SUNBURN AND PARA-AMINOBENZOIC ACID[1]

STEPHEN ROTHMAN, M.D., AND JACK RUBIN, PH.D.

(Received for publication November 20, 1942)

INTRODUCTION

The sunburn action spectrum. Since 1922 it has been known that sunburn and suntan of the human skin are due to the action of a narrow band of rays in the ultraviolet spectrum (1, 2) (fig. 1).

Hausser and Vahle (1) irradiated the human skin with a mercury vapor lamp by interposing a quartz monochromator between the light source and the cutaneous surface. Thus the individual lines of the mercury spectrum were projected upon the skin with considerable spaces between them. In this way a maximum of erythemic effectiveness was found at the wavelength of 2975 Å with a sharp drop of this effectiveness in the direction of either shorter or longer wavelengths. There was practically no erythemic effect at the wavelength 2800 Å in one direction and at the wavelength 3130 Å in the other. A second-lower-maximum of erythemic effectiveness was found at 2540 Å. It was shown (3) that the rays around the maximum of 2975Å cause a persistent erythema with consecutive pigmentation. The range at 2540 Å elicits an erythema of only short duration and with no consecutive pigmentation.

The filtration effect of the p-aminobenzoic acid radical. In 1926 it was observed (4) that if a 1 per cent procaine hydrochloride solution was injected intradermally in man, and immediately thereafter a larger area with the injection wheal in its center was irradiated with a mercury vapor lamp, the subsequent ultraviolet erythema was modified in a characteristic way by the previous procaine injection. First, the erythema developed over the whole area equally. However, subsequently the site of the injection wheal grew pale, and soon the original shape of the old injection wheal became delineated in the form of a sharply limited flesh-colored flat macule in the center of the still intensely erythematous and edematous lesion (fig. 2). When the erythema subsided and pigmentation occurred, no trace of pigmentation could be found at the site of the injection.

It was shown (4) that this phenomenon was due to a filtration effect of procaine. Procaine selectively absorbs and filters out the "sunburn rays" around 3000 Å. It does not absorb the rays at 2540 Å, and therefore the filtration effect becomes visible only after the subsidance of the short lasting erythema due to the line at 2540 Å.

[1] From the Section of Dermatology, Department of Medicine, and Department of Pharmacology, University of Chicago.

Read at the Fifth Annual Meeting of the Society for Investigative Dermatology, Atlantic City, N. J., June 9, 1942. Preliminary report presented at the Meeting of the Society for Experimental Biology and Medicine, Section Illinois, Chicago, Ill., Jan. 20, 1942.

This work was aided in part by grants from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

In 1928 experiments were performed to determine which part of the procaine molecule is responsible for the selective absorption in the ultraviolet spectrum

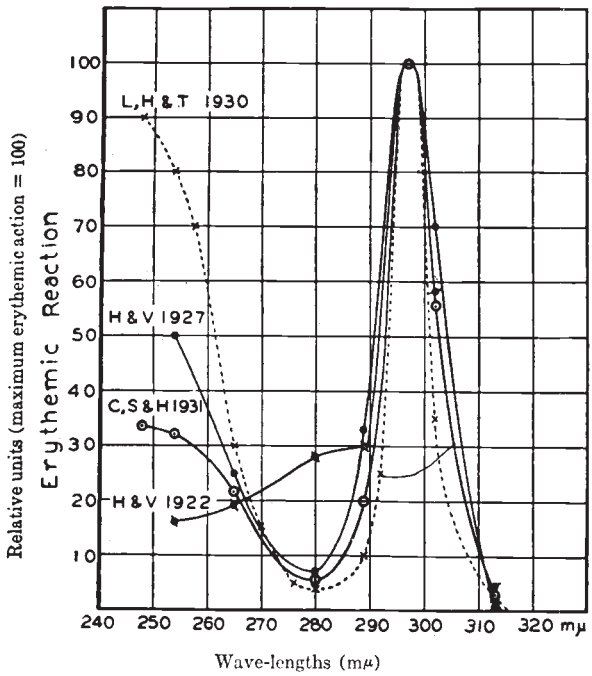


FIG. 1. SUNBURN ACTION SPECTRUM
From: H. F. Blum, Photodynamic action and diseases caused by light, New York, 1941

