cystic lesions. Three cases were mild with a moderate amount of comedones and small papulo-

pustules. The aqueous dispersion of vitamin A (13) was given in teaspoonful (4 cc.) doses (36,000 to 40,000 units) once a day for a period of 2 to 5 months; no local therapy was used. Treatment was interrupted once because, temporarily, the supply of the dispersion ran out. This period was used for checking signs of recurrence. The results are summarized in table 2.

A definite improvement was observed in all but 2 cases in the relatively short period of 2 to 4 weeks after beginning of the treatment with aqueous dispersion 1. This short period is in marked contrast to the 3 to 6 months or more required for improvement of the subjects given vitamin A in oil by Straumfjord (1). Most of the cases continued to improve while on the aqueous dispersion. The

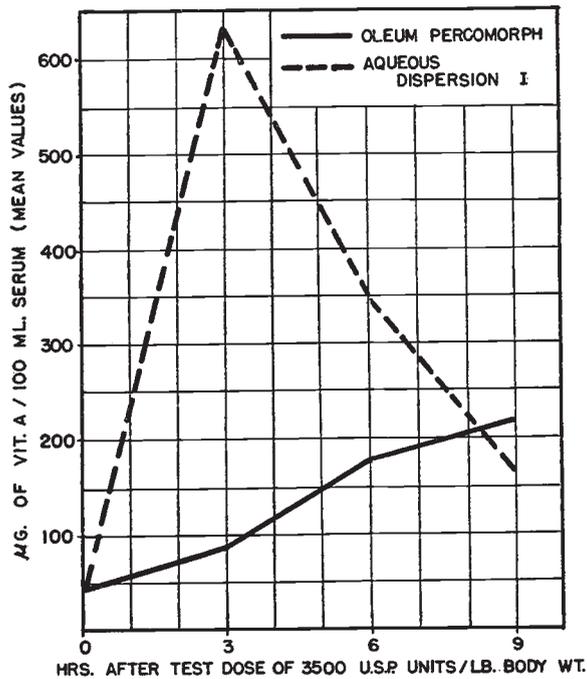


FIG. 1. A comparison of the vitamin A tolerances in subjects with acne vulgaris using oleum percomorph and aqueous dispersion 1.

improvement varied from moderate to complete clearing of lesions. The criteria of improvement was based on the degree of lessened outbreaks of new lesions as well as on the involution of old ones.

The degree of improvement at the end of therapy was as follows: Seven cases practically cleared up or were very much improved after taking the preparation for  $2\frac{1}{2}$  to 4 months. Nine cases were moderately improved after taking the product 2 to 5 months. Two cases, one a severe acne and the other a mild acne cleared up completely. Two cases did not show any improvement, one was a 23 year old white female with a moderate severe acne of 9 years' duration who took the aqueous dispersion for 2 months; the other was a 17 year old white female with moderately severe acne who took the aqueous dispersion for  $2\frac{1}{2}$

TABLE 2

*Clinical course of acne vulgaris in patients treated with vitamin A in aqueous medium*

PATIENT	AGE	SEX	COLOR	DURATION OF ACNE	SEVERITY OF ACNE	LENGTH OF TREATMENT	START OF DEFINITE IMPROVEMENT	DEGREE OF IMPROVEMENT AT THE END OF THERAPY	RECURRENCE OR OTHER COMPLICATION DURING THERAPY
R. B.	22	F	W	10 <i>years</i>	moderately severe	4 <i>months</i>	in 3 weeks	practically cleared up	mild outbreak after 4 weeks
L. H.	18	M	W	4	severe	2½	3	very much improved	mild outbreak after 4 weeks
S. S.	26	F	C	1	mild	4 (3½)	2	cured	none
R. M.	20	M	C	2	severe	5	4	improved	mild outbreak after 2 months
K. M.	19	M	W		moderately severe	3	4	very much improved	none
R. K.	19	F	W	8	moderately severe	3½	4	practically cleared up	none
A. H.	16	F	C	6	severe	3½	2	very much improved	none; increase in epileptic seizures
S. J.	16	F	W	5	moderate	2½	2	improved	none
F. S.	17	M	W	1	mild	2½	1	much improved	none
V. J.	14	M	W	2	severe	3	2	improved	none
S. A.	16	F	W	1	moderate	2½	3	improved	none
N. R.	17	M	W	4	severe	5	2	moderate improvement	
T. D.	18	F	W	1	mild	3½	3	moderate improvement	recurred after 9 weeks; did not respond to therapy thereafter
P. L.	14	F	W	2	severe	2½	in 2 weeks	very much improved	
W. J.	17	F	W	5	moderately severe	2½ irregularly	no improvement	no improvement	

