AD NUMBER

AD833623

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies and their contractors; Critical Technology; MAY 1966. Other requests shall be referred to Department of the Army, Fort Detrick, Attn: Technical Releases Branch, Frederick, MD 21701.

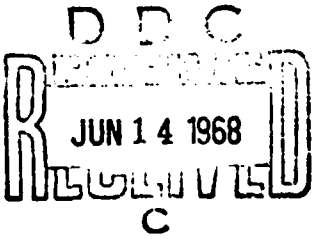
AUTHORITY

Fort Detrick/SMUFD ltr dtd 15 Feb 1972

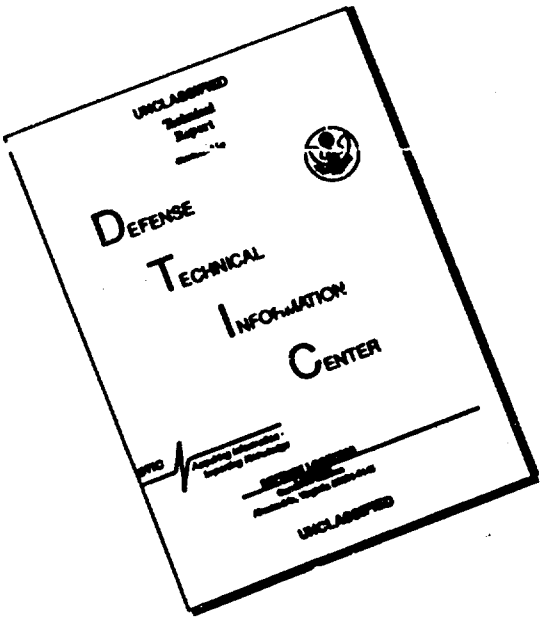
TRANSLATION NO. 1758

[redacted]

DATE: May 1966



DISCLAIMER NOTICE



THIS DOCUMENT IS BEST QUALITY AVAILABLE. THE COPY FURNISHED TO DTIC CONTAINED A SIGNIFICANT NUMBER OF PAGES WHICH DO NOT REPRODUCE LEGIBLY.

ON THE PATHOGENESIS OF FEEBLE-MINDEDNESS DURING PHENYLKETONUREA

Translation No. 1758

May 1966

U. S. ARMY

FORT DETRICK, FREDERICK, MARYLAND

ON THE PATHOGENESIS OF FEEBLE-MINDEDNESS DURING PHENYLKETONUREA

(Following is the translation of an article by F. Lenneweh and H. Ehrlich, Marburg, published in the German language periodical (Klinische Wochenschrift) Clinical Weekley, 40th year, book 5, March 1, 1962, pages 16-17. Translation performed by Constance L. Lust.)

Among the types of feeble-mindedness caused by metabolic alterations phenylketonurea has obtained a special importance. It has been studied very extensively and is one of the heridetery diseases of metabolism which has been explained best in chemical terms. In 50 million inhabitants in a country one has to figure on 1500 cases of phenylketonurea. To this number one must add about 50 newborns each year.

A decrease in activity of phenylalanine oxidase system during this illness results in an increase of from 20-30 times the concentration of phenylalanine in plasma compared to normals. Feeble mindedness is developed already in infancy and in most cases an intelligence quotient of less than 20 is found. However, there is as yet no uniform concept about the question, whether phenylalanine itself or other phenolderivatives such as phenyl-acetic acid or similar products of intermediary metabolism, represt the noxious agent. At the same time feeble-mindedness can be diminished therapeutically, or even prophylactically prevented, by substituting an amino acid mixture without phenylalanine for dietary protein. This procedure is being carried out successfully in several places. The dietary results fully substantiate the pathogenetic presentations.

We have obtained results in 14 cases of untreated phenylketonurea, which lead one to suspect, that the reasons for the pathogenic observations about the genesis of feeble-mindedness must be extended (expanded). Utilizing column chromatography according to Stein and Moore, we have analysed the plasma before institution of dietary therapy. The results we obtained are summarized in tables 1 and 2. If one focuses on the essential amino acids -histidine included- and relates the values found with the normal, average-values (table 1), then the surprising fact becomes apparent that the essential amino acids in part are reduced 50% below normal. We recently reported similar results in two cases of phenylketonurea (5). Only Knox (4) reported that in a column chromatogram of Moore and Stein such a variation occurred.

Our results lead to the question; what mechanism is responsible for the decrease in the essential amino acids. Our knowledge about amino acid transport is inadequate to be able to answer this question at this time. Tubular reabsorption does not decrease, as we demonstrated in clearance studies (5). It can be assumed that the high concentration of phenylalanine in the plasma competitively inhibits the transport of other amino acids and in this way causes metabolic conditions which are presently inexplicible. This has been demonstrated in brain sections in vitro (6).