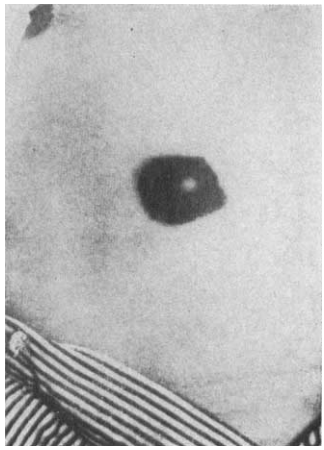


FIG. 2. FILTRATION EFFECT OF 1% PROCAINE HCl SOLUTION IN HUMAN SKIN
From: S. Rothman, Strahlenther, **22**: 729, 1926

(5). It was found that the absorption band is correlated with the para-position of the amino and carboxylic groups on the benzene ring. P-aminobenzoic

acid and its derivatives in which there are substitutions for the H atoms of either the carboxylic or the amino group have the same or similar absorption bands (group of "positive" compounds in fig. 3). Comparable absorption of such intensity was not found with compounds of different molecular configuration (group of "negative" compounds in fig. 3).

The absorption band of p-aminobenzoic acid. In the experiments of 1926 and 1928 (4, 5) qualitative spectrographic methods were used. Photographs were taken of the absorption spectra, and it was found that, under exactly constant conditions, p-aminobenzoic acid and its derivatives totally absorb the lines between 3130 and 2600 Å of the mercury spectrum, whereas the absorption spectrum of compounds with different molecular structure did not cause the disappearance of these lines in the spectrogram if the substances were applied in the same molecular concentration.

Independent of this work, quantitative spectrophotometric analysis of p-aminobenzoic acid was carried out in 1929 (6) and in 1933 (7). Figure 4 reveals that the maximum of the absorption band is at 2785 Å which is rather far away from the maximum of erythemic effectiveness. However, the shape of the curve is such that, at the wavelengths which are effective for erythema, the absorption band is still enormous.

The photochemical theory of sunburn (2). In order to explain the peculiar shape of the sunburn action spectrum, the theory was advanced that in the photosensitive layers of the skin one or more substances are present with absorption spectra which are identical with or similar to the sunburn action spectrum. According to the theory, these substances, by absorbing the effective ultraviolet rays, undergo a photochemical reaction, the product of which

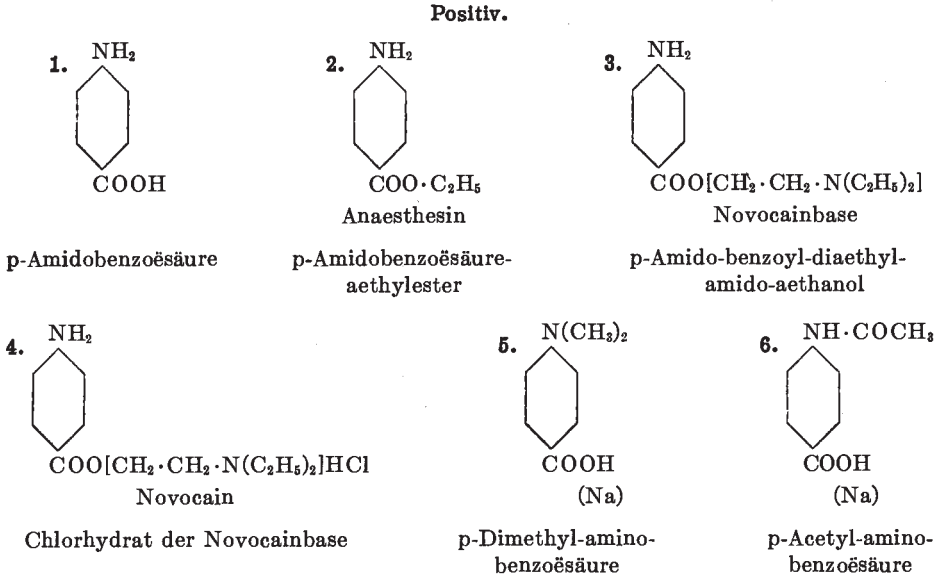


FIG. 3 (*Continued on next page*)

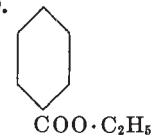
Negativ.