TABLE 2.—Continued

PATIENT	AGE	SEX	COLOR	DURATION OF ACNE	SEVERITY OF ACNE	LENGTH OF TREATMENT	START OF DEFINITE IMPROVEMENT	DEGREE OF IMPROVEMENT AT THE END OF THERAPY	RECURRENCE OR OTHER COMPLICATION DURING THERAPY
C. K.	23	F	W	9 <i>years</i>	moderately severe	2 <i>months</i>	no improvement	no improvement	
S. L.	18	M	W	2	severe	3	2 weeks	cured	
P. G.	20	M	W	3	moderately severe	2	2 weeks	moderate improvement	mild outbreak during 2nd week of therapy
H. M.	17	M	W	1	moderately severe	2	3 weeks	moderate improvement	
W. M.	17	M	W	2½	severe	2	2 weeks	slight moderate improvement	mild outbreak during the 4th week of therapy

months. In this last case, however, it was established that the medication was being taken irregularly. There was one case of an 18 year old white female with a mild acne who, after a definite improvement had a recurrence of the eruption 9 weeks later, and although the medication was continued for another 6 weeks, there was no change in the eruption.

After an initial improvement, following the start of the aqueous dispersion of vitamin A there was a temporary mild aggravation of the condition in 5 cases. on the 2nd week in 2 cases, on the 4th week in 2 other cases and on the 8th week in one case. One case, an epileptic since childhood started to complain a few months after treatment that her epileptic seizure became worse and more frequent when she was given the aqueous dispersion and improved when she stopped it. Two patients had to stop medication after a period of one and two weeks respectively, in one case on account of abdominal pain and in another on account of severe diarrhea. All cases whose therapy had to be interrupted because the dispersion was temporarily not available, had a recurrence. The recurrence appeared 2-3 weeks after the patient stopped receiving the product.

Eight out of nine cases seen about 4 months after discontinuance of therapy had a recurrence ranging from mild to severe.

DISCUSSION

Previous attempts to correlate some skin conditions with a deficiency of vitamin A, as measured by blood levels, led to the conclusion that vitamin A could be expected to be of little benefit in the therapy of dermatologic ailments (21).

Straumfjord's results in acne vulgaris and the results of Dubin and Hazen (22) in keratosis seborrheica and keratosis senilis correlated with those reported here suggest that larger amounts of A than those usually required to prevent deficiency may be important. The favorable results obtained in this study in such a short time suggest that higher blood levels of A may be of equal importance. The blood levels of A obtained with aqueous dispersions are much higher than those obtained with equal doses of A in oil (ref. 5 to 12 and Table 1 and Fig. 1 of this paper).

Theoretically the transference of vitamin A to tissues and to the skin should be higher with higher serum levels. The rate of diffusion across a membrane (if there are no other factors involved) increases directly as the concentration of diffusing substances. In addition, vitamin A absorbed from aqueous dispersions into the blood may be more diffusible because of smaller particle size and lower interfacial tension of particle containing A. (see discussion in ref. 6, 7, 9).

That the transference to the tissues must be better with aqueous dispersion of A is suggested also from our studies on the vitamin A concentration in human milk. Higher values of A were obtained both in the blood and in the milk of mothers given aqueous dispersion of vitamin A than with oily solutions of the same concentration (23).

#### SUMMARY AND CONCLUSIONS

1. Absorption of vitamin A in patients with acne vulgaris (as measured by changes in blood serum vitamin A) was far better with vitamin A in aqueous medium than with vitamin A in oily medium.

2. There was a definite improvement in all but two of the cases of acne vulgaris treated with the aqueous dispersion of vitamin A (36,000 to 40,000 USP units per day) in 2 to 4 weeks. All cases but one continued to improve while under treatment.

3. The short period of time of 2 to 4 weeks which elapsed from the beginning of the treatment until improvement was observed was not sufficient for a spontaneous improvement. In addition, the fact that severe or mild eruptions of various duration improved at a similar rate also suggests that the change was not spontaneous.

4. A recurrence of the acne took place 2 to 3 weeks after the discontinuance of the aqueous dispersion. This supports the contention that the improvement was due to the therapy and was not spontaneous.

5. The promptness of response may indicate greater diffusibility of vitamin A from aqueous dispersion into the tissues. In this connection the possible significance of high blood levels of vitamin A in addition to high doses has been discussed.

