17198. Relief from Pruritus Following upon Administration of Adenylic Acid.

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In December, 1948, muscle adenylic acid was administered to a group of patients suffering from Hodgkin's disease in the hope that it might possibly have a beneficial influence upon their physical energy,† depletion of which is one of the disabling effects of this disease. Though the experiment proved a failure in this respect, a totally unexpected and gratifying result ensued: the only two patients of the group who had pruritus reported that this had completely disappeared. In an effort to establish whether or not this was mere coincidence the co-operation of colleagues‡ was enlisted and medication extended to include persons afflicted with pruritus of diverse etiology.

In all, 36 patients were treated with the sodium salt of adenosine-5-monophosphate,§ injected intramuscularly in a solution of 20 mg in 1 cc of water. The optimum dosage had to be determined by trial and error. Massive doses—100 mg hourly for 6 consecutive hours for a period of 11 days—was given to 4 patients (Nos. 1, 12, 28 and 35 in the table) and produced negative results on pruritis in all except case No. 28. Dosage of 20 mg hourly for 5 consecutive hours over a period of 3 days yielded fairly uniform results, including response by Case No. 1, who had not responded to the massive doses; Cases 12 and 35 were not retreated. Approximately half of the patients responded to the therapy within 24 hours, the others in from 2 to 7 days.

In 5 instances the pruritus was associated with diabetes (4 cases under insulin control and one as yet untreated), 9 with Hodgkin's disease, one with carcinoma of the ovary, one with dermatitis due to hair-dye sensitivity, 18 were idiopathic, and 2 occurred post partum. In almost every instance the pruritus was severe (inducing in some of the sufferers talk of suicide) and had previously been subjected to numerous therapies: salves, injections, x-ray, ultra violet rays, etc. Distribution was general in 20 instances, limited to anus or genitalia in 12 instances, to the legs, feet and hands in 4 instances. Skin of many of the patients was excoriated, in some instances severely so.

Results. Results were negative for 6 patients and positive for 30. There were 9 cases of complete subsidence, 14 of marked improvement, 5 of moderate improvement, and 2 of mild improvement. Not enough time has yet elapsed to make possible the assembling of statistics as to how enduring these results may be. Five patients (2, 28, 29, 30, 36) have remained free of recurrence or maintained the state of improvement from discontinuance of therapy to date, this period varying from one to four months; others suffered recurrence within 24 hours to one month. Three (16, 28, 29) who suffered recurrence and were retreated reacted as favorably to the remedication as to the initial medication.

The only toxic symptom—a sensation of inability to breathe freely—was short-lived and experienced by those receiving massive dosage (1, 12, 28, 35).

Discussion. Considering the fundamental importance of adenylic acid to biologic mechanisms such as glycolysis, the Kreb cycle, muscle contraction, etc., it is surprising that so little is known concerning the

* Supported in part by grants from The National Cancer Institute of The U. S. Public Health Service, The American Cancer Society, and The Damon Runyon Memorial Fund.

† This was done at the suggestion of Dr. Kurt Stern, Brooklyn Polytechnic Institute.

‡ Drs. Lloyd Craver, A. Susinno, Richard Kennedy, O. Canizares, A. Shapiro, J. Corr, W. Stankard, and F. Jost, to whom we express our sincere appreciation.

§ The preparation used was "My-B-Den," made and supplied by Ernst K. Bischoff Co., Inc.

TABLE I.
Summary of Clinical Data on 36 Patients with Pruritus Who Were Treated with Adenylic Acid.

		Pruritus				Results produced by Administration of My-B-Den		
Pt. No. and age	Sex	Etiology	Distribution	Severity	Duration	Relief	Appeared, day	Duration
1—41	F	Idiopathic	Vulva	4+	7 mo.	4+	2nd	1 wk*
2—35	F	”	”	4+	4 wk	4+	3rd	4 mo.*
3—30	F	”	”	4+	11 yr	0	—	—
4—56	F	”	”	4+	1 yr	4+	3rd	2 wk
5—60	F	”	”	4+	15 yr	3+	1st	2 wk*
6—74	M	”	Anus	4+	4 mo.	3+	1st	2 wk*
7—56	F	”	”	3+	3 wk	3+	1st	3 days
8—43	M	”	”	4+	8 yr	4+	2nd	1 wk*
9—42	M	”	”	4+	3 yr	3+	1st	1 wk*
10—39	M	”	”	4+	12 yr	3+	1st	1 wk*
11—56	M	”	Generalized	4+	6 mo.	4+	1st	3 wk*
12—35	F	”	”	4+	30 yr	0	—	—
13—87	F	”	”	4+	yrs	0	—	—
14—45	F	”	”	4+	6 mo.	2+	3rd	1 wk
15—43	F	”	”	4+	1 yr	2+	1st	No follow-up
16—22	M	”	”	3+	12 yr	3+	2nd	2 wk
17—67	M	”	”	4+	5 mo.	2+	3rd	2 wk
18—69	F	”	”	4+	5 yr	2+	4th	3 wk
19—30	F	Postpartum	”	4+	2 mo.	3+	1st	3 wk
20—32	F	”	”	4+	4 days	3+	7th	1 wk
21—62	F	Cancer	”	4+	6 mo.	3+	1st	3 wk*
22—64	F	Hair dye sens.	”	4+	10 days	0	—	—
23—65	M	Diabetes	Feet	4+	6 mo.	3+	1st	3 wk
24—86	F	”	Generalized	2+	yrs	1+	3rd	2 wk
25—60	F	”	Vulva	4+	4 mo.	2+	2nd	†
26—55	F	”	”	4+	9 mo.	3+	1st	2 wk*
27—67	F	”	Legs	2+	2 mo.	4+	3rd	3 mo.
28—39	M	Hodgkins	Generalized	4+	1 yr	4+	1st	5 wk
29—39	M	”	Hands	3+	1 yr	4+	6th	1 mo.*
30—49	M	”	Generalized	4+	1 wk	4+	3rd	1 mo.*
31—48	F	”	”	4+	6 yr	0	—	—
32—43	M	”	”	3+	1 mo.	3+	3rd	2 wk
33—52	F	”	”	4+	1½ yr	1+	1st	1 wk*
34—39	M	”	Legs	3+	7 mo.	3+	1st	1 wk*
35—40	F	”	Generalized	4+	3 yr	0	—	—
36—42	F	”	”	3+	1 mo.	3+	2nd	4 wk*