It is easier to explain the tyrosine decrease which has been known longer. This is presumable because of the blocked defected enzyme which is responsible for converting phenylalanine to tyrosine. Tyrosine is not responsible as a cause of imbecility. This was demonstrated in many experiments where tyrosine was substituted. In this case one of the essential amino acids is not involved.

The decrease of the essential amino acids in plasma on the other hand offered an opportunity to attempt to explain imbecility during phenylketonurea. It is possible that the functional differentiation of brain cells in particularly dependent on an optimum concentration of essential building blocks.

The observations (3) that mothers with phenylketonurea can have mentally normal children and that dietary therapy appears to have no effect after the third year of life leads one to believe that a sensible period exists for cerebral damage occurrs (1). This concept is derived from developmental physiology and may be applicable for pathologic processes. In the area of pathology it would mean that the sensitivity against noxis is limited to a definite time. This time-period for phenylketonurea lies between 4 months of age to the end of the third year. This coincides with the period of myelinization of the brain. On the other hand it may be assumed that other disturbances are occurring simultaneously in protein synthesis of brain cells, especially when one remembers that myelinization is dependent on the intact glial cells.

The various forms of metabolic imbecility point to the fact that different disturbances in metabolism lead to the complex phenomena of imbecility. The defective intelligence represents a uniform reaction to heterogeneous damage.

Summary: During phenylketonurea a 20-30 fold elevation of phenylalanine is balanced by a competitive decrease of the other essential amino acids in the plasma. Values of 50% of normal were representitive. A possible meaning of this deficit for the pathogenesis of imbecility is discussed.

Literature

Literatur. [1] [illegible] M. D., N. [illegible] Bosma: Studies on phenylketonuria: [illegible] on the effect of [illegible] diet on patients with phenylketonuria. Amer. J. clin. Nutr. 5, [illegible] (1957). — [2] [illegible], W.: Die Bedeutung des [illegible] für die Hirnfunktion. [illegible] — [3] Jervis, G. A.: [illegible] 1960. — [4] Knox, W. E.: Phenylketonuria, Chap. 10, p. 357–358. In: J. B. Stanbury, J. B. Wyngaarden and D. S. Fredrickson, The [illegible] basis of inherited disease. New York-Toronto-London: McGraw-Hill Book Company 1960. — [5] [illegible] u. M. [illegible]: Die renalen und plasmatischen Störungen des Aminosäuren-Stoffwechsels [illegible] Klin. Wschr. 38, 904 (1960). — [6] Neame, K. D.: Phenylalanine as inhibitor of transport of amino-acids in brain. Nature 192, 173 (1961).

Table 1

Concentration of plasma amino acids in 14 untreated cases of phenylkotenurea feeble-mindedness

Tabelle 1. *Konzentrationen der Plasma-Aminosäuren bei 14 unbehandelten Fällen von phenylketonurischem Schwachsinn* (in mg-%)

Nr.	Name, Alter	Phe	Val	Leu	His	Leu	Lys	Met	Tyr	Thr	Arg	Try	Glu	Cys	Asp	Ser	Gly	Ala	Pro
1.	R. Sch., $2^{10}/_{12}$ Jahre	19,4	2,34	0,53	0,77	1,01	1,64	0,17	<0,1	0,67	0,72		1,33	0,24	—		1,95	1,25	
2.	J. R., $2^{9}/_{12}$ Jahre	27,2	1,36	0,75	0,86	1,20	1,76	0,40	0,44	0,52	0,69			2,80	—		2,51	1,02	
3.	C. R., $2^{9}/_{12}$ Jahre	21,5	1,60	0,50	0,59	1,10	2,04	0,19	0,31	0,58	0,47		?		0,03		3,32	?	
4.	A. E., $2^{5}/_{12}$ Jahre	28,5		0,91		1,49	1,52	0,14	0,61	0,46			1,26	1,59	0,06		0,87	1,39	0,55
5.	S. H., 5 Monate	38,2		0,66	0,93	1,04	2,20	0,31	0,46	0,94	0,45		1,90		—	1,44	1,28	1,55	0,55
6.	G. H., 9 Monate	26,9		0,72	0,69	1,21	2,60	0,25	0,68	0,86	0,60		1,67		0,006	1,18	1,44	1,99	0,56
7.	H. R., $2^{2}/_{12}$ Jahre	24,4		0,59	2,54	1,22	3,38	0,26	0,45	1,0	0,59		1,59		—	1,44	1,35	1,43	0,56
8.	W. M., 8 Monate	26,3		0,64	1,18	1,11	2,67	0,11	0,59	0,75	1,32		1,02		0,03	1,11	1,29	1,48	0,44
9.	H. B., $3^{2}/_{12}$ Jahre	21,4	2,35	0,54		0,92	2,10	0,29	0,43	0,82			1,45	1,14	—	1,29	1,70	2,55	0,23
10.	H. K., $2^{6}/_{12}$ Jahre	27,9	2,52	0,95	0,46	1,36	1,10	0,27	0,75	0,79			1,54	0,58	—	0,86	1,66	20,7	0,65
11.	C. W., $1^{1}/_{12}$ Jahre	22,1		0,58	0,83	1,0	2,02	0,4	0,25	0,97	0,68		1,26		0,02	1,50	1,43	1,52	0,27
12.	K. A., $1^{8}/_{12}$ Jahre	22,9		0,68	0,81	1,17	1,67	0,20	0,66	0,55	0,66		1,56		—	0,99	1,09	1,13	0,40
13.	C. G., 7 Monate	32,4	3,60	1,32		2,17		0,47	1,16	1,29			2,43	2,9			1,13	3,82	0,95
14.	P. F., $1^{9}/_{12}$ Jahre	21,7	2,43	0,50	0,81	0,92	1,33	0,30	0,59	0,73	0,57		1,26	0,34	—	1,05	1,05	1,43	0,32

