Pantothenic Acid: Experimental Results and Clinical Observations

By

I. Szórády

Department of Paediatrics, University Medical School, Szeged

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Pantothenic acid, a member of the vitamin-B complex, has been known for about three decades, but only the experimental results and clinical observations of the last 15 years have brought its vitaminological significance into a clearer focus [3, 26, 39, 41, 52]. Table 1 shows the most prominent achievements in this field.

In the present paper we shall report on some recent results obtained with pantothenic acid especially in paediatrics, including experimental and clinical observations made by the present author in the course of the last years.

I

Pantothenic acid is supplied to the human organism from endogeneous and exogeneous sources. Biosynthesis by the intestinal flora belongs to the first, nutrition to the second category.

Biosynthesis is influenced by the diet, the quantitative and qualitative changes in the intestinal flora, by the proportion of pantothenic acid and the other vitamins (folic acid, biotin and vitamin C in particular) — an important factor emphasized by Stepp [38] — further by the condition of the absorbtive surface and

Table 1

1933:	The first description and designation of pantothenic acid
1938:	Demonstration of its vitaminic character
1939:	Discovery of correlation between pantothenic acid and adrenal gland
1940:	Synthesis of pantothenic acid in crystalline form, determination of its chemical structure, its earliest therapeutic application
1946:	Discovery that pantothenic acid is synthesized by intestinal bacteria
1947:	Discovery of correlation between pantotenic acid and coenzyme A
1951:	Adoption of pantothenic-acid therapy for intestinal paralysis
1952:	Further investigations concerning the correlation between pantothenic acid and the pituitary-adrenal system
1955:	Systematic study of pantothenic-acid antivitamins

the age factor. Technical difficulties have so far prevented a precise appreciation of the amount of biosynthetically produced pantothenic acid, but it is generally recognized that it does not cover the requirements of the human organism. That pantothenic acid is produced not only by *E. coli* but also by *L. bifidus*, prevailing in the intestines of breast-fed infants, is a fact important in peadiatrics [31]. The intestines contain, on the other hand, microorganisms which consume pantothenic acid synthesized there [16].

Foodstuffs contain free pantothenic acid and also pantothenic acid in ester, amide and glucuronide bonds. These compounds have an identical dietetic value. Practically all human foodstuffs contain pantothenic acid, but yeast, liver, rice, wheat flour, egg yolk, beef, mushrooms and roe are especially rich in it, their average pantothenic acid-content amounts from 3 to 20 mg/100 g. Milk and vegetables are comparatively poor in pantothenic acid, they contain 0.1 to 3 mg/100 g. The pantothenic acid content of fruits is negligible. Human milk contains 0.16 to 0.30 mg, cow's milk 0.3 to 0.5 mg, per 100 g. The pantothenic acid content of human milk diminishes temporarily during the 2nd and 3rd months of lactation, and shows even thereafter certain seasonal and geographical variations. Colostrum contains less pantothenic acid than milk. Boiling reduces the pantothenic acid content by about 25 per cent, and similar or even higher losses are caused by culinary or industrial manipulation of the foodstuffs [19]. Deep freezing seems to be the best means of preservation [7]. It is regrettable that manufacturers usually omit to indicate on the labels the pantothenic acid content of the food preparations. Of recent, there has been a certain improvement in this respect [25].

A healthy adult person requires about 15 mg of pantothenic acid daily. This estimation is based on the optimal ratio of 5 mg per 1000 cal. To refer the required amount of pantothenic acid to calory intake irrespective of age is generally preferred to an estimation based on body weight [32]. The normal diet of healthy adults satisfies this requirement [8].

Physical work, surgical intervention, injury, burns and grave infections, those of the gastrointestinal tract in particular, may double the pantothenic acid requirement of adults.

Growing organisms need much pantothenic acid [39]; their requirement is presumably not significantly inferior to that of adults [10, 37]. Embryonic tissues are known to contain a considerable amount of pantothenic acid, and it is likewise known that such tissues need much of the substance.

Data as to the pantothenic acid requirement of premature babies, newborns and infants are not available. Nor have exact computations been made in respect of children; all we know in this respect is that their consumption (and presumably also their requirement) of pantothenic

acid does not depend on the protein content of the food [9].

Our investigations concerning the pantothenic acid requirement and supply of infants [42] were based on purely theoretical foundations, so that their results are by no means conclusive. When establishing the amount of pantothenic acid needed by healthy infants one has to rely on the physiological state, and should disregard the effect of antibiotics [2], sulpha drugs [30], pantothenic acid antagonists [28, 30, 54], and sorbitol [22], which modify the requirement under experimental conditions.

