THE RÔLE OF THE UNSATURATED FATTY ACIDS IN THE ACRODYNIA (VITAMIN B_6 DEFICIENCY) OF THE ALBINO RAT*

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In 1929 Burr and Burr (1, 2) described a disease of the rat produced by a fat free diet and due particularly to the lack of unsaturated fatty acids. Cutaneous manifestations of this fat deficiency disease attracted the interest of dermatologists and a series of publications appeared dealing primarily with the effect of the unsaturated fatty acids on allergic eczema or atopic or allergic dermatitis (3, 4, 5).

Recent advances in the field of nutrition and biochemistry have led to a complete change in the conception of the fat deficiency syndrome of the rat. The implications of this change for Dermatology seem so important that I feel justified in presenting the subject before this gathering.

Although I believe that the story of rat pellagra is generally known, I shall recapitulate shortly the vitamin B deficiencies of the rat. What was originally known as rat pellagra was shown by Birch and György to be a deficiency in a vitamin different from that curing pellagra, and they gave this vitamin the name of Vitamin B_6. These authors called the condition *rat acrodynia*, and further work differentiated this deficiency from a denuding dermatitis caused by riboflavin deficiency. It soon became evident that the heat stable fraction of the Vitamin B complex contained other factors besides riboflavin, the pellagra preventive factor and Vitamin B_6. For chemical reasons the remaining fraction was called the filtrate factor. Riboflavin, nicotinic acid and Vitamin B_6 have been available in synthetic form, and this fact has aided in clarifying the function of the filtrate factor. It is clear that this fraction is of multiple nature (6), containing pantothenic acid, recently synthesized, an additional growth factor

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for the rat, the anti grey hair factor (7, 8), and another factor curing some of the skin manifestations of the rat acrodynia (9). It is this last factor which we shall have to bear in mind in addition to Vitamin B_6, if we want to clarify our views.† It can be definitely stated that the skin manifestations of so called rat pellagra or rat acrodynia are the result of a deficiency in Vitamin B_6 and in this accessory skin factor of the filtrate fraction. The other manifestations like retarded growth, greying of dark fur and rusting of white fur, and possibly some other manifestations, are also the result of filtrate fraction deficiency. I shall omit the role of nicotinic acid for the rat since it is still a controversial issue, but I have to mention the role played by choline and the unsaturated fatty acids in the mechanism of the entire B complex. The purpose of this paper is to stress the importance of the unsaturated fatty acids for the proper function of Vitamin B_6 in the rat.

Although Hogan and Richardson (10) showed the curative effect of wheat germ oil on the Vitamin B complex deficiency of the rat, it was left to Birch (11), and Quackenbush, Platz and Steenbock (12, 13) to identify the skin lesions of the fat deficiency disease of Burr and Burr with those of the so called rat acrodynia. In a painstaking biochemical and experimental study, Quackenbush, Steenbock, and Platz (13) demonstrated that linoleic acid and its ethyl ester, was the active factor of the unsaturated fatty acids. They found wheat germ oil, cotton seed oil, and corn oil, highly active; butter fat far less active; cod liver oil and haliver oil inactive. Furthermore, they demonstrated that the unsaponifiable fraction of wheat germ oil, hydrogenated oil and the elaidinized ester of linoleic acid were biologically inactive.

As mentioned before, the synthesis of Vitamin B_6 led to the formulation of an accessory skin factor for the rat contained in the filtrate fraction of liver, yeast, rice bran, and other food stuffs, since Vitamin B_6 had only a temporary effect on certain skin manifestations of the deficient rat. Therefore, it can be stated that the cutaneous manifestations of the rat receiving riboflavin, thiamin and choline, but deficient in all other components of the B complex and fat, are *the result of three factors:* (*a*) *Vitamin* B_6, (*b*) *the accessory factor of the filtrate fraction, and* (*c*) *linoleic acid and its ester.*

Through certain experiments on the curative action of linoleic acid and the

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† Since the presentation of this paper, experiments with synthetic pantothenic acid have clarified to a certain degree the function of the filtrate fraction. If administered to rats receiving vitamin B_6, pantothenic acid cures the dermal lesions of filtrate fraction deficiency, namely the crusting of the snout, the spectacled eye condition, the rusting of the fur and alopecia. In the same manner, it shows a curative action on the greying of black rats and produces a considerable increase in weight. It seems therefore probable that pantothenic acid will be identified with the accessory skin factor of the filtrate fraction and with the achromotrichia factor. A final conclusion has not been reached as yet and an additional factor curative of the greying of hair and an accessory weight factor contained in the filtrate fraction must be postulated at present on the basis of certain facts ascertained by a number of research workers in this field. The rôle which the mouse alopecia factor, recently discovered by Woolley, plays in the nutrition of the rat, also awaits further clarification.

