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COMMUNICATIONS

THE X RAY AND RADIUM PHOSPHENES*

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OPHTHALMOLOGISTS, as well as radiologists, are aware that radium radiations and *x* rays can produce a sensation of light on striking a person's eye. This phenomenon is being used clinically to locate foreign bodies within the eye and to test the retinae of cataractous eyes. It has recently been used to measure the diameters and refractive power of living human eyes. But the mechanism by which these radiations arouse a visual sensation is still unknown.

In this paper, which is the first of two dealing with an attempt to determine that mechanism, the literature on the *x* ray and radium phosphenes is critically reviewed, and conclusions are drawn as to its probable nature. In the second paper (Lipetz, 1955) a test of these conclusions for the *x* ray phosphene is described.

History of the *X* Ray Phosphene

Search for the X Ray Phosphene.—When Roentgen (1895) announced his discovery of *x* rays, he stated that he had tried but had been unable to arouse a visual sensation with *x* rays. His reason for trying was the logical speculation that since *x* rays, like light, affected the photographic plate, then *x* rays, like light, might also affect the visual system. For this same reason many other experimenters continued to look for an *x* ray phosphene. At first no phosphene was found and this was ascribed to an opacity of the ocular media (Salvioni, 1896; Dariex and de Rochas, 1896; Harnisch, 1896; Battelli, 1896; Chalupecký, 1897; Antonelli, 1897; Brandes, 1896; Brandes and Dorn, 1897). But even when the thickness of ocular media in the rays' path was reduced by using lensless (aphakic) eyes, or by passing the rays directly to the retina, through the sclera, no phosphene was produced (Battelli, 1896; Dwelshauwers-Dery, 1896; Gallemaerts, 1896; Harnisch, 1896; Guilloz, 1896; Cowl and Levy-Dorn, 1897; Crzellitzer, 1902). It was later realized that these negative results occurred because the *x* rays used by these experimenters had insufficient penetrance and intensity to stimulate the eye. Other early workers had somewhat better *x*-ray generators and found that the rays penetrated the ocular media (Wuillomenet, 1896; Bullot, 1896; Gallemaerts, 1896; Destot and Bérard, 1897; Scholtz, 1902; Birch-Hirschfeld, 1904).

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Some effects on vision which possibly were produced by x rays were reported by some early workers and denied by others (Edison, Morton, Swinton, and Stanton, 1896). Seeing by partially blind persons through use of x rays was announced (Clark, 1896), but it was correctly attributed (Edison, 1896b) to vision *via* light from a fluoroscope screen rather than *via* a direct action of x rays. Some cures of blindness by x rays were reported (Bell, 1896), but these were considered to have been cases of hysterical blindness (Bosc, 1896; Stephenson and Walsh, 1899).

Discovery of the X Ray Phosphene.—Brandes (1896) announced that he and Dorn had been able with x rays to produce a visual sensation in a blindfolded aphakic. What was more, when they performed a control experiment with normal subjects, these, also, received a visual sensation. Independent discoveries of the phosphene were soon announced and were followed by confirmatory reports (Edison, 1896a,b; Robarts, 1897; Destot and Bérard, 1897). Roentgen (1897), in his third communication regarding x rays, retracted his earlier statement and confirmed that the rays could elicit a visual sensation.

Brandes and Dorn (1897) published a full account of their experiments. Other studies were published in the next few years (Strauss, 1897; Bardet, 1897; Harrison, 1897; Foveau de Courmelles, 1898; Himstedt and Nagel, 1901; Crzellitzer, 1902; Belot, 1905; Ammann, 1906; Bossalino, 1906a,b). No more experiments were reported after 1906, probably because the workers had become aware of the harmful effects of x rays. The x ray phosphene then seems to have been forgotten, except for a few reviews (Apatoff, 1910; Meyer, 1912; Heinicke and Perthes, 1925).

Desjardins (1931) considered x rays to be invisible. Taft (1932) and Pirie (1932) independently rediscovered that visibility, and further reports have since been published about every 2 years.

Doubts as to the Reality of the X Ray Phosphene.—Cowl and Levy-Dorn (1897) strenuously objected to the conclusion that x rays could arouse a sensation of light. On the basis of their many experiments they believed that whatever light sensations were perceived could be explained in other ways. Their arguments were disposed of in a series of neat experiments by Brandes (1896), Brandes and Dorn (1897), Dorn (1897), and Bardet (1897).

