

# Some Therapeutic Considerations in Diabetic Retinopathy

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With the increasing emphasis on photocoagulation therapy in diabetic retinopathy, its potentials and, most probably, the beneficial effects such therapeutic modality may have in arresting or even improving diabetic retinopathy, one should realize the limitations, the present lack of factual knowledge, and the theories underlying such treatment. One should also keep in mind that light—including laser—coagulation of the retina is still employed selectively in quite a number of other pathological fundus conditions with time-proven effectiveness though it no longer receives the same wide general attention that its use in diabetic retinopathy receives today. Other ocular conditions exist, however, where investigators and practitioners in the field of ophthalmology differ strongly in their opinions as to the efficacy of this therapeutic tool, and even to the advisability of its use, for example, chorioretinal malignant tumors.

Much overemphasis has been placed on the use of laser in clinical retinal photocoagulation over the already established “white light source,” a high pressure Xenon arc lamp, as employed in the Zeiss

Photocoagulator. However, the latter is as useful today as it has been for over a decade prior to the invention of lasers. Of the many hundreds of laser sources now developed, only the solid state pulsed Ruby laser and the Argon gas laser—either with a continuous wave (CW) or in a pulsed operation—have, as of now, found wide utilization in clinical ophthalmology. Their use, sometimes in combination with the “white light” coagulator, add to our therapeutic armamentarium in certain clinical situations.

Figure 1 shows diagrammatically the spectral emission of the Xenon arc coagulator and the narrow band emissions within the visible, near ultraviolet (UV) and near infrared (IR) ranges of various lasers which are primarily of ophthalmological interest. Of those, the Ruby laser light is of a deep red color ( $\lambda$  694.3 nm), and the Argon laser has several bands of spectral emission primarily in the blue-green region ( $\lambda$  485-515 nm). Figure 2 presents the absorption characteristics of the retinal pigment epithelium and choroid for light of equal intensity and incident on the cornea.

The Ruby laser, usually operated in a single pulse mode in the microsecond range, and the variable retinal image diameter of the laser beam

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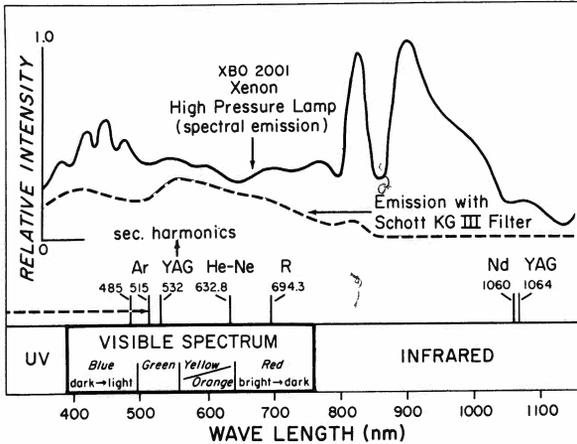


Fig. 1—Spectral position of light emitted from various laser sources in comparison with emission characteristics of a Xenon high-pressure light source.

of about 100-500  $\mu$  have proven to be of particular value in the treatment of small lesions close to the macula. The dark red color of the emitted laser beam allows for treatment without retrobulbar anesthesia, since in this spectral range no photophobia is elicited, and the eye has "no time to move" during the short exposure time. On the other hand, light of this wavelength is greatly reflected by the red blood vessels and only minimally absorbed by them, which makes it less usable for coagulation of vascular lesions. If those are located within the retina, the heat generated by absorption of the light in the retinal pigment epithelium may secondarily