To establish the pantothenic acid requirement of infants we took it for granted that the highest amount needed was 5 mg/1000 cal., the tenfold of the actual thiamine requirement [16]. After dividing healthy infants in five age and weight groups, (i) premature, 2500 g; (ii) newborn, 3200 g; (iii) 3—4 months old, 5000 g; (iv) 6 months old, 6400 g; (v) 10 months old, 9000 g, we computed the optimum daily caloric requirement which amounted to 120 calories per kg of body weight in prematures and to 100 cal/kg in the other groups. The required amount of calories allowed to calculate the necessary amount of pantothenic acid on the basis of the aforementioned ratio. Accepting the data of HOLT [23] according to which the thiamine requirement of infants varies between 0.2 and 0.4 mg daily, we multiplied this figure by ten so as to arrive at the required amount of pantothenic acid. Values so obtained, as also their means, are assembled in Table 2.

TABLE 2

Age group	Pantothenic Acid Requirement, mg/day		
	With reference to		Mean values
	calories	thiamine	
Premature babies	1.5	2	1.7
Newborn babies	1.6	2	1.8
3—4 month old infants	2.5	3	2.7
6 month old infants	3.2	3	3.1
10 month old infants	4.5	4	4.2

With a view to studying whether the usual diet of infants contained the required amount of pantothenic acid, we have computed the quantity of ingested pantothenic acid.

As regards standard nutrition in the various age groups, we considered exclusively breast milk for group (i); three kinds of diet, separately, for each of groups (ii), (iii) and (iv), *viz.* (a) breast milk alone, (b) mixed diet, (c) artificial nutrition; artificial nutrition alone for group (v). Artificial nutrition was taken to consist of a milk formula 2 in 3, semolina pudding,

TABLE 3

Age group	Requirement	Uptake	Extent to which intake covers requirement %
	of pantothenic acid (mg per day)		
Premature babies	1.7	0.8	44
Newborn babies	1.8	1.0—1.1	58
3—4 month old infants	2.7	1.5—1.7	59
6 month old infants	3.1	4.0	129
10 month old infants	4.2	5.8	136

vegetables, egg yolk, meat, liver and fruit, in the order and quantity usual in Europe.

As can be seen from Table 3, the usual diet of infants under 6 months does not contain sufficient pantothenic acid, irrespective of whether the food is natural, mixed or artificial. The fact that such a diet does not give rise to pantothenic acid deficiency is presumably due to that newborn infants are able to utilize their congenital stores of pantothenic acid for weeks, even months; resort to these stores, combined with biosynthesis, compensates for exogenous shortage. The assumption that newborns possess prenatal stores of pantothenic acid is supported by the observation that the excretion of pantothenic acid is relatively high during the first days of extrauterine life [6], and that the pantothenic acid level in umbilical cord blood is many times that of maternal blood [1].

II.

The pantothenic acid supply of the organism is realiably indicated by the blood level which also provides information on the supposed congenital stores in young infants.

The human organism absorbs pantothenic acid through the intestines. Before being absorbed, bound pantothenic acid is split enzymatically, while no active biological process is needed for the absorption of free pantothenic acid. Pantothenic acid ingested in the bound form is split only as far as the pantothenic-acid phosphates and is absorbed like thiamine, i.e. in a phosphorylated form.

Pantothenic acid, after being absorbed, is either stored or excreted. Storage takes place in the cells, mainly in the liver, in the form of coenzyme A (CoA in the following). Pantothenic acid, a component of CoA, is involved in the conversion of choline into acetylcholine, in the breakdown of carbohydrates, in the synthesis of proteins, in the synthesis and decomposition of lipoids, as well as in the production of steroids and cholesterol.