Crzellitzer (1902), working in Cowl's laboratory with improved x-ray apparatus, demonstrated to both Cowl's satisfaction and his own that x rays were visible to the normal eye, and thus ended the controversy.

Characteristics of the *X* Ray Phosphene

Light Sensation during Irradiation of the Whole Eye

Appearance.—The phosphene produced by x-irradiation of the entire eye has been described (Bellucci, 1947,1951; Belot, 1905; Bossalino, 1906a,b; Godfrey, Schenck, and Silcox, 1945; Taft, 1932) as a homogeneous luminous glow filling the entire visual field.

Stimulus Intensity Threshold.—Brandes and Dorn (1897) noticed that their observers showed varied sensitivities. Newell and Borley (1941) were the first to measure the threshold *x*-ray intensity required to produce the phosphene in humans. They found that for an area of 1 sq. mm. on the retina, the threshold varied from 0·5 to 1·4 r./min. in three normal subjects. Bornschein, Pape, and Zakovsky (1953) found the threshold to vary from 1·6 to 8·7 mr./sec. for normal subjects.

Similarities between the *X* Ray and the Light Phosphenes

Effect of Dark Adaptation.—It was found by all experimenters that, as for weak light, the eye had to be dark-adapted before *x* rays could be seen, and certain of them emphasized this fact (Bardet, 1897; Harrison, 1897; Pirie, 1932, 1934; Taft, 1932; Bellucci, 1951). Jalet and Olivier (1947) noted that the length of dark adaptation required to see the *x* rays varied greatly among one hundred normal subjects; some even saw them immediately on entering the dark. Newell and Borley (1941) determined in one subject the time course of the drop in the just visible *x*-ray intensity during dark adaptation, and found it similar to the drop in the light threshold.

Pupillary Reflexes.—Bellucci (1951) observed that intense *x*-irradiation of the eye produced a pupillary contraction in both the irradiated eye (direct reflex) and the non-irradiated eye (consensual reflex), just as did light.

Persistence of Vision.—Bellucci (1951) placed between the eye and the *x*-ray source a metal disk having 1-mm. diameter holes at 3 and 6 mm. from the centre. When the disk was spun rapidly, the subject saw two concentric circles of light. A similar effect can be produced using a light source.

Lack of Afterglow.—Braun (1897) believed that the *x*-ray image persisted on the retina, but he did not give the basis for his belief. Taft (1932) and Jalet and Olivier (1947) found that the sensation of light ceased as soon as the *x* rays were stopped, with no afterglow. This is what would be expected on the basis of the reports (Bardet, 1897; Brandes and Dorn, 1897) that the phosphene flickered in synchronism with a low frequency (1 to 10 cycles per second) alternating current applied to the *x* ray generator.

Behavioural Response of Animals.—Axenfeld (1896a,b) found that if various insects (coleoptera, diptera, hymenoptera) and crustaceans (*Porcellius*) were placed in a light-tight container, half of it wood and half of it lead, and this container was exposed for a short time to *x* rays, then the enclosed animals moved to the wooden half, which was penetrated by the rays. Blinded animals did not do this. He found that caged house-flies tended to move from dark to light regions, and (apparently assuming that all the animals used had the same photophilia) concluded for all the animals that the *x* rays had probably produced a sensation of light when it struck their eyes.

Chalupecký (1897) noted no behavioural response when he irradiated one eye of a dark-adapted dog, though a one hour dose produced subsequent pathological changes in the eye. But the low intensity of the *x* rays used may account for this lack of response.

Electrical Responses of the Eye.—Himstedt and Nagel (1901) measured, with a string galvanometer, the change in current which flowed between electrodes at the

cornea and fundus of an animal eye when the retina was stimulated. This change was called an " action current ". They found that when an excised, dark-adapted frog eye was illuminated with light, an action current was produced. Exactly the same form of action current was produced on irradiation with x rays. This demonstrated objectively that the visual system (at least in the frog) is affected by x rays in much the same way as it is affected by light. After some minutes' exposure to intense light, the eye did not respond for about five minutes to either light or x rays—demonstrating objectively that sensitivity to these two stimuli decreased with light adaptation and increased with dark adaptation.

Nagel (1901) reported that dark-adapted frog eyes gave a considerably stronger action current than light-adapted ones, and that they also reacted very decidedly to x rays; "as well, in fact, as the thoroughly dark adapted eye of the mist owl (*Strix flammea*) "*.