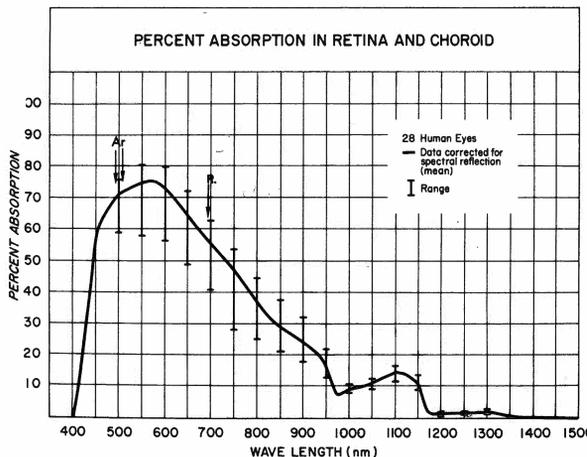


Fig. 2—Percent absorption in human retinal pigment epithelium and choroid for equal intensities and light incident on the cornea. Ar = Main Argon laser emission bands. R = Ruby laser wavelength.

cause vessel obliteration. In cases where vessel proliferation into the vitreous has developed, as seen primarily in diabetic retinopathy (fig. 3) among other pathological conditions, the Ruby laser light is relatively ineffective and may even be hazardous if the light energy is increased to achieve coagulation of vascular structures within the vitreous itself (7). This is the area where the Argon laser has found its principal and dominant role in clinical ophthalmology. The bright bluish-green laser beam produces photophobia similar to white light and, thus, in most situations retrobulbar anesthesia is required. This spectral wavelength is strongly absorbed by the hemoglobin and achieves coagulation of the blood with vascular obliteration most easily and successfully (6, 9).

In early stages of diabetic retinopathy with retinal microaneurysms, hemorrhages, and exudates (figs. 4 and 5), and in more advanced stages where neovascularization has already developed (fig. 6), both white light and Argon laser light are equally effective. Only in conditions where the lesions are close to the macula is the Argon laser superior since its greater light intensity permits retinal coagulation of very small foci, thus creating a condition of less potential danger to the macula and fovea.

More recently, Blair and Gass (2) showed that "mild photocoagulation" in the area of the maculopapillary bundle did not produce large central scotomata due to destruction of nerve fibers passing over the coagulated site to the optic nerve. This observation had been described in animal experimentation using histological techniques at various time intervals following light exposure (7), and in human volunteers whose eyes had to be enucleated for other pathological reasons (8).

The effectiveness of photocoagulation in diabetic retinopathy has not been statistically established on a large scale. Its evaluation is difficult since the natural pathological condition may frequently undergo periods of arrested states or even improvement. It is, therefore, not astonishing that a number of ophthalmologists are not in favor of this relatively destructive form of therapy. Proponents for photocoagulation therapy can be largely separated into two groups, that is, 1) those who prefer to coagulate only those lesions which may potentially cause vitreous hemorrhages and areas of neovascularization; and 2) those who want to therapeutically produce large chorioretinal scars involving areas of diseased and ophthalmoscopically

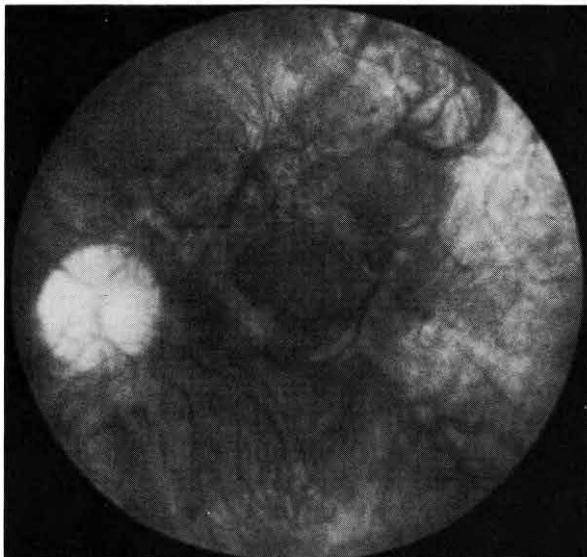


Fig. 3a—Massive vascular proliferation.

