THERAPEUTIC POSSIBILITIES OF PARA-AMINOBENZOIC ACID *

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Para-aminobenzoic acid (PABA) is generally considered to be a member of the B-complex group of vitamins, and is known to be a constituent of many food substances. 1, 2 Although it is a chemical which has long been known, this substance has been of medical interest only during the past decade. From the available literature, however, the principal interest has been largely confined to studies of its effects on bacterial metabolism, pigment metabolism, and other fields of laboratory investigation. The first important clinical use of PABA was evolved during World War II, when it was found to be of value in the treatment of several of the rickettsial diseases. 3 More recently, a series of studies has been directed toward the investigation of further therapeutic possibilities of PABA. Results have been encouraging in a number of diverse conditions of unknown etiology. For example, a beneficial effect has been noted in lymphoblastoma cutis, 4, 5 in certain forms of lupus erythematosus, 6, 7, 8 in active dermatomyositis, 7, 8 in scleroderma, 5, 9 and dermatitis herpetiformis. 7, 10 In addition, it has been observed that PABA will cause a striking fall in the leukocyte counts of patients with chronic myelogenous leukemia. 11, 12 The purpose of this communication is to review briefly the results obtained with PABA therapy in each of these disorders, and thereby direct attention to the apparent broad range of activity of the compound.

For administration to patients, it has been found that para-aminobenzoic acid (PABA) is best tolerated as a neutral salt. This may be in the form of sodium para-aminobenzoate (NaPAB) † or potassium para-aminobenzoate (KPAB). † The latter form (KPAB) is particularly useful in patients who may develop edema on the sodium preparation. KPAB has been used extensively without evidence of potassium intoxication. It should not be administered, however, in the presence of far advanced renal insufficiency. At present, only NaPAB is available in tablet form. ‡ For this series of studies, PABA was placed in solution by conversion to KPAB with potassium bicarbonate. The final volume was adjusted to make a 10 per cent solution of KPAB. A 10 per cent solution of NaPAB was prepared in a similar fashion. These preparations have a yellow or amber color and

† The solutions of NaPAB and KPAB administered to the cases reported herein were prepared from crystalline para-aminobenzoic acid which was generously contributed by Merck and Co., Rahway, New Jersey.
‡ Tablets of “PABA Sodium” were kindly supplied for use in these patients by Wyeth and Co., Philadelphia, Pennsylvania.
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darken upon exposure to ultraviolet light. The solutions of PABA salts should, therefore, be kept in a dark place, preferably refrigerated. The compounds are administered orally, in doses of one to four grams (10 c.c. to 40 c.c. if the 10 per cent solution is used), at intervals of two to three hours. Most patients prefer to take the solution with a small amount of milk, fruit juice, ginger-ale, or other soft drink. The size of the dose, the total daily dosage, and the intervals between doses are influenced by the size of the patient, by the clinical entity being treated, and by the clinical status of the individual patient. PABA is rapidly excreted in the urine. This is of importance in treating certain disease entities where it is desired to maintain a high blood level of the compound. The optimal dosage schedules have not yet been determined for the several clinical conditions to be discussed below. That there is considerable latitude in the amount of PABA required, however, will be evident from the respective case histories.

PABA in Leukemia

Study of the effect of large doses of PABA in patients with leukemia was an outgrowth of the work in rickettsial diseases. The mode of action of PABA on the respective intracellular rickettsial organisms is not completely understood. It appears, however, that PABA inhibits rickettsial multiplication by increasing the metabolism of the parasitized cells. This concept of the mechanism of action of PABA in the rickettsioses led to the thought that cells of disordered metabolic function, i.e., neoplastic cells, might not be able to adapt to a substrate containing PABA in high concentration. The latter hypothesis was tested in patients with leukemia. Briefly, it was found that PABA would lower the leukocyte count in chronic myelogenous leukemia. This effect, however, could be maintained only through the continued administration of large amounts of PABA. Furthermore, concomitant clinical improvement was slight and temporary. For these reasons it was concluded that PABA therapy is not to be considered a practical adjunct to the treatment of leukemia. It is to be emphasized that the same opinion is held at this time. The following case report, hitherto unpublished, is given to illustrate the type of response obtained with PABA in chronic myelogenous leukemia. An additional reason for the selection of this particular case will become apparent in the succeeding section.

Case Report

A 43 year old white male was admitted to the University Hospital on May 27, 1947, with the chief complaint of pain in the abdomen. During the preceding year there had been a gradual loss of 20 pounds in weight. Ease of fatigue had been present for six months, and symptoms of hypermetabolism for four months. About two weeks prior to admission, the patient experienced the sudden onset of left upper quadrant pain. This was sharp in character and became more severe on inspiration. The
Fig. 1a.