Himstedt and Nagel (1902) performed similar experiments on dark-adapted frogs, owls, chickens, turtles, and pigeons. The only significant findings were that chicken eyes showed a weak response to light but none to x rays, and frog eyes and owl eyes (from *Syrnium aluco*) gave a very large response to light and a smaller but similarly varying, response to x rays.

The action currents of the type recorded by Himstedt and Nagel (*b*-waves) are now believed to originate principally with rod activity. So this is evidence that x rays, directly or indirectly, excite the rods.

Reciprocity of Area and Intensity of Stimulus—Ricco's Law.—Brandes (1896), Crzellitzer (1905), and Gifford and Barth (1934) found that a fixed intensity x-ray beam became invisible when its cross section was reduced beyond some critical area.

Newell and Borley (1941) found that at the threshold of visibility for two fine x-ray beams, the product of their intensity and cross-sectional area was a constant for total retinal areas of at least from 0·025 to 0·60 mm. The largest value is for two excited retinal areas each 0·62 mm. in diameter or about 2·2° of visual angle across. A similar relation of intensity and area is found for threshold light stimuli. But it holds exactly in the peripheral retina only for areas less than one degree across (Haig, 1950†).

Reciprocity of Duration and Intensity of Stimulus—Bunsen-Roscoe Law.—Bornschein, Pape, and Zakovsky (1953) found that the threshold dose (the product of duration and intensity of x rays for perception of the phosphene) was nearly constant for durations of stimulus less than 20 msec., the threshold dose being as low as 0·5 mr. For greater durations the threshold dose increased with increase in duration.

Similarly, Graham and Margaria (1935‡) have shown that the threshold dose of light for perception of the light is a constant for stimulus durations below a certain critical value. The critical duration depends on the region of the retina and the total area stimulated. At a region 15° peripheral the critical duration was about 20 msec. for a light stimulus 16 min. of arc in diameter.

Effect of Age on Absolute Threshold.—Newell and Borley (1941), using three normal subjects, and Bornschein, Pape, and Zakovsky (1953), using four normal subjects, found higher x ray phosphene thresholds for their older subjects.

*Author's translation.
† ‡ See Additional References.

Similarly, the absolute rod and cone thresholds are found to rise slowly with age, the mean threshold at 50 years being nearly double that at 20 years of age (Hecht and Mandelbaum, 1939*).

DIFFERENCES BETWEEN THE *X* RAY AND LIGHT PHOSPHENES

Colour.—The colour of the *x* ray phosphene has been described as a clear opalescent green by Bossalino (1906a,b); as a clear, bright, shining yellow by Crzellitzer (1902); as a diffuse bluish green by Godfrey, Schenck, and Silcox(1945); as a desaturated yellow-green by Newell (1952); as white for one eye of a subject and greenish-blue for the other by Jalet and Olivier (1947); and as white by Denier (1950). Pape and Zakovsky (1954) found that *x* rays produced at 71 kV. and 2 mA. caused a blue-green phosphene. Bellucci (1951) found that the phosphene remained unchanged in colour as the *x* ray generator's voltage varied between 50 and 180 kV., though the brightness changed. The colour did depend on current, being uniform yellow-green at median values and changing towards blue with smaller currents (about 4 mA.) and towards yellow with larger currents (about 80 mA.). The phosphene became brighter as the current was increased.

These colours differ from the highly desaturated blue of scotopic light vision. Further, the reported change of colour with intensity of *x* rays seems to be unobtainable with a similar intensity change in any light stimulus.

Appearance of X-Ray Shadows.—Detailed descriptions of the spatial appearance of the phosphene were given by Strauss (1897) for a pencil beam of *x* rays, Bellucci (1951) and Rushton (1938) for a ribbon beam, Bossalino (1906a) for a cruciform beam, and Crzellitzer (1902) for the shadow of a lead sheet. Briefer descriptions were given by other authors (Brandes and Dorn, 1897; Dorn, 1898a; Goldmann and Hagen, 1942; Jalet and Olivier, 1947; Nagel, 1911; Pancoast, Pendergrass, and Schaeffer, 1940; Pirie, 1932, 1934; Roentgen, 1897; Taft, 1932; Toniolo, 1948).

In every case the appearance can be explained in the following terms:

(*a*) The *x* rays are not refracted by the ocular media and therefore pass through the eye in straight lines.