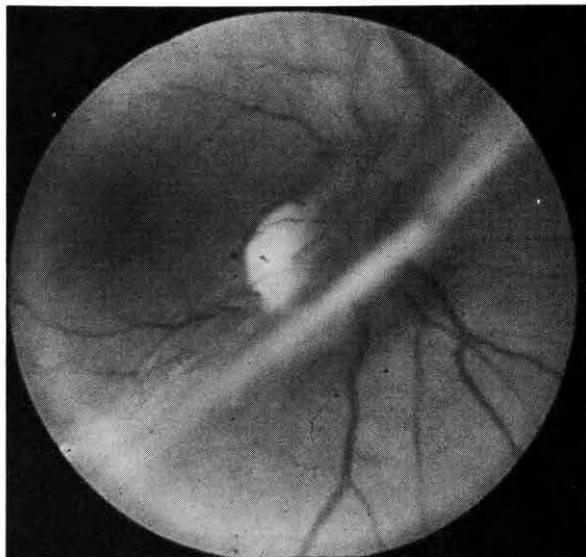


Fig. 3c—Moderate glial proliferation.

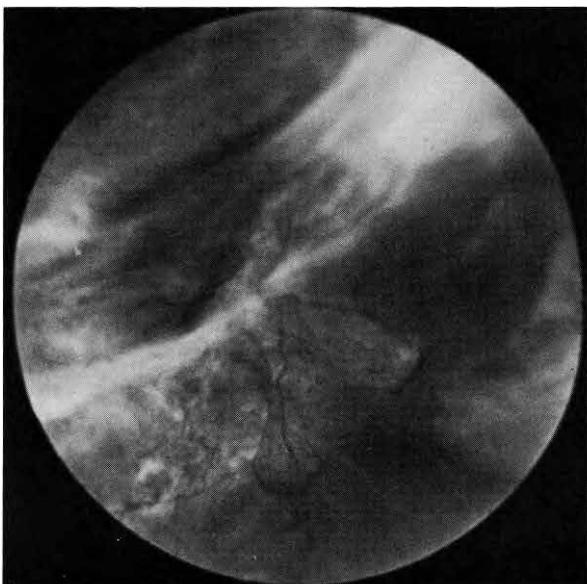


Fig. 3b—Glial and vascular proliferation.

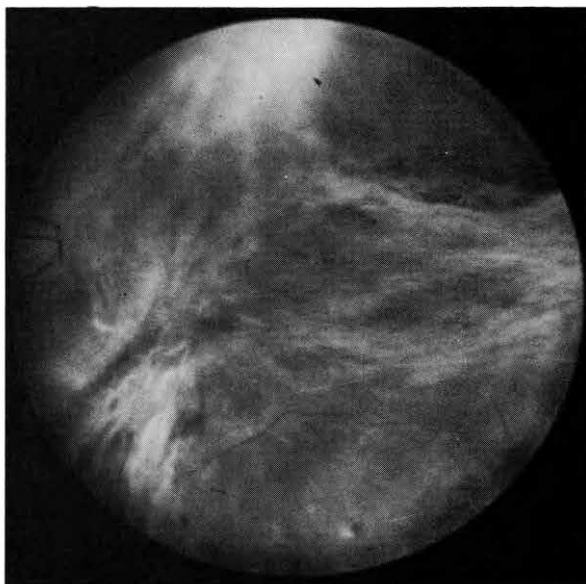


Fig. 3d—Extensive glial proliferation.

normal-appearing retinal tissue as well. The latter concept is based on certain naturally occurring pathological processes involving the eye which have seemingly prevented the development of diabetic retinopathy or at least have retarded its progression to a significant degree.

Such conditions have been described in eyes with severe glaucomatous optic atrophy, severe myopia, conditions with decreased retinal arterial blood supply, retinitis pigmentosa, large chorioretinal

scars following inflammatory reactions, and so forth. In many of the latter instances, the disease was present unilaterally with the fellow eye serving as a control. Hence, production of similar large chorioretinal scars with photocoagulation was expected to create a similar arrest of the progressing stages of diabetic retinopathy by way of reducing retinal blood supply as is common in all of the above mentioned disease entities.