Human erythrocytes contain pantothenic acid in the form of CoA; it is attached to albumin in the circulating plasma. According to deter-

minations made with the classical *(Lactobacillus arabinosus)* method, the pantothenic acid level in the blood of healthy adults amounts to 10—38 μg/100 ml. Japanese authors using a modified technique found higher values [27]. As no earlier investigations in this respect had been made, we determined in Finland the serum pantothenic acid-

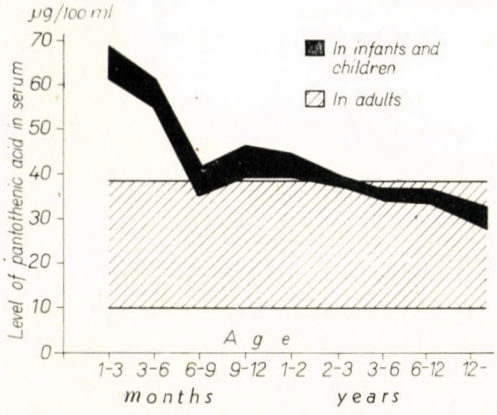

FIG. 1

level of 83 healthy infants and children with the *Lactobacillus arabinosus* method [45]. As can be seen from Fig. 1, the concentration of pantothenic acid was found to be much higher during the first 6 months of extrauterine life than that of adult persons. Values gradually diminished with advancing age and reached the adult level at about the 2nd year of life.

Our results support, therefore, the assumption concerning the pantothenic acid stores of newborn infants and supply a basis of comparison for a reliable estimation of the available amount of vitamin B in infants and children.

III

The problem of pantothenic acid-deficiency is of importance in both experimental medicine and human pathology.

Experimental deficiency can be induced by a diet lacking in pantothenic acid, by the administration of anti-vitamins, or by a combination of the two methods.

Pantothenic acid deficiency induced in animals has been found to damage the embryonic tissues and thus cause developmental anomalies [13]. Apart from being teratogenic, the effect manifests itself in postnatal life with a number of pathological changes, e.g. hypotrophy, dermatitis, alopecia, change of hair colour, inflammation of the mucous membranes, neural lesions, reduced renal filtration, increased susceptibility to infections, and — a very important phenomenon — decreased synthesis of adrenocortical steroids.

Experimental deficiency of pantothenic acid in healthy adults [20] gives likewise rise to various pathological manifestations, such as weakness, adynamy, anorexia, obstipation, irritability, paraesthesias, increased tendon reflexes, tachycardia, orthostatic hypotension, decreased adrenocortical activity, hypacidity, hypocholesterolaemia, etc. Recent experiments [21] have shown that — as in animals [24, 53] — pantothenic acid deficiency in human subjects leads to a decrease in the production of specific antibodies and to reduced immunological defence.

Spontaneous deficiency of pantothenic acid may also occur in humans. Certain conditions are now regarded as typical forms of apantothenosis, e.g. the so-called burning feet syndrome, characterized by paroxysm of burning sensation in the feet, their rubescence, cyanosis and desquamation. This syndrome was often encountered in the Spanish civil war and in Far-Eastern P. O. W.-camps. The occurrence of the syndrome in infants and children is extremely rare. The condition promptly responds to the administration of pantothenic acid. Secondary pantothenic acid-deficiency in adults has been observed in connection with sprue, colitis, pneumonia, diphtheria, beriberi and pellagra.

Foetal or embryonic damage due to lack of pantothenic acid in the maternal diet has not been described. This is not surprising considering that none of the known developmental anomalies have been traced to maternal avitaminosis alone [51].

Pantothenic acid-deficiency in humans may be due to exogenous, enterogenous or endogenous factors. The deficiency is exogenous if the diet does not contain sufficient pantothenic acid; it is enterogenous if the mechanism of absorption or that of biosynthesis is inhibited, further, if intestinal parasites consume the ingested or produced pantothenic acid; it is endogenous if the available amount of pantothenic acid is sufficient, its absorption is satisfactory, but the utilization of the absorbed vitamin is disturbed. It occurs occasionally in association with some organic diseases, especially those involving the liver or the metabolism, further intoxications and allergic conditions, and sometimes as the side effect of certain drugs.

Pantothenic acid deficiency may be absolute or relative; the latter occurs when the organism's requirement is increased, e.g. in infants and children, thus in the period of growth. Pantothenic acid deficiency is accompanied by a low blood level and decreased urinary output. The decrease is pathological if less than 1 mg per day is excreted [38, 48]. A state of deficiency should be conjectured if after a pantothenic acid load a considerable part of it is retained.