Fig. 1b.
pain radiated to the left shoulder area. He had consulted his physician who referred him to the University Hospital for therapy.

The past history was of no interest except for the occurrence of a skin lesion which appeared on the left thigh in 1927. This lesion was papular and erythematous in nature, and was mildly pruritic. It persisted for several years in spite of treatment and finally disappeared spontaneously. Four years ago a similar lesion appeared on the right calf. This lesion remained essentially unchanged in size and character to the present admission.

Examination of the skin revealed a well demarcated, 6 by 8 cm., raised, erythematous lesion over the medial surface of the right calf (figure 1a). The lesion was superimposed over a mass of varicose veins. Several small lymph nodes were palpable in the axillae and in the inguinal regions. The liver was enlarged to three fingers' breadth below the right costal margin. It was firm and non-tender. The spleen was very large, extending 20 cm. below the left costal margin in the mid-clavicular line. The remainder of the examination was noncontributory.

Pertinent laboratory findings were as follows: hemoglobin 11 grams per cent; red blood cells 3,500,000; leukocytes 321,000 per cubic millimeter. The white cell differential revealed: 1 per cent basophiles, 2 per cent eosinophiles, 3 per cent lymphocytes, 3 per cent promyelocytes, 32 per cent myelocytes, 17 per cent metamyelocytes and 41 per cent neutrophiles, of which 16 per cent were nonsegmented. The basal metabolic rate was +64 per cent; plasma cholesterol level 112 mg. per cent. Repeated urine analyses showed a small amount of albumin and 6 to 10 white cells per high power field.
FIG. 2b.

FIG. 3.

CHRONIC MYELOGENOUS LEUKEMIA TREATED WITH PABA AND URETHANE
After the patient was placed on PABA therapy, a positive test for reducing substances was noted. A biopsy specimen was taken from the skin lesion on the right calf on June 6, 1947. The pathologist reported this to be "premycotic stage of mycosis fungoides; lymphoblastoma cutis" (figure 2a).

While in the hospital the patient was given NaPAB, 4.0 grams every two hours, from June 14, through July 15, 1947. On July 12, the administration of urethane was begun, 3 grams daily. This was discontinued on July 15 because of nausea and vomiting. With this course of therapy, the patient's leukocytes decreased from an initial count of 321,000 to 8,700 per cubic millimeter on July 15. The white cell differential count showed 3 per cent blasts, 9 per cent myeloblasts, 4 per cent metamyelocytes, 19 per cent nonsegmented neutrophils, and 45 per cent segmented neutrophils, 1 per cent monocytes, 10 per cent small lymphocytes, 2 per cent large lymphocytes, 2 per cent eosinophils, and 5 per cent basophils. The basal metabolic rate had declined to 34 per cent on July 18. The lesion which was present on the right calf had gradually become flat, the erythema faded, and the pruritus ceased (figure 1b). Another biopsy was taken from an area adjacent to the site of the previous specimen. The pathologist noted "the presence of small perivascular infiltrations which would not have been considered diagnostic without previous knowledge of the case" (figure 2b). The patient was discharged with instructions to resume urethane medication a few days thereafter. This was done and the patient's leukemic process has since been well controlled on urethane therapy. In the accompanying chart (figure 3) are given the patient's leukocyte counts and the red blood cell and white blood cell hematocrit values as related to the administration of PABA and urethane.

**PABA in Lymphoblastoma Cutis**

The patient with chronic myelogenous leukemia described above had a localized infiltrated skin lesion which was diagnosed on biopsy as "premycotic phase of mycosis fungoides." This lesion was observed to regress during the period of PABA therapy. Since lymphoblastoma cutis is considered by many to be a primary lymphoblastoma of the skin, it was deemed justifiable to administer PABA to patients with this disorder. The results of therapy in six subjects have been detailed elsewhere. All experienced relief from pruritus and objective improvement of the skin. This was characterized by diminution in erythema and in the degree of infiltration. Treatment with NaPAB was eventually discontinued in four of the cases because of the development of edema. In two patients, however, edema was circumvented by the administration of KPAB with continued improvement. The case presented below was diagnosed from the history and clinical findings as probable lymphoblastoma cutis. It illustrates the character of change which follows KPAB therapy in patients with this disorder.