(*b*) Wherever the rays intersect the partial sphere of the retina, an area of excitation is produced if the ray flux is above threshold intensity.

(*c*) The resulting phosphene is perceived as whatever external light source would produce on the retina of the normal eye a light image that would excite just that area of retina excited by the *x* rays.

For example, if a 1·5-mm. diameter cylindrical beam of *x* rays were aimed so as to intersect the macular retina at right angles, a 1·5-mm. diameter circular patch of the macular retina would be excited by the rays. That same retinal patch would be excited by a 5° disk of light viewed straight ahead, and, in fact, the *x* ray phosphene aroused is seen as a 5° disk of light, located straight ahead. Similarly, if that *x*-ray beam were aimed so as to intersect the upper nasal retina at an acute angle, an oval patch of retina would be excited by the rays, and the resulting phosphene would be an oval patch of light with a minor axis 5° across seen in the lower temporal visual field.

As a corollary, a ray intersecting the retina at two points would produce two corresponding spots of light, as was observed by Himstedt and Nagel (1901).

Another corollary is that the *x*-ray shadow of an object would appear much larger than the object and reversed left for right and up for down, as in fact it does. This was recognized by Braun (1897), as well as by many other early workers. Crzellitzer (1903) calculated that, on the basis of a visual resolution threshold for light of one min. of arc, an object 4·4 microns in size should cast a just visible *x*-ray shadow. But he was confusing resolving power with detecting power—4·4 microns would be the separation of two shadows that could just be seen as two, and this assumes that the foveal cones would be sensitive to *x* rays, something that has not been demonstrated.

It was shown by Pirie (1932, 1934) that if appropriately different patterns of *x* rays were presented to the two eyes, a stereoscopic effect could be produced in the phosphene.

* See Additional References.

Thus, with regard to the viewing of form, the only reported difference between the x ray phosphene and light phosphene is that light, but not x rays, can be refracted by the media of the eye to form an image on the retina. Images are formed with x rays only by silhouetting objects against a source of x rays.

Regional Variations in the Retina's Sensitivity to X Rays.—The x ray phosphene, particularly when weak, appears brighter in the peripheral visual field than in the central field (Brandes and Dorn, 1897; Himstedt and Nagel, 1901; Crzellitzer, 1902; Bossalino, 1906a; Newell and Borley, 1941; Jalet and Olivier, 1947). Bossalino reported this to occur only for irradiation from the side of the eye. Both he and Bellucci (1951), in contrast to the other authors, found that with irradiation from the front of the eye the entire visual field appeared homogeneous. Brandes and Dorn (1897) described the phosphene as an outer bright ring which was wider and brighter on the temporal and upper sides and was filled with a weak, diffuse light.

These conflicting reports make it difficult to compare the regional variations in the retina's sensitivity to light and to x rays, but the periphery seems to be more sensitive to both stimuli.

Appearance to Colourblind Subjects.—Dorn (1898) and Nagel (1907) found that totally colourblind subjects were more sensitive to x rays than were normal subjects. This might have been caused by the tendency of some total colourblinds to avoid light-adaptation, but further investigation of this phenomenon is needed to settle the question.

Murani (1899) tested four " red-green blind " children and found that they could not perceive the x rays, but it is not reported whether normal subjects could perceive x rays with his apparatus.

Uses of the *X* Ray Phosphene

TESTING RETINAL FUNCTION IN PARTIALLY BLIND EYES.—It was realized from the start (see, for example, Edison, 1896b), that it should be possible to produce distinct x ray images even in eyes which because of clouding or distortion of the ocular media could not get a clear image with light. Many tests of this principle were made.

Edison (1896a) reported that persons blinded by cataract received a sensation of light from x rays. Bock (1896), apparently believing that the lens was opaque to x rays, suggested that the rays might be used to enable aphakics to see objects. Bloch (1896) doubted that the rays would help, but Robarts (1897) did find that blind individuals with adherent lids or atrophy of the globe could distinguish x ray shadows. Destot and Bérard (1897) tested patients with various diseases, including total leukomic staphyloma of the cornea, iridocyclitis, and atrophy of the eye, and found that if they could distinguish between day and night, they could see x ray shadows. Foveau de Courmelles (1898) tested 204 blind children, but apparently he did not allow sufficient dark-adaptation since the x rays were perceived only by some nine whose retinae were always kept shadowed by their afflictions and so were always partially dark-adapted. Bossalino (1906a) tested patients having aphakia, cataract, "phthisis bulbi", traumatic lesions,

total and partial retinal detachment, and primary optic atrophy. From the results he concluded that, where the retina and optic nerve were intact so that light could be seen, *x* rays could also be seen. One subject could not distinguish the forms of *x* ray shadows with his cataractous eye, and this prompted Bossalino to look for and find a partial detachment of the retina in that eye.

