# General Review

# PHOTOSENSITIZATION AND THE PHOTODYNAMIC DISEASES OF MAN AND THE LOWER ANIMALS

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Although the relation of sunlight to some of the skin diseases of man and the lower animals had been recognized for many years, a basic explanation for the action of sunlight was not available until 1900, when Raab published the results of his studies concerning the effects of acridine hydrochloride on paramecia. In determining the lethal action of acridine he found that in the presence of direct sunlight dilutions of 1: 20,000 killed paramecia in six minutes, while sixty minutes was required for the same result in diffuse light, and there was no lethal effect in the dark. He observed in these phenomena a possible explanation for the action of light in certain skin diseases. Tappeiner reported on work of the same type and called attention to the fact that the lethal action in the presence of light is not due to heat. He advanced the theory that this action is due to increased activity of the light in connection with its conversion from one wavelength to another. Tappeiner and Iodlbauer studied 54 fluorescent compounds, part of which were activated by visible light and the remainder by ultraviolet rays. In the presence of the activating rays these compounds were found to have a destructive action on enzymes as well as on paramecia. Jodlbauer and Tappeiner found that the photodynamic action of eosin included a destructive effect on both tetanus and diphtheria toxins, as guinea-pigs tolerated large doses of either toxin if the toxin had been mixed with eosin and exposed to sunlight. Hemolysis of erythrocytes was observed to be a photodynamic action of eosin as well as of several other dyes by Pfeiffer and by Sacharoff and Sachs. The latter investigators obtained hemolysis of erythrocytes in the dark with previously irradiated Indigosalz, but similar results could not be obtained with previously irradiated eosin. Blum (1930) obtained hemolysis of

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erythrocytes in the dark with previously irradiated solutions of eosin, erythrosin and fluorescein.

Straub and also Jodlbauer and Tappeiner showed that one of the requirements for photodynamic action was the presence of oxygen. Blum (1930) found that the iodide ion could be oxidized in the dark by previously irradiated eosin and concluded that the hemolysis of erythrocytes was also an oxidation. This conclusion is strengthened by the fact that reducing agents such as sodium sulfite and sodium hyposulfite were found by Awoki and by Dognon to prevent photo-dynamic action.

In turning to natural sources of photodynamic agents, Hausmann (1908) obtained hemolysis of erythrocytes in the presence of bile and sunlight, the bile and the erythrocytes having been obtained from the same rabbit. He also observed that impure bilirubin had a destructive action on erythrocytes and paramecia in the presence of sunlight, but not purified bilirubin (1908). Hausmann (1908, 1913, 1931) and Hausmann and Portheim extracted a large number of plants such as corn, wheat and grass with alcohol and by testing with erythrocytes and paramecia found that the extracts possessed photodynamic properties. Fischer and Kemnitz compared the photodynamic properties of hematoporphyrin and mesoporphyrin and found that the latter agent would kill paramecia in the presence of sunlight in dilutions of 1:200,000, whereas hematoporphyrin had practically no killing power under the same conditions.

The activating light in a photodynamic action is generally assumed to be the same as that absorbed from the spectrum by the given photodynamic agent. However, by exposing mixtures of paramecia and eosin to light which had been passed through a spectroscope, Metzner found the greater part of the dead protozoa clustered in the region which had been exposed to light with wavelengths from 5,300 to 5,700 angstroms, which, according to him, does not correspond to the light absorbed from the spectrum by eosin (wavelength, 5,250 angstroms). Yellow light as well as ultraviolet rays hemolyzed erythrocytes in the presence of hematoporphyrin according to Forber and Simonnett. Hausmann (1934) and Hausmann and Sonne also observed that ultraviolet rays would activate hematoporphyrin in the presence of erythrocytes and that rays with a wavelength of 3,130 angstroms were the most effective. However, in a previous experiment with paramecia and hematoporphyrin Hausmann (1910) had concluded that the activating light was located in the region of 5,000 angstroms. Hausmann and Krumpel observed that the spectral absorption of mesoporphyrinogen was practically the same as that of hematoporphyrin, and since ultraviolet rays activated hematoporphyrin they concluded that adequate explanation

was at hand for the fact that some patients with hydroa aestivale have been found to be sensitive to ultraviolet rays. However, it should be borne in mind that their experiments were conducted on a simple form of animal life, and the results may not be applicable to human disease.

With the photodynamic sensitization of infusoria as an established fact it was but a short step to the application of this phenomenon to the higher animals. Jodlbauer and Busck injected eosin, fluorescein, erythrosin and rose bengal into rabbits, rats, mice and guinea-pigs and on exposure of the animals to direct sunlight observed pruritus and edematous swellings of the face and ears. Necrosis of the skin in the edematous regions occurred later with considerable sloughing, especially of the ears. Exophthalmos was observed in mice treated with rose bengal. Pfeiffer (1911) gave the technic for producing this condition in animals and stated that an electric light of from 30 to 40 amperes at a distance of 1 meter was a sufficient source of light to induce the complete reaction. Quin (1933) produced subcutaneous edematous swelling of the face, ears and lower portions of the legs in sheep by exposing them to direct sunlight following the intravenous injection of 1 Gm. of eosin. The first evidence of sensitization occurred within a few minutes after the exposure to light. No sensitization occurred in diffuse light. Several other fluorescent dyes gave similar results, but nonfluorescent dyes did not. In severe cases there were shedding of the wool and marked sloughing of the skin. In contrast to the positive results of the aforenamed workers, Strauch obtained practically no evidence of sensitization in rabbits by exposure to direct sunlight following the intravenous injection of eosin. With the use of a mercury arc for his source of light Gassul also failed to produce sensitization in mice by the injection of eosin.

The report of Raab's work supplied the stimulus for a more scientific investigation of photosensitization. However, about ten years elapsed before attention was directed to the porphyrins and their effect on the higher animals. Hausmann (1909, 1910) by injecting hematoporphyrin into white mice and subjecting them to solar irradiation became one of the pioneers in this field. He divided the disease produced in this manner into acute, subacute and chronic forms. The acute form was characterized by convulsions, nervous disturbances and death within a few minutes after the first exposure, which he attributed to severe doses of either porphyrin or light. The subacute and chronic forms differed only in the degree of the reaction and consisted of pruritus and edematous swellings of the face and ears followed by necrosis of the skin and sloughing, which in some cases resulted in loss of the ears. With gray mice the disease was limited to the chronic form, and with black mice no sensitization was produced. With the

use of light filters consisting of solutions of copper sulfate and potassium dichromate he concluded that the activating light was in the region of from 4,800 to 5,300 angstroms. In a later publication (1914) he claimed to have produced the acute form of the disease in mice by the injection of 0.01 Gm. of hematoporphyrin with exposure for one minute to the light of a mercury arc. In view of the results of other investigators this appears to be an unusual reaction. In this work he attributed the manifestations of the disease, especially the chronic form, to the action of ultraviolet rays, but since filters were evidently not employed, this conclusion was not justified.