**Case Report**

A 40 year old white male entered the University Hospital on December 13, 1948, complaining of a dermatitis. Ten months previously he had first noted a small, red, scaly, and pruritic area on the lateral aspect of the left ankle. There was a gradual spread of involvement until the entire surface of the body had become red, pruritic, with weeping and crusting. He had consulted a specialist in dermatology who treated
him with superficial roentgen-ray therapy and other measures with definite improvement at first. In late July, 1948, however, the involvement had again become generalized, but the same forms of therapy were then unavailing, and there had been no significant change since.

The past history revealed that the patient had whooping cough at the age of one, following which he was spastic and unable to walk until he was nine years old.

Physical examination revealed an individual with obvious signs of spasticity who appeared chronically ill. There was a generalized erythematous, lichenified, scaling eruption. Small, firm, non-tender, easily movable lymph nodes were palpable in the cervical, axillary, and inguinal regions. The liver was felt two fingers'-breadth below the right costal margin. The edge was firm and non-tender. The remainder of the physical findings were related to the patient's postencephalitic syndrome.

Laboratory examination revealed the blood and urine to be normal. After PABA therapy was instituted, however, a reducing substance was detected in the urine. Two biopsies of the skin were taken and two lymph nodes were also removed for histologic study. The skin specimens were reported as psoriasiform eczematoid dermatitis (figure 4). The lymph nodes revealed no definite evidence of lymphoblastoma.

On admission the patient was placed on routine therapy, including starch baths, wet soaks to weeping areas, and calamine liniment. His skin definitely failed to respond to the local measures, however, and pruritus remained a disturbing symptom despite large doses of benadryl. Because of the possibility of a diagnosis of lymphoblastoma cutis, it was decided to undertake a trial of PABA therapy; accordingly, the
patient received 3 grams of potassium para-aminobenzoate every three hours beginning on January 5, 1949. After 10 days, the patient's skin showed definite signs of improvement which was characterized by loss of crusts, cessation of weeping, loss of erythema and infiltration, and diminished pruritus. The patient was discharged from

Fig. 5a.
the hospital on January 29, to continue on KPAB, 18 grams daily. The trend of improvement has continued and the program of therapy with KPAB is being maintained at the present writing. The appearance of the patient's legs at the beginning and after eight weeks of therapy is shown in figures 5a and 5b.
PABA in Lupus Erythematosus

Several reports have dealt with the effects of PABA in certain forms of lupus erythematosus. The rationale for administering PABA to patients with lupus erythematosus is based on considerations quite different from those which led to its use in the preceding conditions. There is no general agreement as to the etiology of lupus erythematosus. It is recognized, however, that exposure to sunlight (ultraviolet) may precipitate a relapse or cause an exacerbation of the disease. Sensitivity to sunlight has also been encountered in patients receiving sulfonamide therapy. Since PABA and sulfonamides are metabolically antagonistic, it was reasoned that the former compound might possibly exert a beneficial effect in lupus erythematosus. In view of the experiences in the treatment of the rickettsial diseases and leukemias with large amounts of PABA, it was judged safe to undertake a trial of like therapy in patients with lupus erythematosus. Observations on the effects of PABA in 18 cases of lupus erythematosus have been re-

<table>
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<th>Type of L.E.*</th>
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* Classified after criteria of Ormsby and Montgomery (1943).
† Totals include 18 cases previously reported in detail.
†† Patient died 4 days after brief course of PABA therapy.
§ Patient died of acute toxic hepatitis on 11th day of treatment; L.E. Lesions clearing at time of death.

ported previously. Since that time 15 additional patients have been treated. An attempt to evaluate the results of therapy in the total of 33 patients is given in the accompanying table (table 1). The classification of the clinical forms of lupus erythematosus is arbitrary and is based on criteria indicated by Ormsby and Montgomery. In addition, it is evident that evaluation of the degree of response to therapy can only be an estimate. Generally speaking, when a response was observed, it was characterized by objective improvement in the cutaneous manifestations. Gradual fading of erythema and diminution of the infiltration and edema were usually noted. In some instances a slight exacerbation of the skin lesions has been noted during the first few days of therapy. Regression of these lesions, however, has followed with continued administration of PABA. Many of the cutaneous lesions disappeared completely. Atrophic, scarred, and telangiectatic
areas, however, were not affected. Subjectively, the patients experienced relief of symptoms of pruritus and/or burning in the involved areas. Some noted improvement in their sense of well-being. One patient had marked alleviation of severe arthralgias. In many instances, prolonged administration of PABA is necessary in order to bring about a clinical response. It should also be emphasized that PABA is not curative and that relapses usually occur after cessation of therapy. The first of the case histories described below will illustrate the result attained during eight months of continuous treatment.