Since the *x* ray phosphene was rediscovered in 1932, it has regularly been used to test the functioning of the retina in eyes in which light could not be used for that purpose (Pirie, 1932; Gifford and Barth, 1934; Newell and Borley, 1941; Godfrey, Schenck, and Silcox, 1945; Jalet and Olivier, 1947; Bellucci, 1951). Newell and Borley were able to locate relatively small scotomata by testing the ability to resolve two neighbouring, narrow *x* ray beams directed at the retina.

Bornschein, Pape, and Zakovsky (1953) found that the threshold for the *x* ray phosphene in a congenital hemeralope was several hundred times the normal, being from 1,000 to 1,600 mr./sec. His absolute light threshold was also raised about that much. No phosphene was produced in a patient having retinitis pigmentosa with a grave loss of vision, even at 7,500 mr./sec., again showing the close relation between the *x* ray and light thresholds.

Appearance to Blind Subjects.—It was found that blind persons who could distinguish between light and dark could perceive *x* rays (Bellucci, 1951; Bossalino, 1906a; Destot and Bérard, 1897; Edison, 1896b; Foveau de Courmelles, 1898; Gifford and Barth, 1934; Goldmann and Hagen, 1942; Jalet and Olivier, 1947; Kolle, 1897; Newell and Borley, 1941; Pirie, 1932; Robarts, 1897). The appearance to them was like that to normal subjects except where abnormalities of the retina were involved. Jalet and Olivier (1947) reported that a patient having a unilateral cataract, probably of endocrine origin, perceived the *x* rays on that side as dimmer and as " gritty " in appearance. Another patient had a bilateral cataract, recently operated on the right eye. He perceived a luminous bluish sensation on the right and a much more intense white light on the left eye when exposed to the rays.

LOCATION OF FOREIGN BODIES IN THE EYE.—Foreign bodies in the eye or orbit could sometimes be located by the *x* ray shadows they cast on the retina. This technique was extensively developed by Godfrey, Schenck, and Silcox (1945).

MEASUREMENT OF EYE DIAMETERS.—The diameters of living human eyes have been measured *in situ* with the *x* ray phosphene (Rushton, 1938; Goldmann and Hagen, 1942; Sorsby and O'Connor, 1945; Stenström, 1946; Deller, O'Connor, and Sorsby, 1947). The technique was to project a ribbon beam of *x* rays so that it traversed the eyeball with the plane of the beam at right angles to the diameter to be measured. The beam was moved until it aroused the sensation of a point of light, at which time the beam was at a tangent to the retina and its position could be measured.

MEASUREMENT OF TOTAL REFRACTIVE POWER OF THE EYE.—Goldmann

and Hagen (1942) measured the total refractive power of the human eye by use of the phosphene. They directed onto the retina of a dark-adapted eye two parallel *x* ray ribbon beams of which the separation was known precisely. This gave the sensation of two shining lines. They then projected two parallel lines of light onto a wall that was a known distance from the eye, and adjusted them so that the light lines appeared to lie on the *x* ray phosphene lines. The total refractive power (in dioptres) was then computed as the ratio of the separation between the light lines to the product of the separation between the *x* ray beams and the distance between the wall and the nodal point of the eye. A brief review is given by Hartridge (1946).

Experiments on the Mechanism of the *X* Ray Phosphene

Many suggestions have been made in the literature regarding the means whereby the *x* rays act on the visual system. All these theories are based on the concept that the *x* rays initiate in the eye a chain of processes which links up somewhere with the chain of processes initiated in the eye by light, so that from there on the processes (and the response) are the same for light and for *x* rays.

LACK OF DIRECT EFFECT OF *X* RAYS ON THE CENTRAL VISUAL SYSTEM.—Kolle (1897) and Godfrey, Schenck, and Silcox (1945) tested patients having recent enucleations and evisceration and found an absence of response on the operated side. They concluded " the response is not due to direct stimulation of the optic nerve ".