7. 

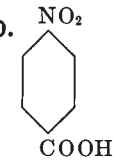
Anilin

8. 

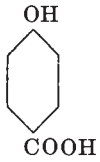
Dimethylanilin

9. 

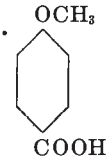
Benzoësäure-aethylester

10. 

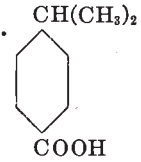
p-Nitrobenzoësäure

11. 

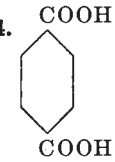
p-Oxybenzoësäure

12. 

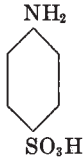
p-Methoxy-benzoësäure

13. 

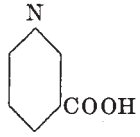
p-Isopropyl-benzoësäure

14. 

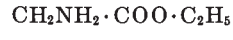
Terophtalsäure
Benzol-p-Dicarbonsäure

15. 

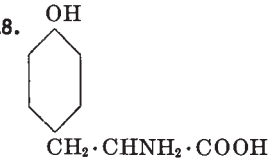
p-Aminobenzol-sulfosäure

16. 

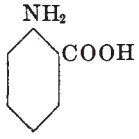
Pyridin-carbonsäure

17. 

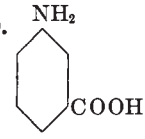
Glykokollaethylester
Aminoessigsäure-Aethylester

18. 

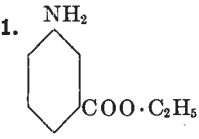
Tyrosin
p-Oxyphenyl-α-amino-propionsäure

19. 

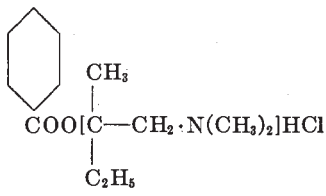
o-Aminobenzoësäure

20. 

m-Aminobenzoësäure

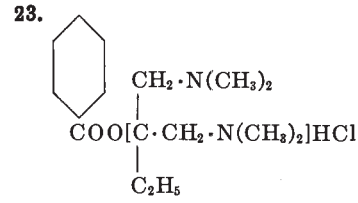
21. 

m-Aminobenzoësäure-aethylester

22. 

Stovain

Chlorhydrat des Dimethyl-amido-benzoyl-pentanols

23. 

Alypin

Chlorhydrat des Tetramethyl-diamino-benzoyl-pentanols

From: O. Behaghel, S. Rothman and W. Schultze, Strahlentherapie, **28**: 110, 1928