Table 2

Average values and standard deviations of amino acid concentrations in plasma of the cases of table 1

Tabelle 2. *Mittelwerte und Standardabweichungen der Aminosäure-Konzentrationen der Plasmen der Fälle in Tabelle 1*

Aminosäuren	Gesunde				Phenylketonurie				P
	Variationsbereich	n	M	σ_M	Variationsbereich	n	$M \pm \sigma_M$		
Phenylalanin	0,69—1,22	10	0,89	0,05	19,40—32,40	14	$25,05 \pm 3,72$		0,001
Valin	2,37—3,71	10	2,76	0,13	1,56—3,60	7	$2,31 \pm 0,18$		0,01
Histidin	0,79—1,23	10	1,20	0,07	0,46—2,54	11	$0,95 \pm 0,09$		0,05
Lysin	2,10—4,18	10	2,70	0,18	1,33—3,38	13	$2,00 \pm 0,08$		0,001
Isoleucin	0,61—1,28	10	0,86	0,07	0,50—1,32	14	$0,70 \pm 0,01$		0,05
Leucin	1,20—2,59	10	1,61	0,11	0,92—2,17	14	$1,21 \pm 0,03$		0,01
Methionin	0,27—0,49	7	0,38	0,01	0,11—0,47	14	$0,27 \pm 0,003$		0,02
Threonin	1,21—2,06	10	1,53	0,10	0,46—1,16	14	$0,79 \pm 0,01$		0,001
Arginin	1,00—2,50	10	1,52	0,13	0,45—1,29	10	$0,68 \pm 0,02$		0,001
Tyrosin	0,68—1,45	10	0,99	0,07	0,10—1,16	14	$0,53 \pm 0,02$		0,001
Tryptophan									

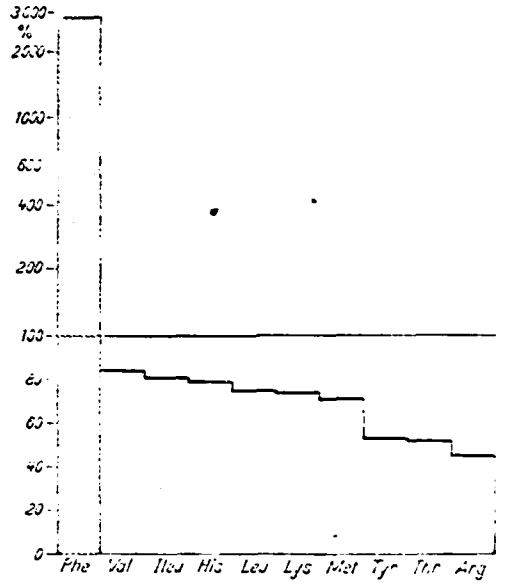


Abb. 1. Mittelwerte der essentiellen Aminosäuren im Plasma von 14 unbehandelten Fällen von phenylketonurischem Schwachsinn im Vergleich zu den Mittelwerten Gesunder (= 100%)

Figure 1

Average values of essential amino acids in plasma of 14 untreated cases of phenylketonurea-feeble mindedness compared to the average values of healthy individuals (=100%).

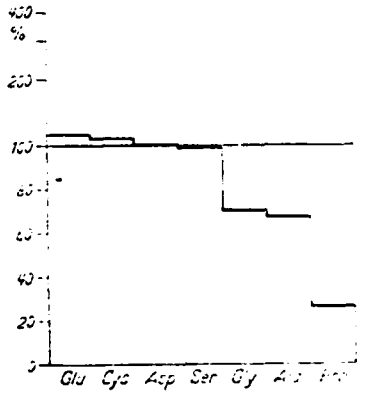


Abb. 2. Mittelwerte der nicht essentiellen Aminosäuren im Plasma von 14 unbehandelten Fällen von Phenylketonurie mit Schwachsinn im Vergleich zu den Mittelwerten Gesunder (= 100%)

Figure 2

Average values of the non-essential amino acids in plasma of 14 untreated cases of phenylketonurea feeble-mindedness compared to average values for healthy individuals (=100%).