* Indicates patient was still free of pruritus at time this table was made.
† Only with medication. 20 mg hourly for five consecutive hours per day since May 7, '49.
4+ indicates complete relief from pruritus.

clinical disorders resulting from pathologic-physiologic disturbance involving metabolism of adenylic acid and related substances.

We feel that the results which were obtained with adenylic acid are too consistent to be attributable to chance and that these results may be interpreted to mean that pruritus is one indication of adenylic acid deficiency. Adenylic acid has previously been used therapeutically[1-9] but so far as we know no one has pointed out the relationship between its administration and subsidence of pruritus. Beneficial effects on skin disorders have been

[1] Bean, W. B., *Med. Clin. N. A.*, March 1943, **27**, 483.

[2] Carlström, B., and Olle Lövgren, *Acta Medica Scandinavica*, 1943, **115**, 568.

[3] Carlström, B., and Olle Lövgren, *Acta Medica Scandinavica*, 1942, **110**, 230.

[4] Dietrich, S., and Schwiegk, H., *Dtsche. med. Wchnschr.*, 1934, **60**, 967.

[5] Herbrand, W., *Dtsche. med. Wchnschr.*, 1937, **63**, 1841.

[6] Holyroyd, F. J., *West Virginia Med. J.*, 1940, **36**, 261.

[7] Rothmann, H., *Rev. Gastroenterol.*, 1942, **9**, 117.

[8] Spies, T. D., Bean, W. B., and Vilter, R. W., *Ann. Int. Med.*, 1940, **13**, 1616.

[9] Vilter, R. W., Bean, W. B., and Spies, T. D., *J. Lab. and Clin. Med.*, 1942, **27**, 527.

alluded to but not expanded upon.[3] We have not hitherto concerned ourselves particularly with this specialized field and can only state that several of our patients made voluntary mention of the fact that their skin had become softer and less dry and that excoriations due to scratching had healed upon subsidence of the pruritus some whose pruritus had not entirely disappeared found that scratching failed to produce the excoriation which had been the result previous to treatment.

Though there is much yet to be done clinically and in the laboratory before the full implications of adenylic acid administration to human beings can be completely evaluated, we feel that the results to date are sufficiently good to make broader experimentation desirable, and hence to warrant passing on our experiences to other workers.

Summary. Thirty-six patients suffering from pruritus of diverse etiology were treated with adenylic acid. In thirty instances there was a subsidence of the pruritus ranging from complete to mild. So far we have been able to find in the rather extensive literature no reference to the beneficial effect of adenylic acid upon pruritus.

Received June 7, 1949. P.S.E.B.M., 1949, **71**.

17199. Chemotherapy of Leukemia. IV. Effect of Folic Acid Derivatives on Transplanted Mouse Leukemia.*

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Since the first report of promising results in the clinical treatment of acute leukemia with 4-amino-pteroylglutamic acid,[1] this drug[2,3] and two other related compounds[3,4] have been reported to be active against certain strains of transplanted mouse leukemia. These clinical and experimental findings suggested the advisability of screening a large number of compounds related to pteroylglutamic acid (PGA) against transplanted mouse leukemia. This series included not only compounds closely related in structure to folic acid, but also pyrimidines, pteridines and purines. The results of the preliminary testing of 90 such compounds are herewith reported.

Method. The technic for evaluation of the chemotherapeutic activity of a given drug by means of its ability to prolong the survival time of mice with transmitted leukemia has been described previously.[3]

In a typical experiment, 240 mice of the inbred Akm stock were injected intraperitoneally with 0.1 cc of a saline suspension of leukemic spleen so diluted that 0.1 cc contained 1,000,000 cells. Leukemia Ak 4,[5] a relatively acute strain, was used in these par-

* This investigation was supported, in part, by a research grant from The National Cancer Institute of The National Institute of Health, United States Public Health Service, and, in part, by a research grant from The American Cancer Society.

† Fellow of The American Cancer Society, recommended by the Committee on Growth of The National Research Council.

1 Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., Jr., and Wolff, J. A., *New England J. Med.*, 1948, **238**, 787.

2 Law, L., Abstract, Cancer Research, 1949, in press.

3 Burchenal, J. H., Burchenal, J. R., Kushida, M. N., Johnston, S. F., and Williams, B. S., *Cancer*, 1949, **2**, 113.

4 Burchenal, J. H., Bendich, A., Brown, G. B., Elion, G. B., Hitchings, G. H., Rhoads, C. P., and Stock, C. C., *Cancer*, 1949, **2**, 119.

5 Burchenal, J. H., Biedler, J. L., Nutting, J., Stobbe, G. D., to be published.