The results of Pfeiffer (1911) with mice and guinea-pigs are in accord with those of Hausmann. However, in some animals with the acute form of the disease the convulsions and nervous disturbances lasted for days before death occurred. Pfeiffer observed also in the acute form a marked lowering of the body temperature, which occurred within from one to several hours after the exposure to light. Quin (1931) produced sensitization to light in sheep and goats by injecting 0.5 Gm. of hematoporphyrin intravenously and exposing them to direct sunlight. Ten minutes' exposure to sunlight resulted in pruritus, and within two hours subcutaneous edematous swelling of the ears and face occurred, which later extended to the intermandibular space. Dry gangrene, sloughing of the skin and opacity of the cornea with blindness were later manifestations. The black areas of spotted animals were not affected, and by painting with bismarck brown most of the action of the light was prevented. No sensitization to light was obtained by feeding the animals porphyrin. Rask and Howell produced the same condition in dogs by intravenous injections of hematoporphyrin and exposure to sunlight. Fischer and Meyer-Betz found that one hour of solar irradiation was required to produce evidence of sensitization in mice after the injection of 0.01 Gm. of hematoporphyrin, and that as a photodynamic agent mesoporphyrin was less active than hematoporphyrin. The results of this comparison of the photodynamic properties of the two porphyrins do not agree with those obtained by Fischer and Kemnitz when they employed erythrocytes and paramecia in making the comparison. Mice given injections of hematoporphyrin and kept in the dark were still sensitive to light at the end of twenty-four hours, but the sensitivity was lost at the end of forty-eight hours. In contrast to these positive results, Smetana obtained practically no sensitization to direct sunlight after injection of hematoporphyrin into mice.

Porphyrinogen, the leukobase of hematoporphyrin, was found to be photodynamic by Fischer, Barthalomäus and Röse. Guinea-pigs were rendered sensitive to the radiation of either the mercury or the carbon

arc by the injection of this product. Some putrefactive porphyrins were proved to be photodynamic for paramecia and mice by Kämmerer and Weisbecker. Three hours of direct exposure to sunlight were required to produce chronic manifestations of the disease in mice.

Quin (1933) ligated the common bile duct in sheep and goats and on exposure to direct sunlight obtained the same evidence of photosensitization as he had obtained by the use of porphyrin. In control animals maintained in the shade icterus developed as in the exposed animals, but no pruritus or skin lesions. In a continuation of this work Quin, Remington and Roets, as well as Rimington and Quin, found that the photosensitization was due to the presence of phyllo-erythrin in the blood stream. The phyllo-erythrin was produced in the intestines by bacterial and infusorial action and was dependent on a chlorophyll-rich diet. By feeding sulfonmethane to rabbits Perutz (1910, 1912; produced porphyrinuria, and on exposing the ears of the animals to the radiation from a mercury arc he observed lesions which he considered similar to the dermatitis of hydroa vacciniforme.

As a general rule, the porphyrins which have been prepared in the V laboratory have been found to be photodynamic, but according to Hausmann (1913) some porphyrins occurring in urine do not possess this property. From the evidence available it appears that the naturally occurring porphyrins vary in their photodynamic properties according to experimental conditions. In working with different specimens of urine, all of which contained porphyrin, Fischer, Awoki and Shibuya rendered mice sensitive to sunlight by injecting such urine, but the same specimens of urine did not prove photodynamic for either erythrocytes or paramecia. However, Hausmann (1916) claimed to have obtained photodynamic action on both erythrocytes and paramecia with a specimen of urine of the same source as that employed by Fischer. Under the same experimental conditions he obtained like results with a sample of urine from a patient with porphyrinuria associated with lead poisoning, although this patient was not reported as being sensitive to light. He stated that the presence of urine will not prevent photodynamic action. Schmidt-LaBaume extracted porphyrin from the urine of a patient with hydroa vacciniforme and injected it into mice. He obtained no evidence of sensitization on exposing the animals to sunlight, although they had received amounts which he considered sufficient to have produced such a condition. Fraenkel extracted porphyrin from urine and injected it several times into young rabbits and guineapigs. He observed discoloration of the teeth due to deposition of porphyrin, but on exposure to sunlight only one animal proved to be sensitive to light.

In the field of human experimentation, Meyer-Betz subjected himself to an intravenous injection of hematoporphyrin. Exposures to direct sunlight of short duration resulted in pronounced subcutaneous edema of the hands and face followed by superficial necrosis in a few areas. The hypersensitivity to the sun's rays persisted for several weeks. He considered that he had reproduced lesions similar to those of hydroa vacciniforme and hydroa aestivale, but the evidence of this similarity is far from convincing. In another heroic gesture, backed by no logical justification for so doing, Strauch attempted to treat rickets in children by the intravenous injection of hematoporphyrin followed by exposure to direct solar radiation. A subcutaneous edema of the exposed parts with formation of vesicles and sloughing in the region of the vesicles was the result.

Accidental photodynamic sensitization in man has been observed as a result of intravenous therapy. Marceron and also Jausion and Marceron observed the development of itching, erythema and vesicles in exposed regions as a result of the intravenous injection of acridine vellow and of exposure to direct sunlight. In the second case the reaction appeared immediately after the exposure to light, but in the first there was a lag of thirteen hours between the exposure to light and the appearance of the dermatitis. The sensitivity persisted for from twenty-four to forty-eight hours. Noltenius experienced similar results following the use of acriflavine, but the patient whose case was reported by Rathery and Marie was subjected to a milder exposure to light and escaped with slight subcutaneous edema and no vesicle formation. In a patient treated with trypaflavine and exposed to radiation from the mercury arc Haxthausen later observed hypersensitivity to sunlight. He found that the activating light in this case was in the region of 4,000 angstroms, although the light absorbed from the spectrum by this drug is supposed to be in the region of 4,580 angstroms.

### HYDROA VACCINIFORME SEU AESTIVALE, SUMMER PRURIGO, ETC.

As is well known the skin diseases associated with exposure to sunlight exhibit some well marked clinical variations, and these variations have been employed as a basis for subdividing the group into various disease entities. However, there is considerable controversy as to whether or not the clinical variations are more than different manifestations of a single disease. A consideration of the histology of the various clinical manifestations has failed to clarify the situation. Glaubersohn and Goldenberg observed that the microscopic changes in summer prurigo were confined to the skin and consisted of erythema, edema and round cell infiltration. In hydroa aestivale Adamson and Sellei each observed the same inflammatory reaction with the addition of hemor-

rhage. The microscopic lesions of hydroa vacciniforme, according to Bowen, Malinowski and Scholtz, extend to the subcutis and consist of erythema, edema, round cell infiltrations, hemorrhage and necrosis, followed by healing with scar formation. The variations in the microscopic changes, therefore, appear to be quantitative rather than qualitative. A pathologic basis for subdividing this group is further complicated by the observations of Wolters, and Mibelli, who found that the extent of the inflammatory reaction frequently varied in different regions in the same case of hydroa vacciniforme. In addition to the lesions noted by other investigators, these authors observed thrombosis of the superficial blood vessels. Möller was able to vary the degree of the reaction by varying the amount of light energy, the extent of the reaction being proportional to the amount of light energy to which his patient with hydroa vacciniforme was exposed. Günther's (1912, 1922) classification of porphyria for this group of diseases, including the acute "idiopathic" porphyrinuria and the porphyrinuria associated with sulfonmethane, lead and other poisons, has added little but confusion since, according to his own reports as well as those of other investigators, photosensitization does not appear to be a constant clinical manifestation of acute "idiopathic" porphyrinuria or of the porphyrinurias associated with various forms of poisoning. Therefore, if in this group of skin diseases, which evidently represent true photodynamic sensitization, one is to find more than one disease entity it must be done on the basis of etiology.