However, regardless of whether one follows

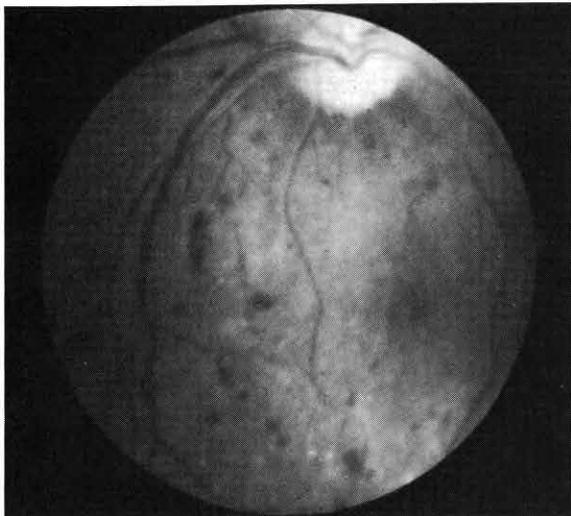


Fig. 4—Retinal hemorrhages, few exudates, and microaneurysms.

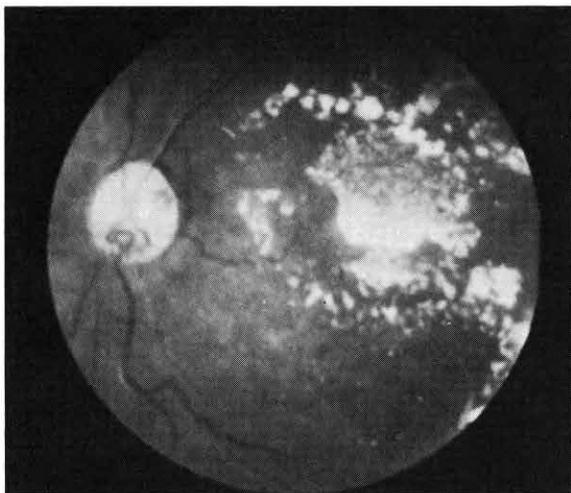


Fig. 5—Hard exudates with some new vessel formation at the optic disc.

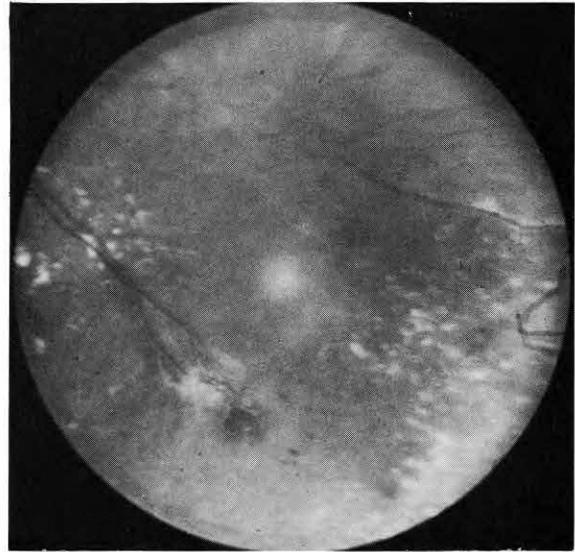
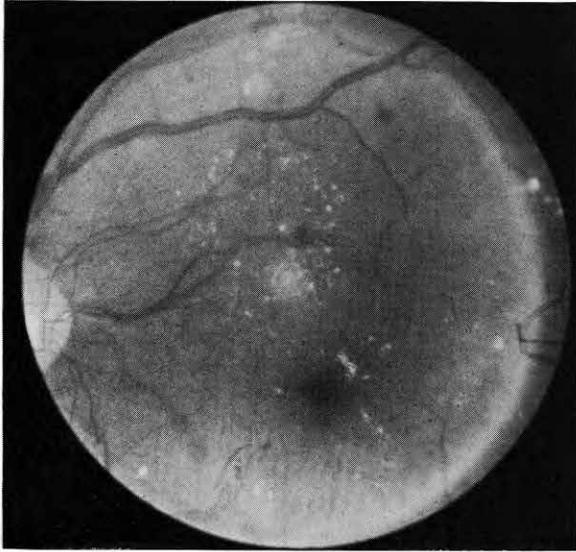
the more conservative and restricted application, as we do, or the more aggressive approach, photocoagulation therapy of diabetic retinopathy seems presently to be the most effective of all therapeutic attempts to bring this disease process under control. It is at the same time considered relatively safe as measured by experiences and data collected over the last 10 years with many hundreds of patients treated in this fashion. Also, in contrast to the surgical approach of pituitary ablation, the general state of the diabetic patient is not affected by photocoagulation. Pituitary ablation was amenable only