B complex, Schneider, Steenbock and Platz (14) came to the conclusion that "acrodynia, as it is known in the rat, can be cured by two different means. It can be cured by the so called "essential fatty acids." This action is independent of Vitamin B_6, since "essential fatty acid" preparations have been shown not to contain any Vitamin B_6. It can be cured by rice bran concentrate. This action is independent of fatty acids, but is dependent upon Vitamin B_6 plus a second "accessory factor." This second factor has been shown to be included in the filtrate from the Fuller's earth treatment of rice bran concentrate." Salmon (15) finds the presence of Vitamin B_6 and the essential fatty acids necessary for normal nutrition of the rat. Nevertheless he believes that Vitamin B_6 and the essential fatty acids can "to a certain extent mutually alleviate the deficiency of each other."

These authors have arrived at their conclusions on the basis of curative experiments. Oleson, Elvehjem and Hart also deduced from such experiments that the "spectacled eye condition" of the rat can be cured by Fuller's earth filtrate as well as by two or three drops of corn oil a day.

In a repeated series of experiments on the action of unsaturated fatty acids I have depended on the preventive effect of the factors concerned and not on the curative action. This may account for the fact that the analysis of our experiments leads to conclusions which differ considerably from those stated so far.

White rats weighing about 40 grams at ages from 21 to 25 days, were kept on a basal ration consisting of sucrose 76, casein (Labco) 20, salts (Osborn Mendl) 4. They were fed the various supplements by using a tuberculin syringe as medicine dropper. Some of the animals were depleted before weaning. Others were on the stock diet up to weaning (a factor influencing the deficiency only as to its onset and not as to its character). Throughout the experiment they were kept in individual cages with screened bottoms. All animals received daily the following supplements:[1] Riboflavin 20–50 micrograms, thiamin chloride 10–20 micrograms, choline 1 milligram, Vitamin A 10 micrograms, and Vitamin D 5 micrograms dissolved in Propylen Glycol.

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Dr. O. W. Barlow of the Winthrop Chemical Company for Vitamin A and D and Propylen glycol.
Dr. J. F. Biehn of the Abbott Laboratories for pressed wheat germ oil.
Dr. Ezra Levin of the Viobin Corporation for Viobin wheat germ oil.

On this regime the animals developed skin manifestations of acrodynia in four to five weeks and died within seven weeks. The addition of three percent filtered butter fat caused a moderate delay in the onset of the deficiency and occurrence of death, to five and ten weeks respectively. In several series of experiments, four to six drops of wheat germ oil daily were given to the animals, thus supplying a rich source of lineolic acid. Various oils were used: pressed wheat germ oil, wheat germ oil extracted with purified ether (prepared by Dr. Marianne Goetsch), and a special stable wheat germ oil. No differences were noticed. Feeding the unsaturated fatty acids of wheat germ oil caused a significant delay in the appearance of the deficiency symptoms but the longer survival period allowed more severe skin manifestations to develop.

The most characteristic skin lesions of the deficiency disease resulting from lack in vitamin B_6 and the filtrate factor were as follows: crusting of the mouth, crusting of the eyelids and spectacled eye condition, scaling and crusting of the tail, thickening of the ears and crusting in the more advanced stage; scaling, oozing, crusting and swelling of the fore and hind paws and legs. These occurred with sufficient regularity. In addition, denudation, especially of the face and neck, changes of the fur including rusting, and hemorrhagic lesions and paralysis of the extremities were observed, but their charting will be omitted in this paper.

To further analyze the cause of the skin manifestations mentioned above, several series of animals were fed the basal ration, supplemented as before, but in addition they were given daily vitamin B_6 (40 micrograms) and wheat germ oil (4 drops). None of these animals developed any thickening of the ears or the severe condition of the paws and legs, which was responsible for the name acrodynia.

On the other hand, the crusting of the mouth, the spectacled eye condition, and scaliness of the tail occurred with sufficient regularity to permit the conclusion that: *crusting of the mouth, spectacled eye condition and scaling of the tail are the result of a deficiency in the filtrate fraction.*

Since *swelling and crusting of the ears and the dermatitis of the paws* were prevented by feeding of vitamin B_6 with the addition

TABLE 1

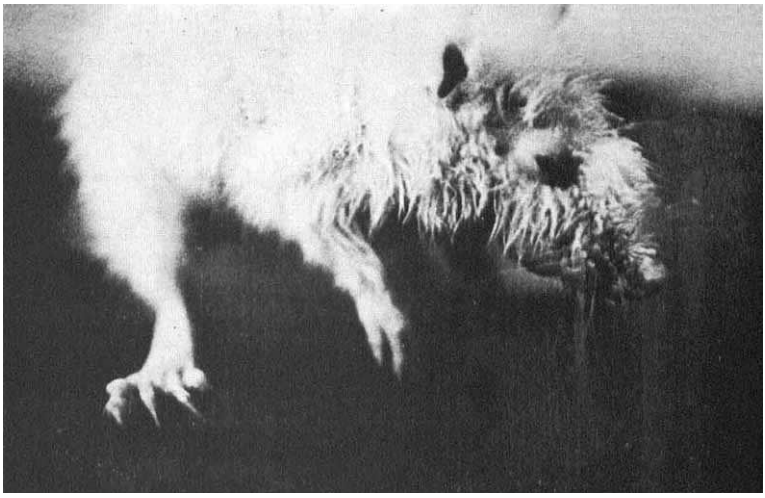
Effect of subcurative doses (butterfat, percomorph oil) and curative doses (wheat germ oil) of unsaturated fatty acids on the development of skin manifestations of rat acrodynia (deficiency in Vitamin B_6 and filtrate factors)