Untoward reactions to PABA therapy will be discussed elsewhere in this presentation. It seems pertinent at this point, however, to note that the incidence of reactions to PABA has been greater in patients with lupus erythematosus than in those with other disorders. This may be a reflection of the already well known fact that patients with lupus erythematosus are hyper-reactive individuals. Occasionally, patients develop hyperpyrexia while receiving PABA. An example of this type of response is given in the second of the cases presented below. It will be seen from the case summary that "desensitization" can be accomplished when this phenomenon is encountered.

**Case Reports**

**Case 1.** A 27 year old white housewife was first seen in the University Hospital outpatient department on July 6, 1948. Approximately one year before the patient had noted the appearance of dusky red papules on the forehead. Shortly thereafter, similar lesions appeared over the entire face and just behind and below the ears. The eruption was more erythematos and became pruritic on exposure to the sun. She had received various forms of therapy for eight months, but the lesions persisted and gradually increased.

On physical examination the abnormal findings were limited to the skin. Scattered over the face were a number of irregularly shaped, discrete, papular, dusky red, scaly lesions which varied in size from 2 mm. to over 1 cm. in diameter (figure 6a).

Laboratory examination revealed a hemoglobin of 12.3 grams per cent and a white count of 8,500 per cubic millimeter, with a normal differential. Urine findings were normal until PABA therapy was begun, at which time a reducing substance was detected. A biopsy specimen was taken from one of the skin lesions and the pathologist observed "slight hyperkeratosis with plugging of dilated hair follicles. Perivascular chronic inflammatory infiltrations are present, and there is slight basophilic degeneration of the collagen in the corium. These findings are compatible with lupus erythematosus, but are not sufficiently advanced to be diagnostic" (figure 7).

The patient was seen in the Dermatology staff conference and the diagnosis of lupus erythematosus was made. Therapy with a mixture of NaPAB and KPAB was begun on July 8, 1948. The patient was instructed to take 18 to 21 grams of medication per day. This program has been continued until the present writing, with the exception of two brief interruptions necessitated by the appearance of nausea and vomiting. During the course of treatment the lesions have shown progressive improvement, as is evident in the accompanying photographs (figure 6b).

**Case 2.** A 21 year old trained nurse was admitted to the University Hospital on February 5, 1949. She had experienced severe episodes of sunburn during the summer of 1947 and of 1948. In September, 1948, the patient noticed that the skin of each forefinger had become dry and cracked. Within a period of three weeks,
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Fig. 6a.

Fig. 6b.

Fig. 7.
pain and swelling appeared in all the fingers. Gradually, the wrists, elbows, shoulders, knees, ankles and toes became similarly involved. She began to have low-grade fever. Periorbital swelling and erythema were also observed. The degree of erythema became more marked on exposure to sunlight. The patient was hospitalized elsewhere three times in November and December, 1948. Treatment consisted of bed rest, aspirin, vitamins, quinine, and intramuscular injections of bismuth. Despite attempts at therapy, however, her condition became worse. Two blood transfusions were administered and the patient was started on NaPAB therapy, 2 grams every three hours, in mid-December. The patient became more severely ill with chills, fever, increased edema, pain, weakness, and rapid pulse. On December 30, the temperature rose to 106° F.; NaPAB was discontinued, penicillin was administered, there was gradual improvement, and the fever fell to its previous level of 100° to 101° F. After two weeks NaPAB was begun again but was discontinued after the second dose because she developed a severe chill and the temperature became elevated to 104° F. Two
days later one dose of 2 grams of NaPAB was administered with similar results. This compound was discontinued entirely and after additional transfusions, the patient was discharged home to remain at bed rest until her admission to this hospital.

Examination revealed a well developed white female in no acute distress. The temperature was 100.8° F.; pulse rate was 136 per minute; respirations were slightly increased. The skin was dry with erythematous areas about the eyes and over each elbow. Periorbital edema was present bilaterally. There were small erythematous nodules over the palmar aspects of her fingers at the interphalangeal joints. A small ulceration was noted on the right border of the tongue. A blowing systolic murmur was heard over the apex. Except for the presence of bilateral inguinal adenopathy, the remainder of the examination was normal.
Laboratory findings revealed normal hemoglobin and red blood cell values (history of recent transfusions). The leukocytes numbered 5,200 per cubic millimeter with a normal differential. Examination of the urine revealed no abnormalities; however, after PABA therapy was instituted, a reducing substance was detected in each specimen. The blood nonprotein nitrogen was 28 milligrams per cent.