The excretion of pantothenic acid is so evenly distributed over the different parts of the day that this factor can be neglected in the examinations which usually do not last more than 4 hours [14]. The average concentration of pantothenic acid in the urine of healthy adults varies from 2 to 9 μg/ml [13, 14], while children excrete between 1.3 and 4.5 mg daily [29, 34, 35]. Healthy individuals excrete the entire amount of introduced pantothenic acid within 4 hours, whereas persons suffering from pantothenic acid deficiency retain part of the whole of it [4, 11, 13]. Retention of pantothenic acid after intravenous administration of calcium pantothenate (1 mg per kg) was observed by us in an infant and two children (one patient had Salmonella enteritis, the other pneumonia, the third chickenpox). However,

the number of our cases was not sufficient to justify general conclusions. Pantothenic acid load, a method recommended by other authors [11] and tested by us seems — like paediatric tolerance tests with other members of the vitamin-B complex [15] — suitable for demonstrating apantothenosis.

We observed a low pantothenic level in the serum of 21 patients (5 infants and 16 children) of whom 18 were boys and 3 girls (Fig. 2). Blood was drawn, as a rule, during the first 48 hours of the disease; the method of assay was the same as that employed in the case of healthy individuals.

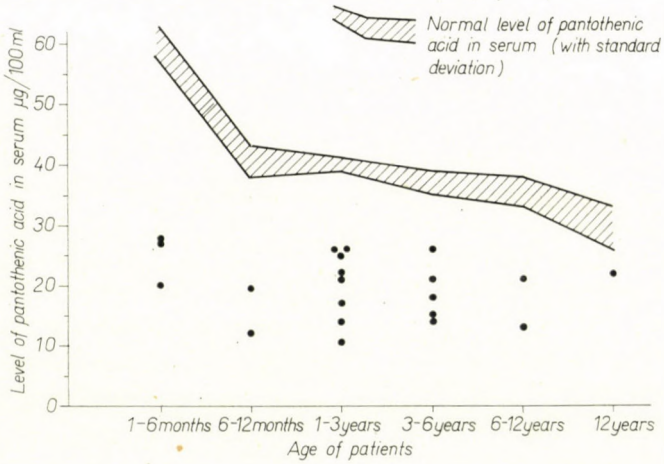

FIG. 2

Since these analyses were not specific, no simultaneous excretion and tolerance tests were performed. Although some of the phenomena described in connection with experimentally induced pantothenic acid deficiency were observed in these patients (weakness, adynamy, obstipation, etc.), these symptoms were not more pronounced than what was attributable to the primary disease.

As regards the aetiology of the transitory and not too marked pantothenic acid-deficiency observed in our patients, we can summarize our conclusions as follows.

Exogenous factors were not involved.

Enterogenous factors may have played a role in those 4 patients (1 infant, 3 young children) who had been treated for 3 to 17 days with broad-spectrum antibiotics and sulphonamide derivatives for enterocolitis or upper respiratory infection. The disturbed biosynthesis may have been accompanied by decreased absorption in the patients suffering from enterocolitis.

Endogenous factors were presumably predominant in the remaining 17 patients.

Ten of these 17 patients received no drug treatment prior to the withdrawal of blood. so that — excluding the possibility of exogenous or enterogenous factors being involved — the decrease in the blood level of pantothenic acid must have exclusively been due to metabolic and organic disorders caused by the primary disease. Allergic conditions (eczema and urticaria) were present in four cases, influenza in three cases, mumps, pertussis and serous meningitis in one case, each. The low blood level in the four allergic patients was especially noteworthy since it supported some recent observations concerning the disturbance of pantothenic acid metabolism in allergic adults [49].

Of the other 7 children, whose pantothenic acid-deficiency was thought to be likewise of endogenous origin, six had been treated, prior to blood sampling, with penicillin for respiratory infection, and one child with atropine for asthmatic bronchitis. Let us note that a moderate reduction of the pantothenic acid serum level has been observed in adults in connection with penicillin treatment [5], and that pantothenic acid-deficiency has been described as a concomitant of pneumonia However, when establishing a direct connection between the low blood level of our patients and their treatment with penicillin, one has to bear in mind that determinations made in these cases may have been greatly disturbed by the presence in the blood of the antibiotic.

IV

Pantothenic acid has been employed in therapy since 1940, partly in the form of its calcium salt, partly in that of its alcohol derivative (pantothenyl alcohol), and partly in combination with other vitamins.

Prophylactic administration of pantothenic acid to infants and children is justified if there is a danger of pantothenic acid deficiency, e.g. in cases of postoperative starvation or lasting parenteral feeding, gastrointestinal and other infectious diseases, metabolic diseases (especially those affecting adrenocortical and thyroid activity), and, finally, whenever an infant or child is subjected to prolonged treatment with sulphonamides, antibiotics affecting enteric biosynthesis, or some antituberculous drug such as streptomycin, isoniazid or viomycin. A prophylactic dose of 5 to 15 mg of pantothenic acid daily has been found satisfactory in paediatrics.