SUPPLEMENTS	ANIMAL NUMBER	LIPS, NOSE	EYES	NECROTIC TAIL	EARS	PAWS	AVERAGE SURVIVAL
							weeks
Riboflavin thiamin Vit. A + D	A-9	++	0	0	0	++	
	A-41	+++	+	0	++	++	7
	A-49	+++	++	0	0	++	
	A-53	++	++	0	0	0	
+ 3% butterfat	J-63	+++	+	++	++	+++	
	J-66	+++	++	+++	+++	++++	10
	J-72	++	++	++	+	++	
+ Wheat germ oil	L-62	+++	0	0	0	++	
	L-65	++	0	+++	++	++	
	L-80	+++	0	0	+	+	
	C-11	++	0	++	++	++	
	C-19	++++	+	+++	++	+++	
	C-27	+++	+	0	++	+++	
	C-401	++++	0	0	0	++++	12
	C-403	++++	+	0	0	+++	
	C-405	+++	0	+++	+++	++++	
	C-408	+++	++	0	++	+++	
	C-413	+++	+	0	0	++	
	C-417	+++	0		±	+++	
	C-415	+++	+++	+++	0	++	
+ Nicotinic acid, + wheat germ oil	E-13	+++	0	++	+	+++	
	E-21	+++	++	+++	+	++	
	E-45	+++	±	0	+	++	
	E-424	++	0	0	++	++	
	E-426	+++	0	0	+++	++	
	E-428	+++	++	0	+	±	
	E-432	+++	++	0	++	++	14
	E-433	++++	++	0	++	±	
	E-434	+++	++	0	++	±	
	E-437	0	0	+++	+++	+++	
	E-438	+++	0	+++	+	+	
	E-439	+++	+	0	+	+	
	E-440	++++	0	0	+	++	

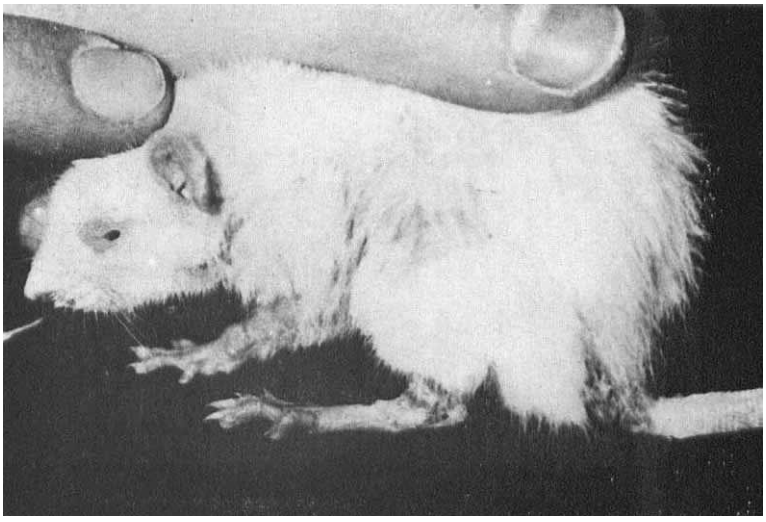
of wheat germ oil, these lesions have to be *considered the result of lack of vitamin B_6.*

It should be mentioned that the severe *crusting and ulceration*

at the root of the tail which is seen in the florid acrodynia did not occur and may therefore be considered *an additional sign of* B_6 *deficiency*. Denudation of the face, neck, and areas of the trunk



PHOTOGRAPH I. DEFICIENT RAT SHOWING THE SPECTACLED EYE CONDITION



PHOTOGRAPH II. DEFICIENT RAT SHOWING THICKENING OF THE EAR, SEVERE CRUSTING OF THE PAWS AND LEGS AND ULCERATION AT THE ROOT OF THE TAIL
Also spectacled eye condition and beginning alopecia

developed more frequently in these animals and are signs of filtrate deficiency.

This statement concerning the nature of the vitamin B_6 deficiency has to be modified as the result of the next experiment:

A group of animals were fed vitamin B_6 but no fatty acids; another group vitamin B_6 and 4 drops of Percomorph oil, which apparently contains a small amount of curative fatty acids. As was to be expected, the animals developed crusting of the snout, crusted and spectacled eyes and a scaly tail, since they were lacking the filtrate fraction. In addition, thickening of the ears and crusting of the paws of moderate severity was observed fairly regularly. The shortened survival period characteristic of fat deficiency (8 to 11 weeks) prevented the observation of the severest manifestations. Even so, the symptoms were sufficiently typical to allow the statement that a vitamin B_6 deficiency developed in animals fed large amounts of synthetic vitamin B_6.