to patients who had no other organs involved to any measurable extent, one eye having already become practically blind with the fellow eye still having useful visual acuity, and where the patients' background allowed for a continuous controlled medical substitute therapy throughout the remainder of their lives.

As to the prognosis of photocoagulation therapy, it is generally believed that its greatest beneficial results can be expected if treatment is provided in the early stages of the retinopathy before vasoproliferation takes place. In many cases of macular edema with reduced vision and in cases of extensive retinal exudates, fluorescein angiography allows visualization of vascular leakage which can then be effectively sealed off by coagulation treatment. However, this appears not to be the only mechanism involved in the further prevention of retinal edema. Peyman and Bok (12) have shown in peroxidase diffusion studies in the normal and laser-coagulated retina of primate retinæ that the normal barrier at the site of tight junctions of the pigment epithelium broke down at the site of the coagulation. This allowed intercellular peroxidase diffusion to take place across the original junctional barrier in both directions, that is, from the choriocapillaries to the retina and vice versa. However, diffusion in the retina-to-choroid direction was more extensive than chorioretinal diffusion. The investigators concluded from these observations that the breakdown of the junctional complexes of the retinal pigment epithelium in addition to the alterations in the permeability of the choriocapillaries account for the disappearance of sub- and intraretinal fluid after photocoagulation treatment.

Severe vascular proliferation treated with the Argon laser is at present still experimental and its lasting effect is still questionable. However, in those conditions with extremely poor visual prognosis, photocoagulation as well as the more recent surgical attempts (1) seem to be warranted.

It should, again, be re-emphasized that light coagulation therapy in diabetic retinopathy is still debated as to its efficacy. If effective, it appears that treatment of early stages is more amenable and the response more successful. This possible success is somewhat interfered with by the delay in which the patient is referred for coagulation treatment. This understandable hesitation in subjecting the patient to a not firmly established certain form of therapy may lead on the other hand to more severe grades of the



retinopathy which are much more questionable in their response to photocoagulation.

Other therapeutic approaches using hormones, vitamins, anticoagulants, calcium, aminoacids, lipotropic substances, antimetabolites, and so forth, have not provided a controlling effect on the progression of diabetic retinopathy. Recently, attention has again been focused on the possible beneficial action of salicylic acid on the development and progression of this retinal pathology. Carroll and Geeraets (3) reported clinical observations based on diabetic patients on long-term salicylic acid intake vs. those without or with only occasional intake of this medication. Their statistical evaluation seemed to prove a significantly lower grade of retinopathy in the former. Findings of Dobbie *et al.* (4) seem to support this. They advanced the theory by which salicylates interact with the progression of the retinopathy by the prevention of platelet coagulation due to an abnormal aggregation-enhancing plasma factor in diabetes. Such relatively simple chemotherapy should, therefore, be more closely examined as to its effectiveness under controlled conditions and in a relatively large patient population. In the apparently effective low dose in which salicylates would have to be prescribed, other side effects, that is, gastrointestinal hemorrhages, would not be expected. Caution would, however, be indicated in hepatic disease, hypoprothrombinemia, hemophilia, vitamin K deficiency, and other hemorrhagic diseases in association with diabetes. However, controlled studies of drugs in humans have been almost