The patient's history clearly indicated that the administration of PABA had induced bouts of hyperpyrexia. It was, therefore, decided to begin with minute quantities of the compound in an effort to bring about “desensitization” to PABA. Accordingly, on February 7, 1949, the patient was given 1 drop of a 10 per cent solution of potassium para-aminobenzoate, and this dose was repeated every three hours. As there was no reaction, the quantity was gradually increased and by February 15, the patient was tolerating 25 c.c. (2.5 grams) of the compound every three hours. The patient's fever gradually subsided to near normal levels (see figure 8). Concomitantly, there was subsidence of muscle and joint pains, and the patient was allowed to sit up in a chair for brief intervals. She was discharged on February 20, to continue on KPAB, 21 grams per day. On a return visit two weeks later, the patient's general condition was about the same. Anemia was now evident as she had received no further transfusions. She was, however, tolerating the full amount of PABA which had been prescribed.

PABA IN DERMATOMYOSITIS

The utilization of PABA in dermatomyositis stems from the foregoing investigations with lupus erythematosus. It will be recalled that the rationale for the use of PABA in the latter condition was based on the factor of ultraviolet light sensitivity. In view of the observed response in patients with lupus erythematosus, it was reasoned that PABA should be given a trial in other disorders which have associated light sensitivity. Hyper-sensitivity to light is not generally associated with dermatomyositis. One patient with this condition, however, stated that exposure to sunlight aggravated the discomfort in the involved skin areas. Since she was becoming rapidly worse on other attempts at therapy, PABA therapy was undertaken in accordance with the thoughts indicated above. The dramatic result of treatment in this patient has been given elsewhere. The same authors have now treated five patients with features of dermatomyositis, and there has been one death in the group. The remaining four patients have all improved. The first patient to receive PABA for dermatomyositis is still living and active. She has been maintained for 18 months on KPAB. Presented below is the case summary of another patient who is being treated for dermatomyositis.

Case Report

A 38 year old white female had been well until May, 1947, when there appeared edema of the forehead, eyes, and cheeks, associated with erythema of the skin of these areas. This difficulty subsided after a period of two months and she remained in remission until February, 1948. At that time, pain, swelling, redness, and limitation of motion occurred in the knees, ankles, shoulders, elbows, wrists and fingers. This involvement persisted until the time of admission to the University Hospital on September 22, 1948. In addition, she had intermittently a pruritic, tender, erythematous eruption on the palms, soles, and over extensor surfaces of the hands, arms,
and legs. The patient had been continually febrile for at least seven months and had lost 17 pounds in weight. Anorexia, general malaise, and weakness were prominent complaints. She had been seen at the Mayo Clinic in July, 1948, where the diagnosis of dermatomyositis was made.

On examination, the patient appeared to be chronically ill. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic; pulse 110; respirations 20; temperature 101.4° F. A faint erythema and scaling was present on the extensor surfaces of the arms and hands, and on the anterior tibial surfaces. There was limitation of motion of the elbows, wrists, knees, and the interphalangeal joints. The latter were swollen and tender, as were both wrists. The liver was palpable 3 cm. below the right costal margin, while the spleen could be felt 2 cm. below the left costal margin. Neither organ was tender. The remainder of the physical examination was negative.

![Graph](http://annals.org/)

**Fig. 9.**

Admission blood and urine findings were not remarkable except for a hemoglobin of 12 grams per cent. The 24 hour urinary creatine excretion was found to be 760 milligrams on September 23. An ultraviolet skin sensitivity test showed the patient to be three times as sensitive as normal. Muscle and skin biopsies were taken from the left pectoral area. Microscopic examination revealed slight perivascular monocytic infiltrations in the dermis. More marked perivascular monocytic infiltration was present in the subcutaneous adipose tissue and in voluntary muscle. The pathologist interpreted these findings as being compatible with the diagnosis of angiomatositis.

After the preliminary studies were concluded the patient was placed on PABA therapy, 2 grams every three hours initially. There was a gradual fall in temperature towards normal (figure 9) and the patient felt subjectively improved. She was discharged on October 3 to continue on 18 grams daily of KPAB, and to return for monthly check-ups. By mistake the patient took two times the prescribed amount of drug and had a severe gastrointestinal upset. After a few days, however, therapy
was resumed at 12 grams daily. The patient has continued on this program to the present time. She has been afebrile since mid-October, 1948. Appetite, strength and sense of well-being have gradually returned. The joint involvement subsided markedly but there has been residual stiffness, which, however, is also improving.