This only bears out further the conclusions of Birch that "rats may develop acrodynia-like dermatitis if the diet is free from fat even when moderately large amounts of vitamin B_6 are given."

From these experiments it can be seen quite clearly that at least *the dermal manifestations of vitamin B_6 deficiency in the rat, and of the fat deficiency of the rat are identical* and that for the *prevention and cure of these lesions both vitamin B_6 and the unsaturated fatty acids are essential.*

The inability of the rat to utilize the saturated palmitic acid for the production of linoleic acid has been recently demonstrated by De Witt Stetten and Schoenheimer (17) and Bernhard and Schoenheimer (18) by means of Deuterium experiments.

The effect of the various dietary factors, especially of vitamin B_6 and the unsaturated fatty acids on the weight curve and survival period, will not be discussed but will be demonstrated by some characteristic curves. One interesting factor is shown by the comparison of these weight curves. In those series of experiments in which the rats received curative doses of unsaturated fatty acids, with or without supplements of nicotinic acid or

vitamin B_6, there were a number of animals which failed to develop more pronounced dermal lesions and exceeded the survival period characteristic for the type of experiment, by many weeks. By a very slow and steady increase up to about the 18th week of

TABLE 2

Effect of Vitamin B_6 on the development of the skin manifestations in rats fed diets without and with the addition of curative doses of unsaturated fatty acids (wheat germ oil)

SUPPLEMENTS	ANIMAL NUMBER	LIPS, NOSE	EYES	NECROTIC TAIL	EARS	PAWS	AVERAGE SURVIVAL
							weeks
Riboflavin thiamin Vit. A + D + Vit. B_6	D-12	++	±	0	+	++	9
	D-20	++		0	0	++	
	D-28	++		0	0	++	
	D-44	++	+	0	0	+	
+ Percomorph oil + B_6	JJ-45	++	++	0	+	++	10
	JJ-46	+++	+	0	0	++	
	JJ-47	++	++	0	±	+	
+ Wheat germ oil + B_6	F-302	++	0	0	0	0	11
	F-303	++++	+++	0	0	0	
	F-306	+	++	0	0	0	
	F-307	++	++	0	0	0	
	F-308	++	+++	0	0	0	
	F-312	+++	++	0	0	0	
	F-313	+++	++	0	0	0	
	Fv-2	+	±	0	0	0	
	Fv-3	++	+	0	0	0	
	Fv-5	+++	+++	0	0	0	
	Fv-6	++	0	0	0	0	
	Fv-8	+++	++	0	0	0	
	Fv-12	++	+	0	0	0	
	Fv-13	+++	0	0	0	0	
	Fv-16	+	+++	0	0	0	
	Fv-20	0	++	0	0	0	

the experiment, they reached weights between 75 and 95 grams. This phenomenon was never observed in animals kept on a fat free diet, even if supplemented with vitamin B_6 and nicotinic acid.

One is justified in assuming that the survival period of an

TABLE 3

Condensed illustration of the foregoing tables, including survival periods

Vitamin B_6	Fats	Nicotinic Acid	Filtrate Factor Deficiency	Vitamin B_6 Deficiency	Weeks surviv.
0	0	0			7
0	Butterfat 3%	0			10
0	Wheatgerm Oil	0			12
0	Wheatgerm Oil	+			14
+	0	0			9
+	Percomorph Oil	0			10
+	Wheatgerm Oil	0			11