FIG. 3. "POSITIVE" COMPOUNDS DO, "NEGATIVE" COMPOUNDS DO NOT ABSORB ULTRAVIOLET IRRADIATIONS IN THE SUNBURN REGION

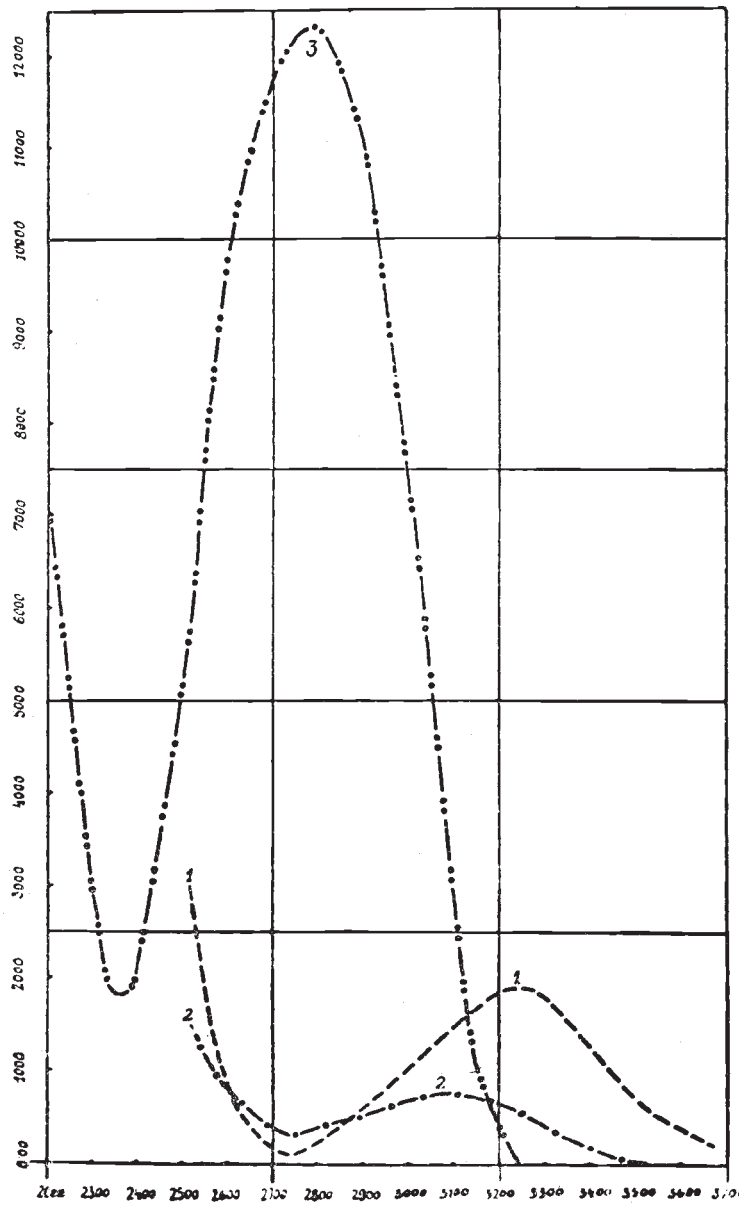


FIG. 4. ULTRAVIOLET ABSORPTION SPECTRA OF AMINOBENZOIC ACIDS; 1, ORTHO; 2, META; 3, PARA

From: Marchlevsky, L., and Mayer, J., Bull. Internat. Acad. Polon., A., 1929, p. 169

is responsible for the biologic reaction. In other words, the particular shape of the sunburn action spectrum is due to and reflects the absorption spectrum of one or more substances which are responsible for the erythema.

Several years ago the hypothesis was put forth that this substance may be histidine because it is transformed into histamine by ultraviolet rays (8, 2). However, for several reasons this assumption has been untenable.

In 1928 (5) while discussing the possibility that p-aminobenzoic acid might be this substance because of the similarity of its absorption spectrum with the sunburn action spectrum, one of us (S. R.) argued against this supposition stating that "p-aminobenzoic acid and its derivatives are not known to occur in the skin, and therefore it is not probable that the selective absorption of the erythema rays by these compounds have anything to do with the response of the skin to ultraviolet light." In other words, the similarity was regarded as coincidental. Therefore, experimentation on this subject was discontinued.

However, since recent publications (9, 10) indicated that p-aminobenzoic acid may possibly play an important role in metabolism, and may occur in the epithelial cells of the skin, calculations and experiments were resumed in this laboratory.

CALCULATIONS

Opponents of the photochemical theory of sunburn (11) claim that the shape of the sunburn action spectrum can be explained satisfactorily by the absorption of ultraviolet rays in the cell proteins of the photosensitive epidermal layers, without the assumption of a substance with a specific spectrum. Proteins, too, have an absorption band in the region of the sunburn rays (12), and it has been known for a long time that this band is due to the presence of the aromatic amino acids tyrosine and tryptophane in the protein molecule (13, 2). The absorption of tyrosine is very slight in this region, that of tryptophane is greater. The absorption band of proteins depends largely upon their tryptophane-content. It is difficult to compare the small molecule of p-aminobenzoic acid with the large protein molecules, and it is impossible to calculate the molecular extinction coefficient of cell proteins. Therefore we based our calculations on the comparison of tryptophane and p-aminobenzoic acid.