Anderson described a case of hydroa aestivale associated with porphyrinuria in 1898, but the possible significance of the excretion of porphyrin in such cases appears to have received little attention until about 1905. As the years passed this subject attracted more interest, and in recent years it has been considered a factor of prime importance. As cases of solar dermatitis have received closer attention it has been found that porphyrinuria is a frequent but not constant clinical manifestation, especially in hydroa vacciniforme seu aestivale; and less frequently it may be associated with the milder forms such as eczema solare, etc. I have reviewed fifty-seven cases of hydroa vacciniforme seu aestivale which have been reported since significance was attached to the porphyrinuria. The presence or absence of porphyrinuria was not determined in twenty-five cases of this group, and in twenty-three of the remaining thirty-two cases the condition was associated with porphyrinuria. However, in nine cases reported by Funfack, Greenbaum, Mühlmann and Akobjan, Senear and Fink, and Wucherpfennig the condition was not associated with porphyrinuria. It is frequently stated that eczema solare and other mild forms of solar dermatitis are not associated with porphyrinuria, but in five of twenty-eight reported

cases in which this subject was considered (reported by Templeton and Lunsford, Goeckerman, Osterberg and Sheard, Pick, and Sellei and Liebner) this association was observed. It is, therefore, evident that porphyrinuria is not a constant factor but may occur in any of the various clinical forms of solar dermatitis. The significance of porphyrinuria is further obscured by such cases as the one reported by Strasser and Urbach in which the porphyrinuria did not occur until after the second reaction on exposure to light and the case reported by Gottron and Ellinger in which the excretion of this pigment was intermittent. It is of interest to note that in the latter case there was a period of two years during which the patient was not sensitive to light, but whether porphyrin was excreted during this period was not made clear. Martenstein (1922), Goeckerman and collaborators, and Templeton and Lunsford found that the appearance and disappearance of porphyrinuria coincided with the appearance and disappearance of the dermatitis which resulted from exposure to either solar or mercury arc radiation; thus support was lent to their opinion that the excretion of porphyrin is the result rather than the cause of the disease, an opinion also shared by Kämmerer. However, a dermatitis following exposure to light is not essential to the appearance of porphyrin in the urine, as Linser reported a case in which exposure of the hands to roentgen radiation was followed by porphyrinuria, although no dermatitis occurred as a result of exposure to light.

Under certain conditions the porphyrinogens have been found to be photodynamic, and their excretion in the urine may be just as significant as the excretion of porphyrin, but this subject has received very little consideration. Schrews and Carrié observed the excretion of porphyrinogen in a case of hydroa vacciniforme following exposure to light; and Rodelius and Schumm and also Perutz (1917) observed that the disappearance of porphyrin from the urine was marked by the appearance of porphyrinogen. The absence of porphyrinuria may be explained on such a basis, but in a case such as the one reported by Marceron in which the sensitivity to light occurred but once during the spring of each year, considerable difficulty is experienced in reconciling the cause of the sensitization to the presence of porphyrin, or its leukobase, of such regular and limited occurrence.

If the sensitivity to light is due to the presence of porphyrin or porphyrinogen, the genesis of the porphyrin is of prime importance. Urbach and Blöch, Stein, and Strasser and Urbach considered that the presence of the porphyrin was the result of a hepatic insufficiency, a condition which they demonstrated in their cases. This opinion is in accord with the results of Schrews and Carrié, who found that macerated raw liver was capable of destroying large amounts of uroporphyrin.

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The presence of basophilic stippling and nucleated erythrocytes in the blood stream caused Gray, Mackey and Garrod, and Ashby to attribute the origin of the porphyrin to a pathologic marrow. The cases reported by Ashby and by Mackey and Garrod, as well as a similar case reported by Soto and Takahashi, are somewhat unusual, as the teeth and bones of the patients were discolored by deposits of porphyrin. In a case reported by Haranghy the porphyrin was considered to be of intestinal origin—the result of bacterial action. The patient, a child, following a sun bath presented a pronounced erythema and edema of all exposed areas, succeeded in a few days by icterus. Later the child died. At autopsy the liver and kidney showed both fatty and necrotic changes. An organism was isolated from the digestive tract which was able to produce porphyrin on artificial mediums in the presence of erythrocytes. The pathology in this case bears considerable resemblance to the pathology of some of the photodynamic diseases of the lower animals.

Attempts to demonstrate a photodynamic substance in the blood stream in persons affected with solar dermatitis have met with little success, although Mühlmann and Akobjan injected the serum of such a patient into rats and demonstrated photosensitization on exposure to the radiation from a mercury arc. With the serum of his patient, Bernstein obtained similar results in both guinea-pigs and rats. He claimed that the sensitizing agent was not porphyrin.

Because of the fact that many persons with hydroa vacciniforme seu aestivale have reacted to light from a mercury vapor quartz lamp it appears to be generally accepted that the ultraviolet rays are the activating rays in such cases. However, this conclusion cannot be accepted without question since unfiltered light was employed in many instances. The use of filters in some well controlled experiments has revealed a noticeable lack of agreement as to the specific activating light in the various forms of solar dermatitis. Möller was evidently the first investigator to attempt to locate the activating light by the use of filters. In a case of hydroa vacciniforme he found that the specific light was absorbed by ordinary window glass, thus placing the wavelength at somewhere below 3,500 angstroms. Martenstein (1922) obtained similar results in one of two cases, but in the second case he obtained a reaction beneath window glass from the light of a mercury arc. In spite of the results in the second case he concluded that the wavelength of the activating light was below 2,800 angstroms. Wucherpfennig reported his observations on three cases in which a wavelength of 2,750 angstroms was effective, but the maximum reactions were obtained with light the wavelength of which was somewhere between 3,000 and 3,500 angstroms, and light with a wavelength of 4,500 angstroms had some activating power. The patient whose case was

reported by Schmidt-La Baume was sensitive to light with a wavelength in the region of 2,900 angstroms but not to light of a greater wavelength. Werther found two persons sensitive to the middle portion of the ultraviolet rays but his methods of filtration were not given. Barber, Howitt and Knott employed a tungsten arc and found that the activating light for their patients had a wavelength of between 3,400 and 4,400 angstroms. By the use of more selective filters Funfack narrowed this band and located the light to which his patients showed sensitivity in the band with wavelengths from 3,700 to 3,900 angstroms. Ehrman (1905) found that all colored glass except cobalt absorbed the activating light for his patient, thus excluding the ultraviolet rays and locating the active band somewhere within the blueviolet. In spite of these observations and without apparent justification he concluded in a later publication (1909) that the red rays were a factor in hydroa vacciniforme. The patient whose case was reported by Urbach and Blöch was sensitive to light of a shorter wavelength than 4,000 angstroms.