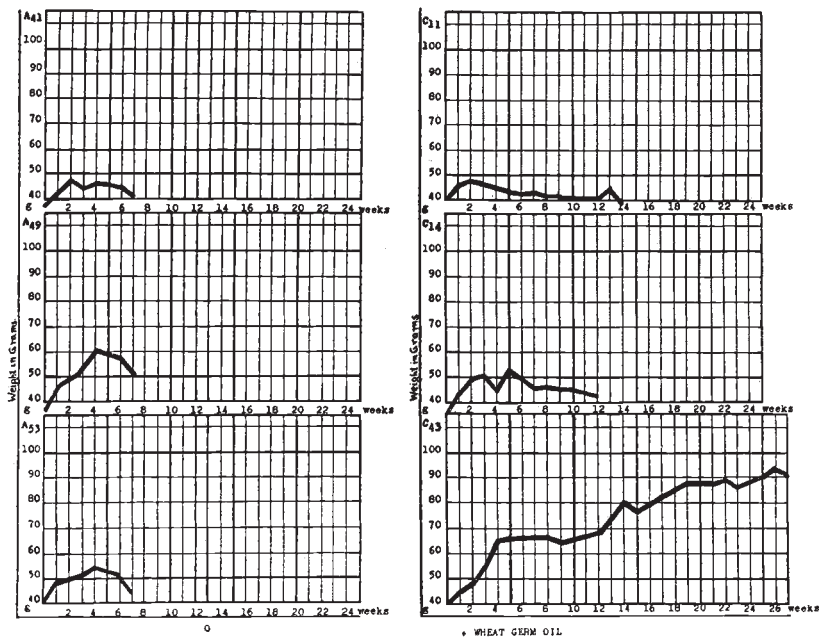


FIG. 1. GROWTH OF RATS FED WITHOUT SUPPLEMENTS OF VITAMIN B_6 AND FILTRATE FACTORS; GROUP A RECEIVING NO FATS, GROUP C RECEIVING WHEAT GERM OIL

animal deficient in one or more members of the vitamin B complex or fatty acids is a result of the accumulated store in these factors at weaning or at the outset of the feeding experiment. Such a marked prolongation of life as observed in the animals mentioned before can hardly be the result of stored vitamins and is probably due to synthesis of vitamin B_6 and other

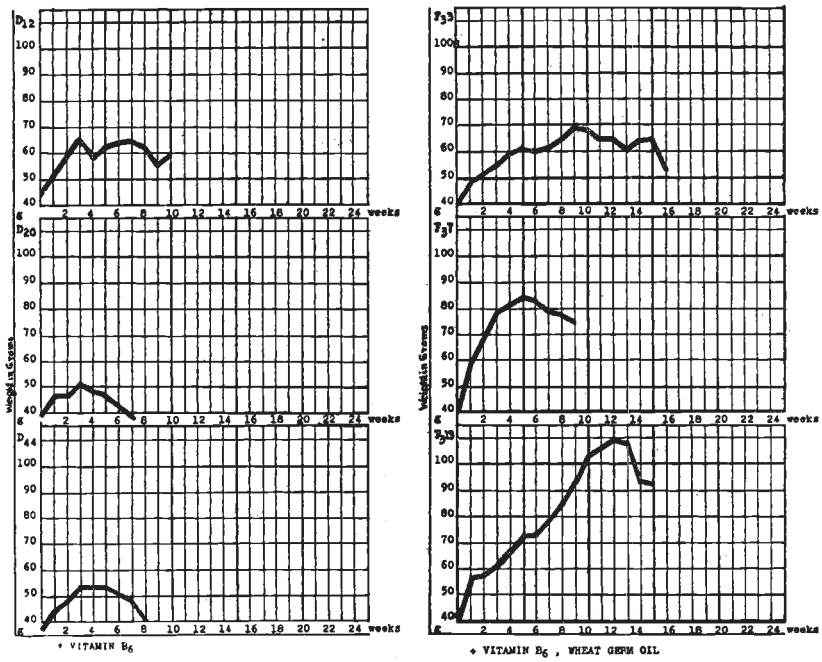


FIG. 2. GROWTH OF RATS FED WITHOUT SUPPLEMENTS OF FILTRATE FACTORS; GROUP D RECEIVING VITAMIN B_6 AND NO FATS, GROUP F RECEIVING VITAMIN B_6 AND WHEAT GERM OIL

factors of the B complex by micro-organisms in the intestinal flora. The absence of this phenomenon in animals on a fat free diet would seem to demonstrate the inability of bacteria to synthesize amounts of linoleic acid curative for the rat. A considerable difference in the depletion time for the store of linoleic acid as compared with that of the vitamins, could be used as an explanation but would hardly account for the irregular incidence

of extremely prolonged survival periods. A third possibility is a true sparing action of the essential fatty acids and fats, reducing the requirements of the animal for some factors of the vitamin B complex. Stirn, Arnold and Elvehjem (19) have shown that rats fed a high fat ration or the synthetic fatty acid esters Tricaproin and Triacetin, have a lower requirement for thiamin and