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## REFERENCES

- 1A. FRAZIER, C. N. AND HU, C. K.: Nature and distribution according to age of cutaneous manifestations of Vitamin A deficiency: A study of two hundred and seven cases. *Arch. Dermat. & Syph.* **33**: 825 (May) 1936.
- 1B. STRAUMFJORD, J. V.: Vitamin A. Its effect on Acne. *Northwest Med.* **42**: 219 (Aug.) 1943.
2. OBERMAYER, M. E., AND FROST, K.: Some phases of vitamin therapy in dermatology. *Arch. Dermat. & Syph.* **51**: 309 (May) 1945.
3. SAUNDERS, T. A.: Favorable effects of vitamin A in a case of acne of long duration, *Arch. Dermat. & Syph.* **50**: 199 (Sept.) 1944.
4. LYNCH, F. W., AND COOK, C. D.: Acne vulgaris treated with vitamin A, *Arch. Dermat. & Syph.* **55**: 355 (March) 1947.
5. SOBEL, A. E., GOTTFRIED, S. P., AND KRAMER, B.: A comparison of Vitamin A serum levels in children following the oral and intramuscular administration of vitamin A in oily and aqueous media, Abstracts of 110th meeting of the American Chemical Society Division of Biological Chemistry, September 11, 1946.
6. KRAMER, B., SOBEL, A. E., AND GOTTFRIED, S. P.: Serum levels of vitamin A comparison following the oral and intramuscular administration of vitamin A in oily and aqueous medium, *Am. J. Dis. Child.*, **73**: 543 (May) 1947.
7. SOBEL, A. E., SHERMAN, M., LICHTBLAU, J., SNOW, S. D., AND KRAMER, B.: Comparison of vitamin A liver storage following administration of vitamin A in oily and aqueous media, *J. Nutrition*, **35**: 225 (Feb.) 1948.
8. SOBEL, A. E., BESMAN, L., AND KRAMER, B.: Vitamin A absorption in newborns, older children, adults and a storage in rats, *Federation Proc.* **7**: 189 (March) 1948.
9. SOBEL, A. E., BESMAN, L., AND KRAMER, B.: Vitamin A absorption in the newborn, *Am. J. Dis. Child.* Accepted for publication.
10. POPPER, H., STEIGMANN, F., AND DYNIEWICZ, H. A.: Treatment of endogenous hypovitaminemia in liver disease. *J. Lab. & Clin. Med.* **32**: 1403 (Nov.) 1947.
11. LEWIS, J. M., BODANSKY, O., BIRMINGHAM, J., AND COHLAN, S. Q.: Comparative absorption, excretion and storage of oily and aqueous preparations of vitamin A, *J. Pediat.* **31**: 496 (Nov.) 1947.
12. MAY, C. D., AND LOWE, C.: The absorption of orally administered emulsified lipid in normal children with steatorrhea, *J. Clin. Investigation* **27**: 226 (March) 1948.
13. Aqueous dispersion 1 is called "Vifort". Each 0.6 ml. contained in addition to 5,000 USP units of the Vitamin A, 1200 USP of vitamin D, 1.8 mg. of thiamine hydrochloride, 0.4 mg. riboflavin, 0.3 mg. pyridoxine hydrochloride, 60 mg. of ascorbic acid, 3 mg. of nicotinamide, 1.2 mg. of calcium pantothenate and 62.5 mg. of extract of rice polishings.
14. RUCH, D. M., BRUNSTING, L. A., AND OSTERBERG, A. E.: Use of vitamin A tolerance test in certain cases of dermatologic disorders, *Proc. Staff Meet., Mayo Clin.* **21**: 209 (May) 1946.
15. LYNCH, F. W.: Nicotinic acid in treatment of acne vulgaris, *Arch. Dermat. & Syph.* **42**: 481 (Sept.) 1940.
16. STILLIANS, A. W.: Pyridoxine in treatment of acne vulgaris, *J. Invest. Dermat.* **7**: 150 (June) 1946.
17. LOZZA, M.: Vitamin C and calcium in treatment of juvenile acne, *Minerva med.* **30**: 235 (Sept.) 1939 (Extract in Year Book of Derm. and Syph. 1940, p. 432).
18. DOKTORSKY, A., AND PLATT, S. S.: Vitamin D in treatment of acne vulgaris, *J. A. M. A.* **101**: 275 (July) 1933.
19. MAYNARD, M. T. R.: Vitamin D in acne, *California & West. Med.* **49**: 127 (Aug.) 1938.

20. SIMPSON, C. A., ELLIS, F. A., AND KIRBY-SMITH, H.: Vitamin D in treatment of acne. *Arch. Dermat. & Syph.* **4**: 835 (May) 1940.
21. CORNBLEET, T., ET AL.: Blood vitamin A and cutaneous diseases, *Arch. Dermat. & Syph.*, **49**: 103 (1944).
22. DUBLIN, W. B., AND HAZEN, B. M.: Relation of keratosis seborrheica and keratosis senilis to vitamin A, *Arch. Dermat. & Syph.* **57**: 178 (Feb.) 1948.
23. SOBEL, A. E., ROSENBERG, A., AND KRAMER, B.: Comparison of the rises in vitamin A level of human milk following the administration of vitamin A in aqueous and oily media. Abstracts of 114th meeting of the American Chemical Society, Division of Biological Chemistry, August 30, Washington, 1948.