Figure 5 shows that the band of tryptophane has its maximum very close to that of p-aminobenzoic acid (2790 vs. 2785 Å). At this maximum the molecular extinction coefficient of p-aminobenzoic acid is three times greater than that of tryptophane. However, the shapes of the bands being different, in the region of the sunburn rays the molecular extinction coefficient of p-aminobenzoic acid becomes as much as 300 times greater than that of tryptophane.

Possibly these quantitative differences are not significant because, if there is any p-aminobenzoic acid in the skin, its concentration is probably less than $\frac{1}{300}$ of the concentration of tryptophane. Therefore, in further calculations, the maximum absorption of tryptophane (or proteins) and that of p-aminobenzoic acid were taken equally as 100%, and the extinction coefficients at different wavelengths were calculated in percentages of the maxima. In this way the qualitative differences in the shape of the two curves were demonstrated graphically (fig. 6). By drawing the sunburn action spectrum into this diagram with arbitrarily chosen units it was shown that the absorption curve of tryptophane

and of proteins lies outside of the highest point of the sunburn action spectrum whereas the absorption curve of p-aminobenzoic acid encloses it completely.

EXPERIMENTS

The biologic response to irradiated p-aminobenzoic acid. The photochemical theory of sunburn postulates that the substance which is responsible for sunburn must, if irradiated, elicit an inflammatory response in the skin.

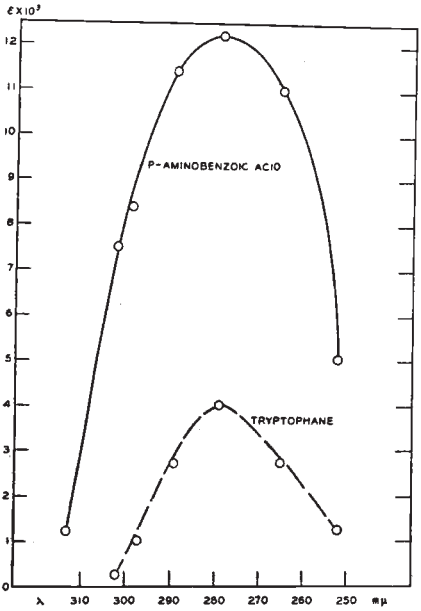


FIG. 5

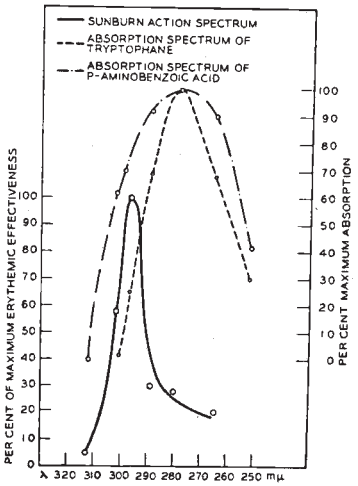


FIG. 6

FIG. 5. COMPARISON OF THE MOLAR EXTINCTION COEFFICIENTS (E) OF TRYPTOPHANE AND p-AMINOBENZOIC ACID

FIG. 6. COMPARISON OF THE SPECTRAL BANDS OF TRYPTOPHANE AND p-AMINOBENZOIC ACID IN RELATIVE UNITS

The band of p-aminobenzoic acid does, the band of tryptophane does not include the sunburn action spectrum

In order to determine whether p-aminobenzoic acid complies with this requirement, saline solutions of p-aminobenzoic acid were irradiated in vitro, and the irradiation product was injected into the skin of normal individuals.

In all experiments, 0.33 per cent p-aminobenzoic acid solutions in normal saline were used. Eight cc. of this solution were measured into a Petri dish, 9.0 cm. in diameter, and irradiated with a standard mercury vapor lamp for 7 minutes at 25.0 cm. distance. This dose corresponded with an average erythema dose of the lamp. During irradiation, the solution lost 0.1 to 0.2 cc. of water by evaporation. Its volume was carefully restored with water to the original volume of 8 cc. after irradiation. It was noted that irradiation caused the solution to turn yellow. After irradiation the solution was run through a Berkefeld filter for sterilization.