As to the less severe forms of solar dermatitis, Goeckerman, Osterberg and Sheard found that the activating light for a patient with eczema solare had a wavelength in the region of 3,000 angstroms. Beinhauer employed the sun as a source of light and observed that the lesions of urticaria solare could be produced beneath a nickel oxide glass filter, thus placing the activating rays for this patient well within the ultraviolet region. The specific light for the case reported by Duke was absorbed by all colored glass except violet, and thus the wavelength was located at about 4,500 angstroms. In perhaps the best series of light filtrations which has been reported, Blum, Allington and West found a patient with urticaria solare to be sensitive to light of wavelengths from 4,100 to 4,900 angstroms, with the probability that the specific light was of greater wavelength than 4,500 angstroms. Bernstein, Frei and Veiel reported similar cases in which the sensitization was evidently produced by some part of the visible spectrum, as window glass failed to absorb the activating light. Vallery-Radot and co-workers (1928) excluded the ultraviolet and infra-red rays in the sensitization of their patient, and Urbach and Konrad narrowed the activating part of the spectral field by locating the specific rays in the red-green end of the spectrum. The patient whose case was reported by Ward was evidently sensitive to the yellow or yellow-green portion of the spectrum, as the activating light was absorbed by red glass, but some reactions were obtained under yellow glass filters. The patient whose case was reported by Weiss was probably sensitive to the ultraviolet rays, but as in the case of several other investigations the failure to employ proper filters renders such a conclusion questionable.

In patients who were known to be sensitive to solar radiation Lehman, Gray, Moro, Taussig, Artz and Hausmann, and Pautrier and Payenville failed to obtain evidence of sensitization by exposures to artificial light. This failure probably rests on one of two explanations: first, there may have been insufficient light energy, and, second, the region of the body employed for the test areas may have been improperly chosen. According to Möller, and his observation has been confirmed by other investigators, the regions normally exposed to light and on which dermatitis has occurred are more susceptible to subsequent exposures to light than are regions normally protected from light and on which no dermatitis has occurred. Moreover, Möller found that dermatitis could be produced in protected regions by repeated exposures to light. Therefore, a negative result from a single exposure to light is of no significance if the region exposed is one normally protected from the rays of the sun.

#### XERODERMA PIGMENTOSUM AND SKIN CANCER

The relation of sunlight to the onset of xeroderma pigmentosum in children is well established. The nature of the initial attack and the continued susceptibility to solar irradiation present a striking resemblance to true photodynamic sensitization. However, in seamen's skin this resemblance is less marked since there appears to be no sudden onset as a result of exposure to sunlight, such as is observed in solar dermatitis or in the photodynamic diseases of the lower animals. There is no reason to question the association of sunlight with the development of xeroderma pigmentosum, but efforts to demonstrate the presence of a photodynamic substance in the blood or arine of such persons have been uniformly negative with the exception of the person whose case was reported by Margarot, Plagniol and Balmes. Stercoporphyrin was being eliminated in the urine of this person, but the relationship of the porphyrin is difficult to determine since the condition was also complicated by tuberculosis.

As to the activating light in xeroderma pigmentosum, Martenstein (1924) observed that the reaction resulting from exposure to ultraviolet rays was about the same as obtained in normal persons but that it persisted for several weeks. He found that exposures to roentgen rays produced pigmentation and desensitization to ultraviolet rays. Martenstein and Bobowitsch observed in this disease in children a greater susceptibility to ultraviolet rays than to roentgen rays, but in mature people with this disease the susceptibility to rays was reversed. The sensitivity of children to ultraviolet rays was also noted by Birnbaugh, Lynch and Margarot and his associates, but in a child studied by

Greenbaum no unusual sensitivity to ultraviolet rays was observed. In a man described by MacCormac no hypersensitivity to ultraviolet rays was detected. The sensitivity to roentgen rays evidently was not determined. A youth 19 years of age reported on by Juon showed hypersensitivity to roentgen rays, and exposures to ultraviolet rays produced abnormal pigmentation. However, the susceptibility to light rays is evidently not determined by the age of the patient, as a person 28 years of age described by Rothman showed no abnormal susceptibility to roentgen rays, but exposures to ultraviolet rays were followed by prolonged erythema and the appearance of telangiectases in exposed regions. Gougerot, without experimental evidence, considered that the activating rays in xeroderma pigmentosum were of shorter wavelength than the ultraviolet rays. Corlett claimed a cure by roentgen ray treatments in a case in which the disease on the hands had progressed to a cancerous stage. Pigmentation has long been considered to be the natural protective reaction to light, but Lukasiewicy observed that in his case the erythema resulting from solar irradiation was greater in pigmented areas than in nonpigmented areas. Since no definite band has been shown to be the activating light and since the presence of a photodynamic substance has not been demonstrated it remains to be proved that this form of cancer is a true photodynamic disease.

The relation of a photodynamic reaction to the development of other cancers of the skin in regions normally exposed to sunlight is even less marked than it is in xeroderma pigmentosum. The statistical review presented by Hyde on the predominance of skin cancer in the white race and the higher incidence of the disease in localities in which there is a greater intensity of solar radiation lend support to the theory that sunlight is an etiologic factor. The relation of sunlight to the origin of cancer was further reviewed and discussed by Foveau de Courmelles, Grynkraut, Bechet (1934) and Dubreuilh, all of whom presented strong arguments in favor of this hypothesis. However, in the present state of knowledge, to attribute the development of such cancers to a photodynamic reaction is hardly justifiable since there is no characteristic reaction on exposure to sunlight nor has any photodynamic substance been demonstrated. The relationship of light probably depends on a decreased resistance of the skin to the irritating effects of light rays as a whole or to long-continued irritation rather than on the presence of a photodynamic substance. The results of animal experimentation are in keeping with such an interpretation since Holtz and Putschar and later Putschar and Holtz subjected rats, and Herlitz, Jundell and Wahlgren, mice, to ultraviolet rays and observed the development of cancers. However, the reactions in these experi-

ments were not the reactions of photodynamic sensitization but rather the responses to destruction of tissue by continued irritation, with the development of cancers in the irritated regions. Chronic irritation also operated in the results of Dormanns and of Findley, who painted white mice with tar, exposed the animals to radiation from a mercury arc and observed the development of cancers. Since two carcinogenic factors were employed in these experiments the results can hardly be attributed exclusively to photodynamic action.

#### PELLAGRA

The dermatitis of pellagra was perhaps the first disease to be associated with exposure to sunlight, as D'Oleggio suggested the designation of this condition by the term "vernal insolation" as early as 1784. However, it remains to be proved that this form of dermatitis is primarily a photodynamic sensitization. After the dermatitis becomes established, sensitivity to solar radiation is demonstrated in some cases, as Enright observed that recovery from the dermatitis might be followed by recurrence if exposure to sunlight occurred too soon. Mook and Weiss found that erythema and vesicles could be produced in a pellagrous skin by a two hour exposure to direct sunlight. However, in some localities such an exposure would be sufficient to produce erythema and vesicles in many normal people. Gougerot and Meyer (1932) tested the sensitivity of three patients to the rays of a mercury arc and observed that one was hypersensitive and the other two hyposensitive to rays from this source. The one patient showed no sensitivity on exposure to infra-red rays, but exposure to either blue or yellow light resulted in an inflammatory reaction. In a later report on a case (1933) they stated that they had found both yellow and red light to be effective, with the red producing the greater reaction. From these results the activating light appears to include the greater part of the visible spectrum, which is a rather wide band, if the sensitization is attributed to the presence of a photodynamic agent in either the skin or the blood stream. In contrast to the positive evidence of sensitization to light, Sambon denied the significance of light as a causative factor on account of the fact that in Gipsy children, who go about naked, the lesions of pellagra are confined to the hands and feet. That the skin of pellagrous patients was sensitive to light could not be demonstrated by Bigland, Cantab and Liverp, who changed the location of clothing so that certain diseased areas were exposed and others protected from the direct rays of the sun. In the cases studied by Oppenheim (1919) there was likewise no demonstrable susceptibility to light. The appearance of the disease in patients who had been confined to a hospital for

months led MacCowan to doubt the importance of light as an etiologic factor, and the patients whose cases were reviewed by Merk showed no unusual susceptibility to light.