**PABA in Scleroderma**

Lupus erythematosus, dermatomyositis, and scleroderma are often grouped together as “diffuse collagen disorders.” It was natural, therefore, that the studies of the effects of PABA in the former conditions should lead to a desire to test its value in patients with scleroderma. An added stimulus arose during the course of PABA therapy of a patient who had features of both dermatomyositis and scleroderma. Since the patient showed remarkable improvement in both aspects of his condition, the transition to therapy in scleroderma was enhanced. The results of treatment in this patient and four additional cases of scleroderma have been described. Improvement occurred in all, and was greater when the involvement was extensive. The sclerodermatous areas gradually softened and became thinner and more pliable. There was a consequent increase in range of motion of affected parts. In some patients there has been observed a definite decrease of pigment in previously hyperpigmented areas. The administration of PABA salts has been extended to additional cases of scleroderma. Summaries of the records of two of these patients are given below. The first patient represents more or less the classical picture, whereas the second case emphasizes the fact that visceral involvement is a common accompaniment of scleroderma. An interesting therapeutic problem arises in connection with the intestinal involvement exemplified by the second patient. It is likely that there is softening of the wall of the intestinal tract during KPAB therapy just as softening of the skin occurs. Conceivably, this might precipitate marked intestinal dilatation with signs of ileus. For this reason, it is believed that all patients with scleroderma should have a complete roentgenologic examination of the gastrointestinal tract prior to the institution of treatment with PABA. In the event widespread small bowel involvement is encountered as in the case below, treatment should be cautiously undertaken. In the light of present knowledge, it seems best to begin with small doses (e.g., 4 to 6 grams per day). Subsequently, the dosage schedule may be augmented as the patient’s progress warrants.

**Case Reports**

**Case 1.** A 40 year old white housewife was admitted to the University Hospital on September 9, 1948. One year before she had noted the onset of numbness and tingling in the fingers. Later the fingers became swollen and it was necessary to have her wedding band cut off. In the six months preceding admission to the hospital, there had been a gradual increase in pigmentation of the skin, especially over exposed parts. In addition, there had been progressive weakness and a weight loss of 40 pounds despite a fair appetite. More recently she had noticed a sensation of
tightness and swelling in the lower legs. The patient also complained of episodes of substernal burning which had occurred since March, 1947. These attacks of discomfort usually appeared at night while lying in bed. There were no other signs or symptoms referable to the gastrointestinal tract.

On physical examination the patient appeared chronically ill. There was a diffuse hyperpigmentation over the face, anterior sternal area, the forearms and hands. The skin over the forehead was somewhat atrophic and bound down, as was the skin over the clavicles and over the dorsal aspects of the hands. There was swelling of the proximal interphalangeal joints with limitation of motion. Dependent cyanosis of the finger tips was noted. The skin of the lower extremities showed similar changes to those noted in the hands. The liver was palpable 5 cm. below the right costal margin in the mideclavicular line. The remainder of the examination was negative.

Laboratory findings included the following: hemoglobin 12.0 grams per cent; leukocytes 13,400 with a normal differential; repeated urine analyses were negative except for the appearance of a reducing substance when the patient received PABA therapy. The urine creatine excretion was 0.48 gram for the 24 hours of September 8. An ultraviolet skin sensitivity test revealed the patient to have two times the

![Fig. 10a.](image1)

![Fig. 10b.](image2)

normal sensitivity. A punch biopsy specimen was taken from the skin of the hand and was histologically compatible with a diagnosis of scleroderma. Roentgen examination of the hands revealed cystic osteoporosis, more marked in the left carpal bones, with destruction of the distal ends of the terminal phalanges of the three middle digits of the right hand. A roentgen-ray examination of the upper gastrointestinal tract was negative.

While in the hospital the patient was started on a 50-50 mixture of NaPAB and KPAB, 2 grams every three hours. Therapy was well tolerated and the patient was discharged on September 23 to continue with six doses a day of 3 grams each. When next seen on October 1, there had been very evident softening of the involved skin areas. Treatment was continued until October 7, at which time the patient developed
FIG. 11a.  

FIG. 11b.  

FIG. 12.
nausea, vomiting and fever. PABA was discontinued until December 3 when it was resumed at five drops each three hours. As there was no reaction, the dose was progressively increased on succeeding days. By December 10, the patient was taking 6 grams daily. The amount was gradually increased and the patient has averaged 12 grams daily to the present writing. In addition to the softening of the skin, there has been depigmentation (figures 10a and 10b). The patient is also experiencing less retrosternal discomfort.

Case 2. A 50 year old white housewife was admitted to the University Hospital on August 19, 1948. For five or six years she had had considerable discomfort from epigastric burning with frequent nausea and vomiting. Since January, 1948, the patient had experienced greater distress with cramping pains, distention, and constipation. The vomitus was observed to contain food ingested the previous day. There had been a gradual weight loss of 20 pounds. Tightness of the skin of the face, fingers, and hands had been present for several years and was progressing slowly. A rash had appeared on the face a few months prior to admission to the hospital.