Amounts of 0.3 cc. of the irradiated solution were injected intradermally into normal persons, followed immediately by similar injection of 0.33% non-irradiated p-aminobenzoic acid in saline, also sterilized by filtration. The two injection wheals were made in a distance of about 2 inches from each other.

Under these conditions 8 experiments were carried out in 5 individuals. The results were uniform in all cases. The site of the injection of the non-irradiated solution showed either no reaction or a punctiform erythema at the site of the puncture. In the area where the irradiated product was injected an area of extensive erythema averaging 2.5 cm. in diameter and moderately edematous developed 6 to 8 hours after injection, and persisted for about 24 hours. Then it disappeared completely with no trace of consecutive hyperpigmentation. The largest observed erythematous reaction due to the injection of non-irradiated p-aminobenzoic acid was 0.3 cm., and it showed no swelling.

The observed difference in the cutaneous response was not due to a change in pH caused by irradiation. The pH of the non-irradiated sample was 3.62, that of the irradiated sample 3.66. The injection of both samples was equally painful as would be expected with such a low pH.

The response could not be intensified by increasing the intensity of irradiation.

Similar experiments were carried out with other substances which have been thought to be responsible for the sunburn action spectrum, namely tyrosine, tryptophane and proteins (2). The first two compounds were used in 1:1000 (saturated) solution; egg white was applied in the dilution 1:100. These solutions were irradiated under the same conditions as was p-aminobenzoic acid. The intradermal injection of the irradiated solutions into normal individuals did not elicit any visible inflammatory response.

We endeavoured to determine whether the yellow discoloration of the irradiated p-aminobenzoic acid solution occurred because the irradiation was carried out in open dishes in the presence of air. A plano-parallel quartz cell, 1.5 cm. thick, was filled with the solution of p-aminobenzoic acid, the air was expelled by vacuum, and the solution was saturated with nitrogen gas. After sealing the cell it was irradiated for 90 minutes at 10 inches distance. No discoloration was observed, and the solution proved to be biologically inactive.

Attempts were made to isolate the yellow product chemically but no conclusive results have been obtained as yet. The solubility of the irradiated product was found to be the same as that of p-aminobenzoic acid. We did not succeed in separation of the two products by adsorption on aluminum oxide and elution by alkalies. Qualitative spectrographic analysis of the non-irradiated and irradiated products revealed no noticeable differences (fig. 7). No differences were found if the two products were diazotized.

Comparison of the ultraviolet spectrum of p-aminobenzoic acid with the spectra of other substances which absorb sunburn-rays. The experiments were carried out with an ultraviolet spectrograph of Bausch and Lomb, and a hydrogen discharge tube. The solutions were used in a 10 millimeter column, the slit was 0.25 millimeter, the exposure time 5 seconds. The picture of the hydrogen spectrum was taken through a water column of 20 millimeter length.

Under these conditions the absorption band of p-aminobenzoic acid could be easily recognized, if applied in a 1/10,000 molar aqueous solution; in a dilution of 1/5000 mol. it extinguished the hydrogen spectrum in the region of the sunburn spectrum completely (fig. 8).

This absorption was compared with the absorption by quinine HCl, tannic acid and the sodium salt of naphthol-6-8-disulfonic acid ("G-Salt"); the latter has been used in the sunburn-protective preparations "Antilux" and "Sunex". Since it has been stated that p-amino-benzoic acid and pantothenic acid are linked in their "anti-grey hair" action (14) the spectrum of calcium pantothenate also was taken.