Jobling and Arnold isolated an aspergillus from the digestive tracts of pellagrins, which on artificial mediums produced a fluorescent substance. They considered these results to be of significance in the etiology of pellagra since the fluorescent substance proved to be photodynamic on injection into rats. However, such results are of lessened significance since the fluorescent substance was not administered through the digestive tract. No appreciable difference was found in a spectroscopic analysis of the blood serum of pellagrins and of normal persons by Scott, Turner and Mayerson. In view of the facts that sensitivity to light is not a constant factor, that Goldberger and Wheeler were able to produce pellagra with rations low in protein, and that Wheeler was able to cure the disease with one daily supplemental meal which supplied the protein requirements, irrespective of light conditions, the importance of light in pellagra appears to be secondary rather than primary. Since the photodynamic diseases of man and the lower animals are confined to the white races and species, or if the animals are spotted, to the white portions of the skin, and since pellagra is of frequent occurrence in Negroes, the classification of this disease with true photodynamic sensitization is open to question. The sensitivity to light is probably of the same nature as that which is sometimes observed in lupus and acne.

Efforts to produce pellagra in the lower animals have been productive of suggestive but not conclusive results. The feeding of rabbits, rats, guinea-pigs and mice on rations of which the chief ingredient was corn and exposing part of the animals to direct sunlight have resulted in the appearance of erythema, edema and loss of hair. A feeding period of from thirty to sixty days was generally required to produce such lesions, and in the animals exposed to sunlight there was a higher mortality than among the animals maintained in the dark or in diffuse light. As a whole, the results of various investigators were not clearcut, and in many cases the evidence of photosensitization appears questionable. Raubitscheck (1910, 1911) fed a corn ration to white and dark-colored mice and on exposure to sunlight noted mild dermatitis in the white mice, while the dark mice were not affected. However, some deaths occurred among mice which were fed little or no corn but which were exposed to sunlight, and also among control animals which were kept in the dark. Deaths among the control animals he attributed to infection. Lode observed loss of hair in guinea-pigs as a result of a corn diet and exposure to light. Horbaczewski observed pruritus, eczema and loss of hair in white mice and rats as a result of

corn rations and exposure to light, but the cause of the dermatitis is questionable since he obtained eczema among the animals which were kept in the dark. In addition to erythema and loss of hair in white mice, Umnus noted enteritis as a result of feeding either white or yellow corn and exposure to sunlight. However, loss of hair occurred in some of his control mice. In one experiment with yellow corn which had been gathered in a pellagrous region he obtained entirely negative results. A dermatitis which Pfeiffer (1911) considered to be similar to the dermatitis of pellagra was produced in a mouse by feeding commeal cakes and exposure to sunlight. Hausmann (1910) fed two white rabbits a strict corn ration and exposed them to the radiation from a mercury arc. Erythema and edema followed, which he considered to be similar to the lesions of pellagra. The earliest experimental work of this nature appears to be that of Bezzola, who fed 150 guinea-pigs on rations of which the chief ingredient was corn. Since he did not consider the relationship to light, it is reasonable to assume that his animals were maintained in a building in diffuse light and were not exposed to direct sunlight; nevertheless he observed enteritis and loss of hair similar to those seen by later investigators. If the assumptions concerning his experimental conditions are correct it is evident that exposure to direct sunlight is not required to produce the mild dermatitis noted under such conditions. Further, if this dermatitis is a manifestation of photodynamic action it is the only example of photosensitization in the higher animals produced by diffuse light, exposure to direct sunlight being required to produce the reaction under both field and experimental conditions. Practical experience has shown that corn can be fed to farm animals without the development of any evidence of sensitization to light. The results of Rühl are in keeping with practical experience, as he fed rats and guinea-pigs on rations composed principally of corn for as long as two months, and following direct solar irradiation observed no evidence of sensitization. Chittenden and Underhill fed dogs on a ration consisting of peas, cracker meal and cottonseed oil and produced pustular stomatitis, which they were able to cure by supplying a more adequate diet. They considered these results to be of significance in the etiology of pellagra. It is therefore evident that the relation of light to the dermatitis produced in laboratory animals by the feeding of corn must be accepted with many reservations. Corn is not a suitable ration for laboratory animals; furthermore, rodents are naturally susceptible to solar radiation, exhibiting ill effects which, according to Lumière, and Remlinger and Bailly, are primarily due to the heat. It is therefore possible that the ill effects of a corn ration and exposure to light may represent the combined action of malnutrition and heat rather than photodynamic sensitization.

### BERLOCK DERMATITIS AND ALLIED CONDITIONS

The development of some peculiar pigmented streaks on the neck and shoulders of a woman led E. Freud to suspect that their occurrence was associated with the application of perfumed spirit N. F. (eau de cologne) prior to a sea bath. The application of this agent to the skin of a boy prior to a sea bath resulted in the appearance of pigmented areas similar to the lesions first observed. Under like conditions a more severe reaction was observed following the application of oil of bergamot. A similar condition was observed by Hoffmann and Schmitz. which they were able to reproduce by painting the skin with perfumed spirit and exposing the painted areas to solar radiation. With a mercury arc as a source of light, Goodman found that either perfumed spirit or perfume produced erythema and pigmentation which persisted for several weeks. Gross and Robinson obtained similar results with perfume and sunshine, and Bonnet observed erythema following the application of perfumed spirit and exposure to sunlight. In eighteen of twentytwo tests with perfume, toilet water and essential oils, Szántó (1928, 1929) obtained erythema and pigmentation following the application of these agents and exposure to radiation from a mercury arc. The application of oil of bergamot followed by solar radiation produced an inflammatory reaction which included the formation of vesicles, according to the investigations of both Richter and Zurhelle. The latter also noted necrosis as a late manifestation. The activating light for the dermatitis produced by the application of oil of bergamot was located by Giraudeau and Acquaviva somewhere between the ultraviolet and the green portion of the spectrum, and that for the dermatitis produced by eau de Javelle (a solution of chlorinated potassium) by Vallery-Radot and his collaborators (1926) in the portion from violet to green. Rosenthal reported an instance of dermatitis of this nature. but the cause was not determined. Wimmer and Goodman found that a large number of the essential oils used in perfumes and toilet waters are fluorescent, suggesting that this phenomenon may be associated with substances productive of dermatitis. On the other hand, it is to be noted that Touraine and Ménétrel observed no reaction following the application of perfume and exposure to sunlight. Negative results were also obtained with applications of perfume and of radiation from the mercury arc by Downing and by Lane and Strauss.