Examination revealed an erythematous, scaling, crusted eruption on the skin of the forehead, face and behind the ears. The skin was thickened on the face, neck, arms, hands and shoulder-girdle. There was limitation of motion of the fingers, and the mouth could not be opened widely (figure 11a). The abdomen was greatly distended and tympanitic. A succussion splash was present. The remainder of the physical examination was within normal limits.

Laboratory examination revealed the urine and stool to be normal. The hemoglobin was 12.7 grams per cent. The leukocytes numbered 2,400 per cubic millimeter
with the following differential count: 41 per cent neutrophiles, 2 per cent eosinphiles, 29 per cent large lymphocytes, 20 per cent small lymphocytes, and 8 per cent monocytes. The 24 hour urinary creatine excretion was 660 milligrams. An ultraviolet skin sensitivity test revealed the patient to have three times the normal sensitivity. Roentgen examination of the gastrointestinal tract revealed a normal colon. There was a cuff-like narrowing of the distal esophagus (figure 12) and profound neuromuscular abnormality of the small bowel. A skin biopsy specimen was taken from the dorsal aspect of the right forearm and revealed homogenization of fibrous connective tissue in the dermis (figure 13).

Initial treatment was directed toward relief of the partial intestinal obstruction. Wangensteen suction was instituted and decompression accomplished. There was gradual relief of symptoms, and PABA therapy was begun on September 2. From 18 to 24 grams daily were administered during the first weeks of treatment.

On this regimen, the patient's skin softened slowly and became loose at the previously hide-bound areas. The patient was able to open her mouth more widely (figure 11b), and the eruption on the face cleared. Episodes of abdominal distention and constipation continued but were less frequent, and nausea and vomiting no longer occurred. Another gastrointestinal roentgen-ray examination was performed on November 24. It revealed loss of gastric and esophageal peristaltic activity

**Fig. 14.**

Initial treatment was directed toward relief of the partial intestinal obstruction. Wangensteen suction was instituted and decompression accomplished. There was gradual relief of symptoms, and PABA therapy was begun on September 2. From 18 to 24 grams daily were administered during the first weeks of treatment.

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and profound disorder of small bowel function. This was evidenced by the extremely
dilated loops of jejunum and duodenum with greatly delayed passage of barium. The
opaque medium was still in mid-jejunum at five hours (figure 14). In view of these
findings, it was decided to continue with PABA therapy but at a reduced dosage of
6 to 9 grams daily. The patient has tolerated this medication with continued
improvement in gastrointestinal function and of the cutaneous manifestations. Con-
comitantly, there has been a definite gain in strength with ability to resume her house-
hold activities.

PABA in Dermatitis Herpetiformis

Para-aminobenzoic acid administered in large amounts has also been
shown to suppress the manifestations of dermatitis herpetiformis. 7, 10 This
disorder is usually well controlled with sulfapyridine or Asiatic pills. 16
Occasionally, however, forms highly resistant to the usual treatments are en-
countered. The first patient to receive a trial of PABA therapy for derma-
titis herpetiformis was severely afflicted and had not responded to other
medications. 19 The reason for trying PABA in that particular patient was
the fact that exposure to sunlight caused more intense pruritus of the lesions.
In the five cases reported elsewhere, improvement was observed in all. 10
Usually there was complete disappearance of bullae and other skin lesions.
In some instances, a few scattered lesions remained. Pruritus gradually sub-
sided and then disappeared. It is of interest that the process recurred about 8 to 10 days after cessation of PABA therapy. Upon resumption of
treatment, control of the lesions is reestablished. In the patients so far ob-
served, continued suppression requires continued administration of PABA.
The following case report illustrates the effect of PABA in dermatitis
herpetiformis.

Case Report

A 78 year old white female was admitted to the University Hospital on July 9,
1948. Eight weeks previously, her eyelids and lips had become swollen. On the fol-
lowing day, a pruritic red rash appeared in the left antecubital space. She had taken
no unusual medications at the time of onset. Within two or three weeks, the eryth-
ematous eruption had spread to involve both arms, the abdomen, lower back, thighs, and
legs. Bullae appeared on the arms. Pruritus was intense.
On examination the pertinent findings were limited to the skin. Infiltrated, ery-
thematosus, plaque-like lesions were present on the lower arms, chest, abdomen, lower
back, buttocks, and thighs. Several large bullae were present in the left antecubital
space. The largest of these was 2.5 cm. long and 1.5 cm. wide, and contained a clear,
straw-colored fluid. All of the bullae were tense. There were no mucous membrane
lesions.
Laboratory examinations revealed the urine to be normal. Blood values were
within normal limits except for a slightly elevated white count of 11,360 per cubic
millimeter. The differential count revealed 6 per cent eosinophiles but was otherwise
not remarkable.