It was found that absorption of the sunburn-rays by quinine and by pantothenic acid is negligible. Figure 9 shows that in a 1/5000 molar concentration

FIG. 7. ULTRAVIOLET SPECTRA OF p-AMINOBENZOIC ACID
1, irradiated; 2, non-irradiated

FIG. 8. ULTRAVIOLET SPECTRA
1, water; 2–5, p-aminobenzoic acid (2, 1/10,000 mol; 3, 1/500 mol; 4, 1/1000 mol; 5, 1/5000 mol)

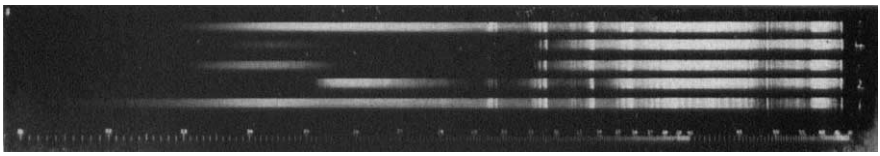


FIG. 9. ULTRAVIOLET SPECTRA
1, water; 2, 1/5000 mol G-Salt; 3, 1/5000 mol p-aminobenzoic acid; 4, 1/5000 mol tannic acid; 5, 1/5000 mol calcium pantothenate

the absorption by G-Salt in the sunburn region is not noticeable whereas that of tannic acid is almost equal to that of p-aminobenzoic acid. An extinction of the sunburn-region by G-Salt has been observed at a concentration of 1/2000 mol.

In the earlier work of one of us (S. R.) (5), it was reported that substitution of one hydrogen atom in the amino group of p-aminobenzoic acid by the acetyl radical causes a shift of the absorption band to shorter wavelengths. This finding has been checked in the present series of experiments and found to be correct (fig. 10). The absorption band of acetyl-p-aminobenzoic acid does not include the sunburn-rays.[2]

Sunburn protection by p-aminobenzoic acid. Experiments designed to protect

[2] The spectrophotometric analysis of the two compounds were carried out by Dr. Mark Fred in the Dept. of Physics, University of Chicago.

the skin against ultraviolet erythema by p-aminobenzoic acid and its derivatives were carried out in two ways: (a) by covering the skin with aqueous solutions, and (b) by application of ointments.

In order to apply aqueous layers of equal thickness three identical glass rings were fixed to the skin of the back and sacral region of normal persons by means of adhesive tape. Into each ring an equal volume of one of the following solutions was placed: water, 2% procaine HCl solution and undiluted horse serum. The region then was irradiated with a mercury lamp, a full erythema dose being given.

Although these experiments were inaccurate because of an unavoidable leakage of liquid through the tape, they clearly demonstrated that the protective effect of a 2% procaine HCl solution is by far greater than that of undiluted horse serum.

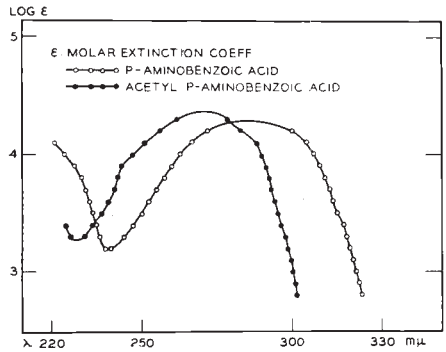


FIG. 10. MOLAR EXTINCTION COEFFICIENTS OF p-AMINOBENZOIC ACID AND ACETYL-p-AMINOBENZOIC ACID

By incorporating 10 to 15% p-aminobenzoic acid into ointment bases an extremely effective preparation against sunburn was obtained. Quantiative efficiency and toxicity tests on these ointments are in progress and will be reported at a later date.

DISCUSSION

The similarity between sunburn action spectrum and absorption spectrum of p-aminobenzoic acid is limited. The maximum of absorption by p-aminobenzoic acid is at 2785 Å, a wavelength at which the sunburn action spectrum displays a minimum absorption. However, the absorption band of p-aminobenzoic acid has a broad shape, and its top includes the whole active region of ultraviolet rays around 3000 Å whereas the bands of tryptophane and of proteins do not. If one assumes that p-aminobenzoic acid is present in the epidermis, and that its photochemical change causes the sunburn, the dissimilarity between action and absorption spectra towards the shorter wavelengths can be explained by the anatomic position of the photosensitive layers in the epidermis (5). Rays shorter than 2900 Å having a low penetrating power do not reach these photosensitive epidermal layers, i.e., the inner half of the Malpighian layer and the basal layer, but

are absorbed outside of these strata. Thus the sunburn action spectrum is not necessarily identical with the absorption spectrum of p-aminobenzoic acid, even if this substance were the photosensitive principle of the skin. In the inner layers of the epidermis p-aminobenzoic acid has no opportunity to absorb rays shorter than 2900 Å.