An analogous condition, although manifested by more extensive lesions, is to be found in the vesicular dermatitis of fig workers which was reported by Kitchevatz (1934). An alcoholic extract of the peel of the figs was applied to the arm and back of a man, and the treated areas were exposed to solar radiation for fifteen minutes. Vesicles

formed at the end of twenty-four hours, but the height of the reaction was not attained until about the forty-eighth hour. Bathing followed by a sunbath in contact with certain plants has been associated with the appearance of bullae which Lanzenberg, Oppenheim (1932) and Ullma considered a form of photosensitization. However, the relation of light to this condition was not proved.

The evidence obtained by Lewin was sufficient for him to consider light as an important factor in a dermatitis which he had observed among a group of asphalt workers. Herxheimer and Nathan observed dermatitis among persons working with carboneol (an ointment consisting of a coal tar distillate prepared in a petrolatum paste on a zinc oxide base). By painting the skin with this agent and exposing the painted areas to sunlight they were able to reproduce the dermatitis. No reactions occurred on areas which had been painted with this substance but protected from direct exposure to sunlight. Fleischhauer found that the local application of dehydrated coal tar and exposure to direct sunlight produced an erythema persisting for seventy-two hours. By the use of filters he found that the activating light for this reaction had a wavelength between 3,500 and 4,500 angstroms.

L. Freud described a form of photosensitization which is manifested by sneezing and is produced by looking at strong light. Colored glasses, either red or green, prevented the sneezing, but glass which transmitted either blue or violet light had no preventive action.

# DERMATITIS WITH SECONDARY SENSITIVITY TO LIGHT

Various skin diseases in man are frequently associated with an abnormal sensitivity to light, according to the literature on the subject. As an example of dermatitis in which the photosensitivity is secondary, Greenbaum cited mercurial dermatitis, and Rasch reported a case of pityriasis simplex in which light therapy was followed by a pronounced inflammatory reaction. Bettmann described an example of acne necrotica in which light therapy was followed by the appearance of lesions similar to those of hydroa vacciniforme. Bechet reported on a photosensitive condition of patients with lupus. Anderson and Ayers also observed lupus associated with photosensitization and described a patient with vitiligo in whom the involuted areas became eczematous and later sensitive to direct sunlight. It is obvious that the reaction in such cases is secondary in a previously altered skin and is similar to the reaction obtained by Grosz and Volk in administering the intradermal test to tuberculous guinea-pigs. They noted a greater reaction in test areas which were exposed to radiation from the mercury arc than in areas not so exposed.

#### FAGOPYRISM (BUCKWHEAT POISONING)

Photosensitization in man as a result of eating buckwheat or the products thereof has not been described in medical literature, but "buckwheat rash" as a visual manifestation in those who use much buckwheat is said to be popularly recognized in the northern part of the United States. The case reported by Smith, which is frequently cited as an example, was an instance of an allergic reaction with no evidence of hypersensitivity to light.

According to Merian, who reviewed the literature prior to 1915, the first published report of buckwheat poisoning in farm animals was that by Hertwig in 1833. Hertwig observed that the occurrence of the disease in a herd of swine was associated with the eating of buckwheat and exposure to direct sunlight. Merian reviewed twenty-three reports of this or a similar disease in cattle, horses, sheep, goats and swine. In some of the cases concerned in the early reports, photosensitization was due evidently to the eating of some other plant since there was no history of contact with buckwheat, but in the remainder of the reports the etiology was established by a history of grazing in buckwheat pastures or, if the animals were stabled, feeding on the plant followed by exposure to bright sunlight. In the earliest reports two forms of the disease were described. The first was an acute condition, manifested by sudden attacks of convulsions and cerebral excitement, with squealing, bellowing, etc. In many cases the" appearance of the first symptoms was soon followed by paralysis and death. The second or chronic form consisted of pruritus, erythema, edematous swellings of the face and ears and necrosis and sloughing of the skin over the edematous areas. Licking and rubbing in addition to the sloughing resulted in large denuded areas. The disease was observed to be confined to white animals or to the white portions of spotted animals. Protection from direct sunlight was generally followed by uneventful recovery. From these early reports it is evident that little has been added to the pathology of the disease in recent years. According to Merian, the first experimental proof of the relationship of light to buckwheat poisoning was reported by Medding in 1887. He fed a cow on buckwheat and after painting one of her sides with coal tar exposed her to bright sunlight. The characteristic reaction developed on the unpainted side, but the painted side was not affected.

Ohmke fed the fruit of buckwheat (Fagopyrum esculentum, the species used by all investigators) to mice, guinea-pigs and rabbits and on exposure to direct sunlight observed manifestations similar to fagopyrism in farm animals. Alcoholic extracts of buckwheat were found to be photodynamic, and the wheat thus extracted was no longer capable

of sensitizing animals to light. J. Fischer found that the feeding of buckwheat to the same species of experimental animals rendered them. sensitive to sunlight, the first evidence of sensitization appearing within seven days. He also observed enteritis in addition to the usual lesions. of photosensitization. Merian produced photosensitization in rabbits. and guinea-pigs by feeding the foliage of buckwheat and obtained like results by feeding F. tartaricum and F. griseum, with the sensitization occurring as early as the fourth day. Similar results were obtained by Lutz and by Lutz and Schmidt by feeding the fruit of buckwheat to mice and the fruit and foliage of the plant to guinea-pigs. Sensitization was demonstrated in some of the guinea-pigs as early as the second day, and it persisted in some animals for thirty-six days after the feeding of the buckwheat had been discontinued. Sheard and co-workers. sensitized guinea-pigs, goats and swine by feeding the green foliage of the plant; they obtained no sensitization in rabbits, rats or dogs by the same method. They found guinea-pigs to be the most susceptible.

Lutz found that his animals were sensitive to radiation from a mercury arc or from a 1,500 watt electric light, but that the reactions to artificial light were less pronounced than those to solar radiation. Sheard and co-workers observed no reaction to radiation from a mercury arc and but slight response to that from a carbon arc. By the use of filters the activating light was located between that with a wavelength of 5,800 angstroms and the red end of the spectrum. Merian found that the activating light was absorbed by fresh solutions of either methylene blue or eosin but that after bleaching of the dyes had occurred the specific light was no longer absorbed. He found artificial light to be unsatisfactory for the demonstration of sensitization in his animals.

Fischer and Lutz each obtained a fluorescent substance from the foliage of buckwheat by extracting with alcohol. This product had some photodynamic properties when injected into laboratory animals, but no sensitization occurred as a result of feeding the extract. Both authors attached etiologic significance to these results, but, as previously stated, results from the injection of plant extracts are of little value in this connection.

Bruce produced vesicular dermatitis by feeding Polygonum persicaria to a swine in the presence of direct sunlight, but negative results were noted on feeding the same plant to a bull.

The observations of Bichlmaier are rather surprising in view of the clinical and experimental evidence of the photodynamic properties of buckwheat. He claimed that buckwheat fields were commonly used as a pasture for calves, swine and birds in Hungary and that no ill effects resulted from this practice. He fed the fruit and foliage of the plant to guinea-pigs, sheep and rabbits and on exposure of the animals to

direct sunlight observed no evidence of photosensitization. Hilz accepted these results as positive evidence that the relation of buckwheat to fagopyrism had not been proved. Brandl and Schärtel stated that they were unable to produce sensitization to light in experimental animals by feeding the fruit of buckwheat or by the injection of alcoholic extracts of the same. The details of this part of their experimental work were not given.