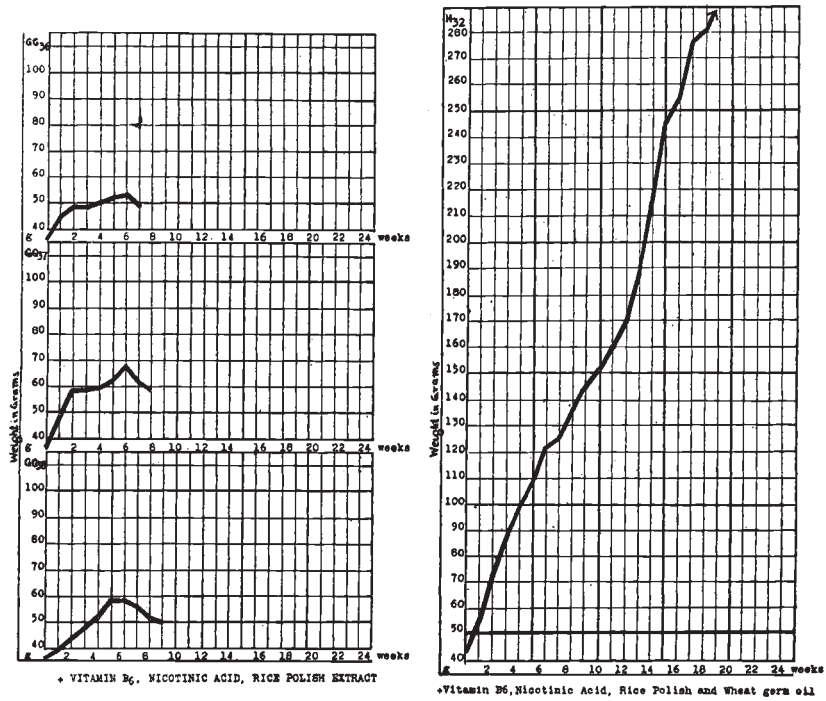


FIG. 3. GROWTH OF RATS FED SUPPLEMENTS OF VITAMIN B_6 AND RICE POLISH EXTRACT CONTAINING ABOUT 10 JUKES LEPKOVSKY UNITS OF THE FILTRATE FACTOR COMPLEX; GROUP GG RECEIVING NO FATS, GROUP H (CONTROLS) RECEIVING WHEAT GERM OIL

cocarboxylase than those fed the usual ratio of carbohydrates and fats.

Synthesis by micro-organisms would account for the interesting occurrence observed in a rat fed the basal ration supplemented by vitamin A and D, thiamin and riboflavin and wheat germ oil plus filtered butter fat.

The animal developed acrodynia in the 7th week of the feeding experiment, which became very severe by the 13th week. During the 13th week the weight which had reached a plateau during the 6th week began to rise slightly and the animal had gained 25 gm. by the 21st week, when it again began losing weight. The skin lesions had disappeared by the 17th week completely, but the animal developed a spastic paralysis and died at the end of the 28th week.

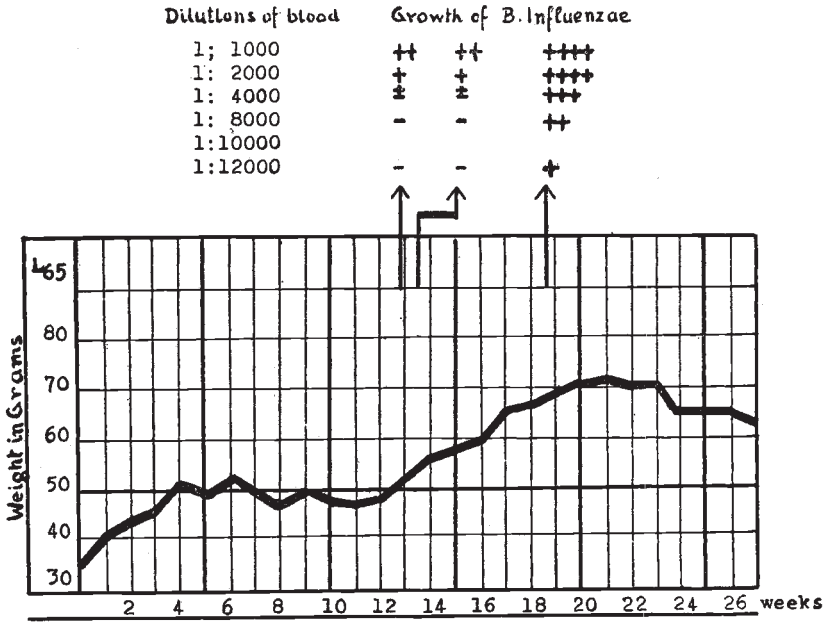


FIG. 4. SPONTANEOUS RECOVERY IN A RAT SUFFERING FROM SEVERE ACRODYNIA VITAMIN B_6 AND FILTRATE FACTOR DEFICIENCY). LOW VALUES OF CODEHYDRASE (FACTOR V OF INFLUENZA BACILLI) COINCIDING WITH SEVEREST DEFICIENCY; RETURN TO NORMAL VALUES AT THE PEAK OF THE WEIGHT CURVE AND RECOVERY

The cozymase in the blood taken from the tail at the height of the deficiency (at the beginning and in the middle of the 14th week) showed extremely low values as observed in animals shortly before death. With the spontaneous recovery of the cutaneous lesions and increase in weight, the cozymase returned to normal value on the 19th week.

The cozymase was determined by the growth factor V for influenza (para-influenza) bacilli (20).