The observed inflammatory reaction to the irradiated p-aminobenzoic acid, with a latent period comparable to that of sunburn, is regarded as inconclusive supporting evidence for the theory that ultraviolet erythema is due in part to the photochemical reaction of p-aminobenzoic acid in the skin. However, this evidence is incomplete for two main reasons. One is that p-aminobenzoic acid has not been shown to occur in the skin, and the other is that no consecutive pigmentation was found to follow the erythema. On the other hand, the doses of irradiation in vitro were small, corresponding to doses causing only an average erythema on the skin. Intensive irradiation in vitro seemed to further oxidize and destroy the active principle. This difficulty in the experimental set-up might have been the cause of our inability to produce pigmentation.

The solution of p-aminobenzoic acid turns yellow if irradiated in the presence of oxygen, and possibly this colored product is the active principle. It is conceivable that the active principle, an oxidation product of p-aminobenzoic acid, is an imine. Oxidation of aromatic amine leads to imine formation, and imines are known to be violent irritants for living tissues (15).

Protection against sunburn by covering the skin with p-aminobenzoic acid preparations seems to be practicable. The absorption band of p-aminobenzoic acid in the sunburn region is at least twice as intensive as that of G-Salt. In comparison with tannic acid, which absorbs about equally, and with derivatives of salicylic acid which have been used with good results in protection against sunburn (16, 17), p-aminobenzoic acid is more stable and does not stain or soil clothing. It is colorless, odorless and does not irritate the skin. Comparative measurements on spectra of newer compounds recommended for protection against sunburn (16, 18, 19) are in progress.

It has been claimed (20) that ultraviolet irradiation having wavelengths longer than 3130 Å, although not causing sunburn, do have beneficial biologic effects. Therefore, it has been postulated that sunburn-protective preparations should be transparent to these rays. P-aminobenzoic acid certainly complies with this requirement. It may be predicted that p-aminobenzoic acid will not inhibit the "long-wave ultraviolet pigmentation" (20). However, this "pigmentation" does not represent a new formation of melanin but rather a transformation of reduced and pale pigment granules into the darker, oxidized form (21). The true ultraviolet-pigmentation, meaning new formation of pigment granules, is inhibited by p-aminobenzoic acid, because the action spectrum of this pigmentation is the same as that of the ultraviolet erythema.

SUMMARY

1. The comparison of the absorption spectrum of p-aminobenzoic acid with those of tryptophane and of proteins shows that, although the spectra are similar,

only p-aminobenzoic acid might be responsible for the shape of the sunburn action spectrum in the region of 3000 Å.

2. Irradiated solutions of p-aminobenzoic acid cause inflammatory reactions if injected intradermally in humans, whereas irradiated tyrosine, tryptophane, protein and non-irradiated p-aminobenzoic acid solutions have no such effect. This finding supports the assumption, discussed as early as 1928, that ultraviolet erythema is due in part to the photochemical reaction of p-aminobenzoic acid in the skin.

3. P-aminobenzoic acid, if incorporated into ointment bases, protects against sunburn.

We are indebted to Dr. E. A. Evans Jr., Dept. of Biochemistry, for placing the spectrograph of his department at our disposal. Dr. A. M. Potts and Dr. A. Dorfman of the same department greatly helped us in the experiments on adsorption and diazotation of the irradiated product. Dr. Mark Fred of the Dept. of Physics was kind enough to carry out spectrophotometric measurements on p-aminobenzoic acid and its acetyl derivative. Merck and Co. kindly supplied us with p-aminobenzoic acid.

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After completion of this manuscript our attention was called to the paper of J. C. Bird: Ultraviolet absorption of surface anesthetics. Jour. Amer. Pharmaceut. Assoc., **31**: 151–154, May 1942, in which the screening effect of derivatives of p-aminobenzoic acid is reported in complete accord with our findings.