The patient was treated with wet dressings, calamine liniment, and daily liquor
carbonis detersens baths. The diagnosis of dermatitis herpetiformis was made and
sulfapyridine, 0.5 gram, four times daily was started on July 12. This was discon-
tinued on July 15 because of nausea. On July 20, administration of potassium para-
aminobenzoate, 1 gram every three hours, was begun. This was gradually increased over the next three days to 3 grams at three hour intervals for five doses. The patient also received superficial roentgen-ray therapy. On this regimen, the lesions gradually regressed and there was only residual hyperpigmentation at the time of discharge on August 15. The KPAB dosage schedule had been reduced to 6 grams daily on August 10. Within 10 days lesions began to reappear. The amount of KPAB was increased to 18 grams daily and the lesions again subsided. Activity of the process in this patient appears to be suppressed by 15 to 18 grams daily of the compound. This program of therapy is being continued at the present writing.

**Discussion**

The clinical course of an individual patient who has one of the foregoing disorders may be unpredictable. It is believed, however, that sufficient patients in each group have been treated with para-aminobenzoic acid to allow a preliminary evaluation. It appears quite evident from the data available that the causal relationship between therapy and response has been too consistent to be attributed to chance remission. That the improvement observed in these patients is due to the administration of PABA is further supported by the fact that relapse usually occurs after cessation of therapy.

The response observed in patients with chronic myelogenous leukemia does not justify the use of PABA in patients with leukemia. In regard to the remaining entities, however, it is believed that PABA may be of value in selected cases. It will be recalled that in these patients all of the usual forms of therapy had been tried and abandoned before PABA therapy was instituted. The most gratifying results have so far been attained in lymphoblastoma cutis, scleroderma, and certain cases of dermatomyositis. Results of therapy in acute disseminated lupus erythematosus have been disappointing as may be noted in the accompanying table. On the other hand, there has been sufficient benefit noted in two cases of the acute form to warrant trial of PABA in additional patients. Dermatitis herpetiformis is usually controllable with other forms of medication. In instances of intolerance to the usual treatment, however, para-aminobenzoic acid therapy may be used.

The mode of action of PABA in these diverse conditions is not known. All of the disorders are of unknown etiology and the pathogenesis of each is poorly understood. It is, therefore, unprofitable to speculate at this time as to the possible mechanisms involved. Surely the diseases referred to above cannot be considered to result from PABA deficiency, since the dosages employed are far greater than the trace amounts required for physiologic vitamin-enzyme activity. 19

A number of toxic manifestations have been encountered during PABA therapy. The most serious of these was a fatal case of toxic hepatitis.8 In addition, drug fever and dermatitis medicamentosa have been observed. When drug fever appears, it is possible to "desensitize" the patient as was illustrated in one of the case reports above. It has already been noted that an initial exacerbation of the skin manifestations of lupus erythematosus is
sometimes seen. It also appears worthy of interest that the preponderance of reactions to PABA have occurred in the lupus erythematosus group of patients.

Nausea, at times associated with vomiting, is the most frequent reaction. This usually subsides after omission of a few doses of the drug. Therapy has often been resumed in such cases without further difficulty.

Leukopenia may be present in patients who are receiving PABA. It is difficult to decide whether this is due to the compound, since several of the above named conditions are characterized at certain stages by a low white blood cell count. There have been no cases of agranulocytosis from PABA. In the light of experiences with other substances, however, it is possible that this might occur rarely in patients receiving PABA. This possibility should be kept in mind.

A reducing substance has been detected in the urine of all patients taking large amounts of PABA. This was believed to be glucose as a result of findings with osazone and other tests. Additional studies have given evidence that this may not be glucose. This finding raises certain implications not hitherto recognized. It is especially important in that at least two instances of hypoglycemic attacks have been observed during the administration of PABA. Through investigations now in progress it is hoped to explain these observations.

From the studies referred to herein, it is concluded that para-aminobenzoic acid has therapeutic possibilities in several diseases of unknown etiology. These are lymphoblastoma cutis, certain forms of lupus erythematosus, dermatomyositis, scleroderma, and dermatitis herpetiformis. Apart from the immediate practical considerations, it is hoped that additional study of the effects of para-aminobenzoic acid will yield information as to the mechanisms involved in these obscure disorders.

BIBLIOGRAPHY