The therapeutic dose of pantothenic acid is the double or threefold the prophylactic one; such treatment appears to be indicated chiefly in cases of intestinal paralysis.

Experimentally induced pantothenic acid deficiency is accompanied by weak peristalsis and intestinal tone. The amount of acetylcholine contained in the intestinal wall fluctuates, on the mucosa ulcers appear, and absorption is impaired. The effect of pantothenic acid deficiency on adrenocortical activity gives rise to changes in the electrolyte household,

which likewise affects intestinal motility. Administration of pantothenic acid prevents such manifestations.

Reports on the treatment of paralytic ileus in adults [12, 17, 18, 36] have encouraged us to apply pantothenic acid therapy in our paediatric patients [40]. Calcium pantothenate was given in the form of infusions (100 mg per 500 ml) or intravenously, less frequently intramuscularly (in a dose of 50 mg for infants and 100 mg for children). The dosage was repeated at 4 to 6-hour intervals, if necessary. Rectal tube, glycerol suppositories or enema completed the treatment. Pantothenic acid therapy proved successful in 75 per cent of our patients during the first year of its introduction; meteorism decreased or disappeared, and intestinal passage was resumed in 24 hours. Particularly satisfactory results were obtained in dehydrated infants, further in children with postoperative intestinal paralysis. Since that time, pantothenic acid has been applied with invariably good results in every case of ileus. Our observations have been corroborated in several institutes [50].

As regards the mechanism through which pantothenic acid exerts its effect on the intestinal tract, our investigations [43, 44] allowed the following conclusions. Pantothenic acid applied *in vitro*, makes the isolated rat intestine to contract and increases its sensitivity to acetylcholine. Intestinal contraction induced by pantothenic acid is inhibited by atropine and papaverine, while barium chloride and nicotine spasms are enhanced by the simultaneous administration of pantothenic acid. Pantothenic acid thus produces its effect partly through an acetylcholine mechanism and partly independently thereof. The existence of the acetylcholine mechanism is borne out by the fact that the sensitivity to acetylcholine of the intestines is increased by pantothenic acid, further by the antagonistic effect of atropine and the in-loco incorporation of pantothenic acid into CoA (intensification of acetylcholine synthesis); the existence of a mechanism operating independently of acetylcholine is indicated by the said property of pantothenic acid to enhance barium chloride and nicotine spasm, further by the antagonism between pantothenic acid and papaverine.

Apart from these mechanisms, pantothenic acid plays a certain role in living organisms by virtue of its effect upon the balance of electrolytes *via* the adrenal cortex, and — in states of deficiency — as a factor of substitution. Chronic treatment of rats did not induce perceptible changes in intestinal passage.

It has been mentioned that the pantothenic acid level was found to be low in the serum of four of our patients suffering from allergic conditions. Relying on the assumption that allergic conditions are associated with a disturbance of pantothenic acid utilization and its consequent deficiency, TUFT [49] applied pantothenic acid treatment of allergic adults with satisfactory results. A certain antiallergic (pharmacody-

namic? substitutive?) action of pantothenic acid has been recognized by several authors. Since no investigations have so far been made in this respect, we carried out experiments with a view to ascertaining the effect of pantothenic acid on the intracutaneous and percutaneous histamine test [47].

The examinations were made in the winter and spring months in 3 to 12-year old children who received no drug treatment, were offered a normal diet and remained in bed during the tests. The persons carrying out the examinations as also the appliances and tools employed were the same in all experiments; even the chemicals were taken from the same batch throughout, and — in order to prevent errors due to the well-known diurnal fluctuations of skin reactions — all examinations were carried out at the same hour of the day.

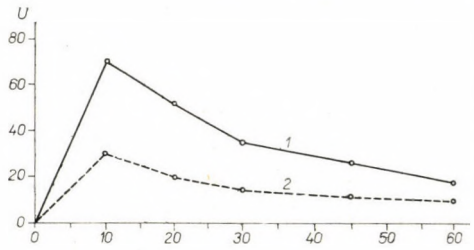

FIG. 3. 1) Histamine reaction before treatment with pantothenic acid; 2) Histamine reaction after treatment with pantothenic acid

In these experiments with self-control pantothenic acid reduced the intensity of the skin reaction by 20 to 50 per cent in all of the four experimental groups of 9, 5, 5, and 5 children, respectively. This effect was observed irrespective of whether pantothenic acid had been administered by the intracutaneous, percutaneous, oral or intravenous route. Fig. 3 illustrates the antihistamine effect of orally, Fig. 4 that of intravenously introduced pantothenic acid. (The intensity of the skin reaction was determined by means of cellophane; 1 unit = 0.16 sq. mm.)