The role that vitamin B_6 and the unsaturated fatty acids play in the normalization of the fat metabolism can only be touched upon. The development of fatty livers with a simultaneous reduction of body fat in vitamin B_6 deficiency has been thoroughly studied (21) and serves as evidence of a disturbed fat metabolism. The lipotropic action of choline has been further analyzed by Griffith and Wade (22) and by Du Vigneaud, Chandler, Mayer, and Keppel (23), and forms an additional link in the regulatory mechanism of fat deposition. Gavin and McHenry (24) have shown the effect of vitamin B_6, thiamin and choline on the deposition of body and liver fat. In recent communications (25) they further believe to have demonstrated that lipocaic is necessary in addition to choline, to reduce the fatty livers produced by feeding certain liver fractions to rats which had been on a fat free diet, devoid of the B vitamins for three weeks. They further found that the liver fat in these animals could also be reduced by a concentrate of rice polish, or by yeast, but that neither of these supplements is as effective as lipocaic when equal weights are used.

These facts should form the basis for the dermatological conception of the action to be expected from the vitamin B complex. It seems that the vitamin B complex and the unsaturated fatty acids are harmonious links in the biologic mechanism which exerts a dermatotropic and lipotropic action. The relationship of these functions to the enzymes of biologic oxidation, for which some of the vitamins of the B complex form the building stones, and their interrelation with the endocrine glands, will be clarified eventually. When this mechanism has been more thoroughly explored and understood, a more rational therapy may develop, and favorable results obtained to-day in a limited number of cases of allergic or seborrheic eczema and psoriasis will become more frequent occurrences.

CONCLUSIONS

I. White rats on a basal diet of sucrose, casein and salt, supplemented with riboflavin and thiamin, were given from weaning, wheat germ oil in daily doses considered effective in curing the skin manifestations of acrodynia. They developed a typical

picture of deficiency in vitamin B_6 and the filtrate fraction. The only action of the essential fatty acids observed, was a marked delay in the onset of the deficiency syndrome and a considerable extension of the survival period. The skin manifestations slowly became manifest from the seventh to eighth week of the experiment and animals even with severe deficiency lived sometimes more than fourteen weeks.

II. Animals fed the same basal diet supplemented with riboflavin and thiamin, received large daily doses of vitamin B_6 but were given either no fat, or percomorph oil, which is a poor source of essential fatty acids. They developed a deficiency which did not differ qualitatively from acrodynia as seen in animals receiving neither vitamin B_6 nor fatty acids.

III. Animals fed vitamin B_6, together with curative doses of essential fatty acids, were fully protected against vitamin B_6 deficiency but developed the skin lesions of the filtrate fraction deficiency and died from the lack of these factors.

IV. The most characteristic skin manifestations of so-called rat acrodynia can be divided and charted as follows:

Vitamin B_6 deficiency:

(a) Thickening and crusting of the ears
(b) Scaling, crusting and swelling of the paws including the legs
(c) Severe crusting of the tail with ulceration and necrosis at the root

Deficiency in the accessory skin factor contained in the filtrate fraction:

(a) Severe crusting of the nose and lips
(b) Spectacled eye condition
(c) Mild brown scaling of the tail
(d) Alopecia, especially of the face, head and neck

There are other manifestations like an erythematous scaly dermatitis of the trunk and changes of the fur which require further analysis as to their relation to the accessory skin factor and achromotrichia factor.

V. Neither the dermal lesions of vitamin B_6 nor those of the filtrate factor deficiency, could be prevented by feeding curative

doses of oils rich in essential fatty acids. The unsaturated fatty acids, especially linoleic acids, studied by various authors in relation to their biologic activity, deserve to be called essential for the nutrition of the rat. Vitamin B_6 can exert a curative action on rat acrodynia only if the animals are maintained on curative doses of essential fatty acids.

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DISCUSSION

DR. WOOLEY: Dr. Gross has tackled the very difficult problem of B_6 relation to pure acrodynia. Even now this is not entirely cleared up. It is rather easy, I believe, to check Dr. Gross' observation on the production of acrodynia in the absence of fatty acid, in the presence of B_6. He is particularly fortunate in having been able to produce the deficiency in the presence of a fatty acid. This is a most difficult task. One must wait for a considerable period before the animal shows the deficiency.

I think it is still a debatable point whether the actual mechanism of action of the unsaturated fatty acid and B_6 are the same. There have been numerous cases postulated in which B_6 or some derivative thereof acted as a mechanism in fat metabolism. This has not yet been confirmed experimentally. It may be that the two mechanisms of action are separate and distinct. We must consider the interaction of a number of the vitamins. These experiments are done with diets which are not complete except for the one factor being studied. This is necessary because we have not had a sufficient number of pure vitamins to produce the normal rat. When we have obtained all of our vitamins we may then be able to show the further relationships between B_6 and the unsaturated fat. For the present we must bear this in mind.

SUSAN GOWER SMITH, *Durham, N. C.:* I have found in my experiments that Vitamin B_6 deficient rats, receiving their vitamin A as cod liver oil which has very little of the unsaturated fats, respond to B_6 treatment with prompt loss of edema and redness in the affected areas. The peripheral dermatitis, however, is not completely healed, and the rats live only a short time if synthetic B_6 is the only therapy.