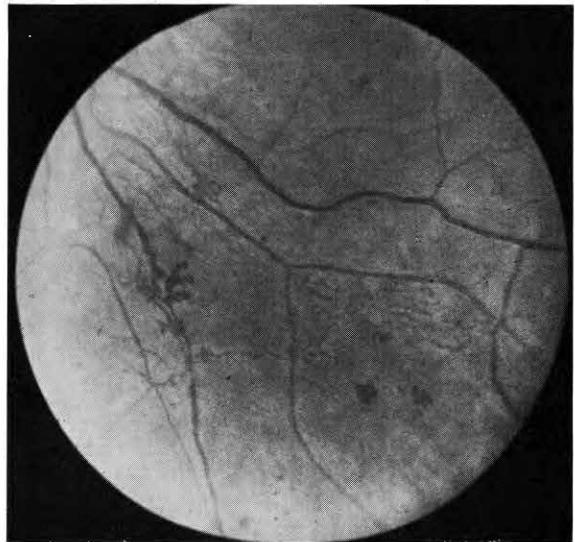


Fig. 6—(Top left) Fine exudates, retinal hemorrhages, and early neovascularization; (Top and bottom right) Early vasoproliferation with neovascularization, hemorrhages, and fine exudates.

impossible because of the random occurrence, random progression, and irregular and unpredictable incidence of spontaneous remissions.

In recent years many authors have stressed that therapy in diabetic retinopathy cannot be successfully accomplished until adequate experimental animal models have been produced to study the various ramifications of the disease, including controlled drug studies. Although diabetic retinopathy in animals has been successfully produced (5), these

time consuming and very costly experiments have left the question unanswered as to the similarity of the pathogenesis of the retinopathy and, hence, whether it is comparable to human diabetic retinopathy. Heath (10) reported a literature review on this topic in 1970.

In previous efforts to study diabetic retinopathy in experimental animals, only two forms have been available: 1) animals with spontaneous diabetes which were kept alive and were bred for further observation, progression of the disease and its ocular complications, and its genetic implications in producing the disease in the offspring; 2) animals which were made artificially diabetic with alloxan or growth hormone, and their clinical status was followed under strict observation for possible development of diabetic retinopathy. The only variation in these two basic approaches has been to vary the degree of diabetic control.

Several important metabolic characteristics of retinas in human and animal diabetics have been ascertained in recent years:

- 1) increased lactate levels
- 2) increased CO<sub>2</sub> levels
- 3) increased glucose levels (higher than in the general circulation and insulin resistant)
- 4) increased lactic dehydrogenase activity

That the increased lactate level may be a direct stimulant to abnormal vascular changes was suggested by Imre's work (11) in which he produced intravitreal neovascularization in the eyes of kittens by injecting 0.1% lactic acid into the vitreous body.

In addition to the abnormal metabolic processes in diabetic retinas and the premise that these may produce the abnormal vascular changes, it is also now under consideration whether abnormal antigen-antibody reactions may be one of the etiologic factors in initiating the vascular changes. The insulin inhibitor may be the antigen in this abnormal immunological response, and increased capillary permeability caused by this reaction may be the initial process in the vascular changes. Abnormal metabolites might also act as antigens.

In addition to the present knowledge about the metabolic abnormalities in diabetic retinopathy, there is also some evidence about the changes occurring in retinitis pigmentosa which apparently prevent the development of diabetic retinopathy. In this disease, taurine is reduced in amount;  $\beta$ -

aminoisobutyric acid is reduced in concentration; and there is a reduction in anaerobic glycolysis which can be reversed by giving pyruvate. One could speculate that by increasing these factors, diabetic retinopathy could be enhanced as well.

With this increasing knowledge of the pathological state of the retinal biochemistry, new chemotherapeutic agents may be developed and investigated.

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