We have, in addition, examined the effect of pantothenic acid in preventing radiation injury [46]. Two hundred mice of 25 to 30 g body weight, originating from the same strain, divided into four groups of 50 animals each, were used. Group I received total body irradiation with X-rays; group II received pantothenic acid during a week and was exposed to irradiation after an interval of a further week; group III was exposed to X-rays immediately after treatment with pantothenic acid for a week; group IV was first irradiated and then treated with pantothenic acid for a week. Treatment consisted in the subcutaneous administration of 0.5 mg/day of calcium pantothenate. All animals were simultaneously irradiated (500 r, 0.5 mm Cu filter, 180 kV, focus = 50 cm). Surviving animals were observed during 30 days after the irradiation.

The results are shown in Fig. 5. As can be seen, the rate of survival was highest in group II where half of the animals were still alive on the 21st day. In group I (control), half

of the animals died within 8 days. It follows that, as compared with the controls, survival was prolonged by 200 per cent. No, or no significant, effect of pantothenic acid was observed in groups III and IV. Due to its metabolic key position, pantothenic acid thus seems to induce slow biochemical processes which ensure enhanced protection against radiation injury. The capacity of pantothenic acid to protect the epithelium, to promote tissue regeneration, protein synthesis, antibody production and corticoid synthesis, further its effect on capillary activity, as also its anti-allergic properties, may all be involved in those biochemical processes.

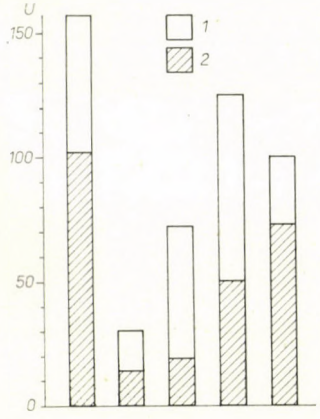

FIG. 4
1) Histamine reaction before intravenous administration of pantothenic acid
2) Histamine reaction after intravenous administration of panthotenic acid

Let us in conclusion touch upon two further therapeutical uses of pantothenic acid. As proved by experimental results and clinical observations, pantothenic acid mitigates the side effects and toxicity of several antibiotics produced from Streptomyces, such as streptomycin, dehydrostreptomycin, neomycin, kanamycin and viomycin [33].

Another use of pantothenic acid is its local application in aerosol form, administered in combination with physiological saline, surface active drugs, hyaluronidase, hydrocortisone and antibiotics. This treatment has been found by us to promote mucosal regeneration, and to ensure favourable results in cases of malignant tracheobronchitis and asthmatic bronchitis.

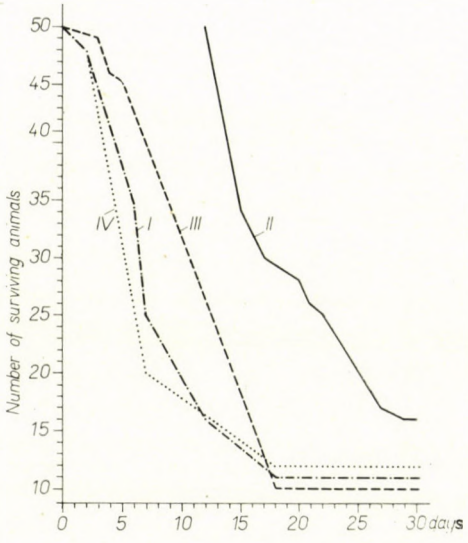

FIG. 5

SUMMARY

After a review of the principal data in the pertaining literature, some points have been discussed in detail: (i) pantothenic acid requirements in infancy and childhood; (ii) the blood pantothenic acid level in infants and children; (iii) the problem of panto-

thenic acid deficiency, with especial regard to certain paediatric conditions associated with a low blood level; (iv) the antiallergic effect of pantothenic acid; and (v) its effect on the tolerance to radiation injury.

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Dr. I. Szórády
Gyermekklinika
Szeged, Hungary.