### HYPERICISM

It is difficult to determine when the effects of grazing Hypericum first began to attract attention. The Arabian custom of painting horses with tobacco or henna to protect them against the dermatitis resulting from the grazing of H. crispum has evidently been practiced for several centuries, although the frequent references in the literature on this subject do not state how long the practice has been in vogue. According to Marsh and Clawson, the earliest published report on the toxicity of H. crispum is that by Cirillo in 1787. Although Cirillo observed that the toxicity was confined to white sheep, he evidently did not associate the toxicity with exposure to light. The significance of sunlight in this disease was recognized by Verheyen in 1849. The clinical manifestations are practically the same as those of fagopyrism and are generally associated with the grazing of the plant. However, Paugoué and Henry (1913) each observed the disease in horses, in which it was the result of eating hay which contained H. perforatum.

Dodd (1920) fed H. perforatum to sheep in the presence of sunlight and observed edematous swellings of the face and ears on the thirteenth day of the experiment. The reaction was probably delayed by cloudy weather. The edema and dermatitis which followed were similar to the lesions he had observed in cattle, horses and sheep under range conditions in Australia. Henry (1922) also reproduced the disease in sheep by feeding the same plant, and by muzzling sheep and allowing them to run in fields which were badly infested with the plant he proved that external contact with H. perforatum was associated with no ill effects. Marsh and Clawson produced mild pruritus, dermatitis of the muzzle and inflammation of brand scars in cattle by feeding H. perforatum, but not the edematous swellings described by other investigators. After feeding the same plant to sheep they observed mild dermatitis of the nose, face and ears with slight edematous swellings about the nose. It is of interest to note that this mild evidence of photosensitization disappeared while the experimental feeding was still in progress. They also noted albuminous degeneration of the parenchyma of the kidney and liver in addition to the external lesions. A form of dermatitis confined to the lips of horses was considered by

Richert to be due to the eating of St. John's wort, but since this lesion was also observed in two colored animals, one brown, the other chestnut, the diagnosis is subject to question. Seddon and White found that the feeding of H. perforatum for three days to a black and white steer was sufficient to render the white portions of the skin sensitive to light, and that the feeding of the plant for one day produced like results in guinea-pigs. Quin (1933) found that 200 Gm. of H. ethiopicum was sufficient to produce photosensitization in a sheep within two days, and that the feeding of H. leukoptychodes resulted in similar photodynamic action, but he considered this plant less potent than the former species.

According to the results of Seddon and White, the activating light for hypericism was not absorbed by either water or ordinary window glass. In sensitized guinea-pigs they painted one ear with carbolfuchsin, toluidine blue or trinitrophenol, leaving the other unpainted as a control. Following exposure to sunlight the unpainted ears and those painted with trinitrophenol showed the usual reaction, but the ears painted with either carbolfuchsin or toluidine blue showed no reaction; thus evidence was presented that the activating light for hypericism is located in the same region as that for fagopyrism. With no apparent justification, Richert considered the infra-red to be the activating rays in this condition.

Ray isolated from H. crispum a fluorescent pigment which he found to be photodynamic for experimental animals but failed to give his method of administration. Rogers found that the fluid extract of H. perforatum was photodynamic for sheep and rabbits, but as in the previous citation the method of administration was omitted. From the same plant Hausmann (1931) and Hausmann and Zaribnicky isolated a pigment which they found to be photodynamic for erythrocytes, and Černý and Mélas-Joannidès also each isolated a fluorescent pigment from Hypericum, but both authors failed to demonstrate the photodynamic properties of their extracts. The isolation from any plant of a fluorescent substance which on injection into experimental animals (either subcutaneously or intraperitoneally) proves to be photodynamic should not be accepted as evidence of the natural occurrenc of a photodynamic disease, as Hausmann (1908, 1909), Hausmann and Portheim, Kitchevatz (1933) and Gray and McIver have isolated photodynamic substances from a number of plants which when eaten by the farm animals do not produce photosensitization. Since the digestive tract is the normal portal of entry in the natural occurrence of the photodynamic diseases of the lower animals, extracts of plants should be administered by this route if a causative relationship is to be established.

### TRIFOLIOSIS (CLOVER DISEASE, ETC.)

Schindelka and Lutz each cited several reports in which the grazing of Trifolium was associated with the appearance of lesions similar to those of photosensitization. Hausmann and Glück reported on the occurrence of dermatitis in cattle which were grazing in a field of T. hybridum. In one black and white cow the dermatitis appeared on all the white spots, but in most of the affected animals the lesions were confined to the udders and teats and consisted of edema and vesicular and pustular eruptions. In view of the nature and location of the dermatitis in this outbreak the etiology is subject to question. The affected animals recovered without removal from the pasture in question. Bruce fed a swine on red clover in the presence of sunlight and observed erythema but no other evidence of photosensitization. From field observations it is evident, therefore, that the grazing of clover is sometimes followed by dermatitis which has all the appearance of true photosensitization. However, experimental proof of the photodynamic properties of the various species of Trifolium has not been presented.

An investigation of the "aphis disease" of New South Wales led Dodd (1916) to believe that it was caused by grazing trefoil (Medicago denticulata). He therefore fed guinea-pigs the fresh green plant and on exposing them to sunlight observed photosensitive reactions on the seventh day of feeding. The reactions were of the usual type, consisting of pruritus, edema of the face and ears, followed by necrosis, sloughing and healing beneath a scab. In his early investigations he had observed the same lesions in cattle, horses and sheep which were grazing this plant extensively. Bull and Macindoe failed to confirm Dodd's results and attributed the failure to the fact that they had fed a more mature plant than was fed by Dodd. In field cases of the disease they observed that the edema was confined to the skin and was not subcutaneous as is generally reported in the literature on photodynamic diseases of the lower animals.

### PHOTOSENSITIZATION FROM SUDAN GRASS

Howarth observed an outbreak of dermatitis in a band of sheep after they had grazed a pasture of sudan grass for ten days. The pathologic condition consisted of pruritus, edematous swellings of the lips, eyelids and ears, followed by oozing of serum from the edematous regions, superficial necrosis and healing beneath a brownish red scab. Black-faced rams were not affected. Removal of the animals to an adjacent alfalfa field was followed by complete recovery, with no new cases developing after the change of pasture. A second flock was observed in which there was erythema, followed by shedding of the wool, but the nature of the pasture in this case was not reported.

#### GEELDIKKOP (TRIBULOSIS)

The geeldikkop of South Africa, an important disease of sheep and goats, presents the usual lesions of photosensitization but differs from fagopyrism, hypericism, etc., in that the dermatitis is accompanied by icterus of hepatic origin. In an early investigation of the cause of geeldikkop, Theiler collected Tribulus terrestris from various sources and fed it to sheep. In this series of experiments fifty-six sheep were employed, but the disease was reproduced in only twelve animals. Feeding periods of from ten to sixteen days were required to produce positive results. Quin (1929) continued the investigation by grazing sheep in paddocks containing nothing but T. terrestris and reproduced the condition in eight of the nine animals employed in one experiment. The sensitization occurred after grazing periods of from three to six days. In subsequent experiments, conducted after geeldikkop had disappeared from the ranges, he obtained negative results in sheep by grazing and by feeding the plant. It is a matter of record that these investigators have obtained more negative than positive results in their experimentation with this plant, but their positive results are sufficiently clearcut to establish T. terrestris as one of the etiologic agents of geeldikkop. From their investigations it is evident that the photodynamic principle is not a constant constituent of this plant. Quin (1930) produced fatal results by drenching sheep with water extracts of this plant, but the pathologic condition which he observed was not that of geeldikkop.