DR. G. J. MARTIN, *New York City:* I should like to state that from the standpoint of the nutritionist, this work clears up a very important problem in the treatment of the disease. Before the B complex or its units were available in crystalline form, experimentation was carried out with the use of ether-extracted yeast, and we were all under the impression that this would supply all of the water soluble B factors. Actually, we included in these diets Vitamins A, D, E, and the unsaturated fatty acids, and the results were incomplete. Certain symptoms persisted, and we naturally concluded that there was another fat soluble factor. We are now led to the obvious conclusion that if ether extracted yeast was taken out, and an adequate supply of B_6 used, there would be no additional fat soluble factor required by the rat.

I would like to ask Dr. Gross one very pointed question. Assuming the accentuation of certain symptoms by feeding one specific vitamin, from the therapeutic standpoint, I think it deserves emphasis that, in certain instances which I believe we should stress, the feeding of one vitamin is apt to give us marked accentuation of the symptoms of a second vitamin deficiency.

DR. CLARK W. FINNERUD, *Chicago:* Since Burr's original work, many of us have been using one of the unsaturated fatty acids in the treatment of different types of dermatitis. I have been using lard, since this is about the only one, with the possible exception of cornoil, used in cooking. We have hospitalized many of our patients, placed them on a controlled diet, and tested the blood before, during and after treatment, for degree of unsaturation of fatty acids. It has been our experience to date, although we cannot make accurate statements as yet as to our results in the different types of dermatitis—atopic, occupational, infectious eczematoid and others, that those patients, who before ingesting lard showed a low iodine number, usually showed clinical improvement after taking lard by mouth for a number of weeks or months, even in the absence of all other therapy. I think Hansen, working along with Burr, showed similar results in the treatment of infantile eczema. I think he employed cornoil, chiefly, rather than linseed oil. Our experience in this regard with infantile eczema has been negligible. This is an important problem which may prove to have practical application.

I have enjoyed Dr. Gross' paper very much.

DR. THEODORE CORNBLEET, *Chicago:* In eczema the amount of the unsaturated fatty acids in the blood does not appear to have great significance. I have seen the quantity both high and low, and more of them in between. I have seen the same kind of eczema improve or get worse with the same level of unsaturated fatty acids in the blood.

The treatment of eczema with oil administration such as I have proposed has

come into disrepute largely because of the unfavorable reports from the use of linseed oil. While linseed oil is rich in unsaturated fatty acids, it is distasteful and is therefore usually given in relatively minute quantities. It appears to me that favorable results depend on giving large amounts of oil, such as corn oil. There is evidence that it serves in a ketogenic capacity. There are undoubtedly other avenues through which it acts, but in spite of several investigations, I have not succeeded in finding them.

Stokes has made illuminating use of the multiple factorial system in analysis of several disorders. It often happens that the quest for solution is missed in attempts at oversimplification in complex matters. Not everything has a specific nor yet a single cause. Dr. Gross, I believe, here underlines the case for multiplicity.

DR. PAUL GROSS, *New York City:* First I want to express my thanks to Dr. Wooley, and Dr. Martin, as well as to the other guests and members of the Society who have taken the trouble to discuss this paper.

I agree that the last word has not yet been said, and I am continuing my studies. I believe that the unsaturated fatty acids do not concern Vitamin B_6 alone. In other words, some of the factors, the lack of which is responsible at least for some of the skin manifestations, cannot exert full action unless the unsaturated fatty acids are present.

Dr. Smith brought out a point which explains the divergence of our findings from those of some other investigators, namely, the therapeutic effect of vitamins differs considerably at least for a short period, from the preventive effect. Dr. Wooley has also brought this out.

In other words, the rat given corn oil will show improvement of the manifestations, but after a while the animal will fail to improve, and eventually die from the filtrate fraction deficiency, perhaps not returning entirely to the acute stage of acrodynia. This can be seen in any number of experiments. I aim to find out the difference between the preventive and the curative experimentation.

I am also grateful to Dr. Martin for his discussion. His remarks about the accentuation of the deficiency of one member of the B complex if another is fed, are quite accurate. I mentioned this in my paper; rats fed Vitamin B_6 develop a more pronounced filtrate fraction deficiency than those who receive neither Vitamin B_6 nor the filtrate factors.

Concerning Vitamin E, I have had no experience with this whatsoever, but believe it a very just question. It might be well to turn the question around and ask, how much of the things that have been described outside of the specific action of Vitamin E, are due to Vitamin E, and how much is really the effect of the unsaturated fatty acids.

In answer to Dr. Finnerud, it is this work on dermatitis and eczema which, as I mentioned before, led me to read this paper before a dermatologic gathering.

This mechanism which we have just demonstrated, may have no bearing on human pathology and physiology, but it at least gives us a pattern as to how to proceed in studying the human pathology. Those cases which do not respond promptly enough to unsaturated fatty acids, may respond better if the treatment is combined with the B complex.

I am quite familiar with Dr. Cornbleet's work, and believe that the remarks I just made fit in well with his concept.