Quin (1933) fed Lippia Rehmanni to sheep and noted photosensitization in three days. The lesions produced by this method were similar but not so extensive as the lesions observed in cases of geeldikkop on the range. He obtained similar results by drenching sheep with alcoholic extracts of the plant. In the same publication he reported on the feeding of L. pretoriensis and the observation of photosensitization on the third day. This sensitization disappeared four days later in spite of continued administration of the plant. Icterus was evidently not observed in this experiment.

As previously mentioned, Quin (1933) produced a condition similar to geeldikkop in sheep and goats by ligating the bile duct. In a continuation of this work Rimington and Quin, as well as Quin, Rimington and Roets showed that the photosensitization of animals treated in this manner was due to the presence of phyllo-erythrin in the blood stream and concluded that the photosensitization of geeldikkop was due to the action of this pigment. However, it remains to be shown that the feeding of T. terrestris to normal animals will produce phyllo-erythrinemia and subsequent photosensitization.

#### BIGHEAD IN SHEEP

The bighead of sheep in Utah and other Western States also presents a picture of photosensitization and of icterus similar to that of geeldikkop. Clawson and Hoffman fed sheep Tetradymia glabrata and T. canescens and observed degeneration of the liver and subcutaneous edema about the face. The lesions thus noted were similar to the lesions in field cases except that the reaction on exposure to light was less marked. However, the reaction to light under field conditions is reported as being quite variable. Judging from the results of this investigation, the bighead described by Frederick was probably due to the eating of one or both species of this plant.

### AGAVE LECHEGUILLA AND NOLINA TEXANA

The disease commonly spoken of as goat fever in the Southwest, though it also occurs in sheep and cattle, is similar to geeldikkop and bighead, but in addition to the usual lesions there is marked destruction of the renal parenchyma. Jungherr fed lecheguilla to sheep and goats and succeeding in killing twenty of twenty-four animals. These animals showed icterus, degeneration of the liver and "turkey egg kidney." Two of the animals had an edematous swelling about the head, twenty-four hours before death, but the swelling was not shown to be due to exposure to light. From field observations he concluded that the disease was due to photosensitization.

Tunnicliff fed the ripe fruit of sacahuiste (Nolina texana) to a sheep and observed an edematous swelling of the head. The condition thus produced is now known to be caused by eating buds, blooms or fruit of this plant and is similar in all respects to that produced by grazing the leaves of lecheguilla.

#### SUMMARY

The destruction of erythrocytes, toxins, paramecia, etc., by photodynamic action is evidently the result of oxidation. The reaction occurs in either diffuse or direct light, but it can also be obtained in the dark by the use of previously irradiated dyes. Direct exposure to light is required to produce photosensitization in animals which have received injections of eosin, erythrosin, porphyrin, etc. Oral administration of such agents has not resulted in sensitization of experimental animals. The porphyrins which have been prepared in the laboratory appear to be more uniform in their photodynamic action than those which occur in nature. In man intravenous injection of porphyrin, acridine hydrochloride, etc., induces photosensitization similar to that produced in the lower animals by injections of the same agents. Alcoholic extracts of a large number of plants have been found to be photodynamic on injec-

tion into experimental animals. However, sensitization has not been shown to occur as a result of oral administration of the same extracts.

Various clinical forms of dermatitis in man have been shown to result from exposure to light, but the nature of the photodynamic agent in these conditions has not been ascertained. It is assumed that the sensitizing agent is the porphyrin which is excreted in the urine of some of the patients. However, the excretion of porphyrin is not a constant manifestation of this group of diseases. Porphyrinuria has been found to appear after exposure to light and to disappear on protection from light; thus a basis is provided for the opinion that the porphyrinuria is the result rather than the cause of the disease. In some cases the disappearance of the porphyrin from the urine has been followed by the appearance of porphyrinogen, the significance of which has not been determined. The formation of the porphyrin is considered by some to depend on hepatic insufficiency and by others to be the result of a pathologic condition of the marrow. Attempts to demonstrate the presence of a photodynamic agent in the blood stream have been successful in only a few cases. The results of various investigations to determine the activating light for hydroa vacciniforme seu aestivale are not in accord, as the wavelength has been found to vary between 2,800 and 4,500 angstroms. In the milder forms of solar dermatitis still greater variations have been observed, since reactions have been obtained by exposures to light from the ultraviolet to the vellow.

The development of xeroderma pigmentosum is related to exposure to sunlight, but no relationship to a photodynamic agent has been proved, and the activating light has not been established. The development of cancer in regions normally exposed to sunlight appears to be associated with exposure, but there is no evidence to show that this is a photodynamic reaction. In experimental animals cancer has developed as a result of exposure to light, but the presence of a photodynamic agent is not required in this reaction.

The relationship of light to the development of pellagra has not been established. After the appearance of the dermatitis there is hypersensitivity to light in some cases, but in others this form of sensitization is not observed. The sensitization therefore appears to be secondary rather than primary and similar to the photosensitization which is sometimes observed in other skin diseases, such as lupus and acne. Dermatitis has been produced in laboratory animals by corn rations plus exposure to light, but there is reason to doubt that the dermatitis produced in this manner is caused by photosensitization.

Local applications of perfumes, toilet waters, coal tar derivatives and plant extracts followed by exposure to light produce a reaction consist-

ing of erythema and pigmentation and in some cases edema, vesicle formation and necrosis. This appears to be a true photodynamic reaction.

Photosensitization in man as a result of eating buckwheat has not been proved. In farm animals the disease occurs as a result of grazing buckwheat pastures or, in stabled animals, feeding on the plant and subsequent exposure to sunlight. The fruit and foliage of the plant are toxic. Fagopyrism is confined to white animals or to the white spots of spotted animals. Artificial light is not so effective as sunlight, and no reaction occurs on exposure to diffuse light. The activating light is located between light with a wavelength of 5,800 angstroms and the red end of the spectrum. Alcoholic extracts have been found to be photodynamic on injection into laboratory animals, but on oral administration the results have been inconclusive.

The disease produced by feeding animals Hypericum or by allowing them to graze is similar in all respects to that produced by feeding them buckwheat. Several species of this plant have been found to be toxic. The activating light appears to be the same as that for fagopyrism. Fluorescent pigments have been isolated from Hypericum, and the extracts have been found to be photodynamic for animals, but the method of administration has not been given.

The grazing of clover and sudan grass is reported as being associated with photosensitization of farm animals. However, there is no experimental proof that sudan grass or the various species of Trifolium have a photodynamic action.

The geeldikkop of sheep and goats of South Africa and the bighead of sheep of the Western States are photodynamic diseases which are associated with icterus of hepatic origin in addition to dermatitis. A similar disease is produced by grazing the leaves of lecheguilla and the buds, blooms and fruit of sacahuiste.

Publications which have added no new material have been omitted from this review. Special mention should be made of two excellent reviews, one on the photodynamic action of light by Blum (1932) and the other on solar dermatitis, especially from the human standpoint, by Hausmann and Haxthausen.

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