All parts of the head were strongly *x* irradiated by Pirie (1932), Gifford and Barth (1934), Jalet and Olivier (1947), Bellucci (1951), and Pape and Zakovsky (1954). A phosphene was observed only when the retina lay in the path of either direct or strongly scattered *x* rays. They concluded that the visual system was stimulated by *x* rays at the retina only.

FLUORESCENCE OF THE OCULAR MEDIA.—The early workers realized that the regional variation in the retina's sensitivity to *x* rays and the increase in sensitivity during dark adaptation paralleled the retina's sensitivity to light. Therefore, it was proposed that the *x* rays produced light in the eye by causing the ocular media to fluoresce, and that this fluorescence was what was perceived. Various experimenters looked for fluorescence in live eyes or in parts of freshly extracted eyes while irradiating them in the dark, but saw none (Brandes and Dorn, 1897; Chalupecký, 1897; Crzellitzer, 1903; Dorn, 1898; Gifford and Barth, 1934; Himstedt and Nagel, 1901; Jalet and Olivier, 1947; Taft, 1932). Newell and Borley (1941) found that the lens of a rabbit eye fluoresced when irradiated with 100,000 r/min. However, as they pointed out, this flux is about 200,000 times (human) threshold. They could see a glow through the pupils of normal human eyes, but not of an aphakic eye, when the eyes were irradiated with 1,000 r/min. (about 2,000 times threshold flux), indicating that the human lens fluoresces. In con-

trast, Crzellitzer (1902) found that when an x-ray beam was passed through the eye so as to hit the lens but not the retina, no phosphene was perceived. However, he used an intensity that was probably not far above threshold.

From the above observations it can be concluded that fluorescence of the ocular media is negligible except at very high intensities of x rays.

SITE OF ACTION.—Since 1897 it has been realized that the sharpness of detail of the x ray phosphene implied that the site of action was next to or in the retina, as otherwise the pattern of excitation would disperse and lose detail before it reached the retina. It was further realized that the excitation must eventually act on the cells of the visual pathway (photoreceptor cells and neural cells of the retina) and cause them to respond as they would respond to light.

If the site of action of the x rays was in the retina but outside the cells of the visual pathway, then there had to be a way of transferring the energy absorbed from the x rays to those cells, and without much spatial dispersion of the energy pattern. This latter requirement would not be met at near-threshold intensities by such transfer methods as the spread of heat or of chemicals produced by the action of the x rays. Only if the energy of the x rays were transformed into light (fluorescence) would there be a possibility of meeting that requirement, because the light would be selectively taken up in the photoreceptor cells (rods and cones) and little absorbed by the intervening tissue.

FLUORESCENCE OF THE RETINA.—Therefore, it was next proposed that x rays produced fluorescence in the retina. Many unsuccessful attempts were made to see fluorescence in irradiated retinae (Brandes and Dorn, 1897; Dorn, 1898; Gifford and Barth, 1934; Salvioni, 1896; Taft, 1932). An extract of visual purple in bile and saline did not fluoresce either (Gifford and Barth, 1934). Himstedt and Nagel (1901) think they saw just barely perceptible fluorescence in (frog?) retinae, both bleached and rich in visual purple.

However, Newell and Borley (1941) were unable to see fluorescence in an excised dark-adapted rabbit retina irradiated with 100,000 r/min. and saw no glow through the pupil of an aphakic human eye being irradiated at 1,000 r/min. These observations are crucial in deciding between retinal fluorescence and direct action on the receptors as the mechanism of the x ray phosphene and deserve careful evaluation. To be visible to an observer a fluorescing layer must be 20 to 30 times more luminous when external to the eye than when lying adjacent to the retina. Their second observation was made on a human retina with an x-ray intensity 2,000 times greater than the human threshold for the phosphene. This signifies that any fluorescence produced in the human retina is less than ($30/2{,}000 \simeq$) one seventieth of the amount needed to account for the phosphene. Their first observation cannot be evaluated because the phosphene threshold for rabbits is not known.

My results with frogs confirm their findings. Fresh frog lenses and bleached and dark-adapted retinae gave no noticeable fluorescence when irradiated with 1,800 r/min. (Lipetz, 1953). This is about 100 times greater than the threshold for electric response of the frog eye (Lipetz, 1955). The light threshold for such a response is about 10 times greater than the human absolute light threshold. Therefore the fluorescence produced in a frog retina must be less than ($30/1{,}000 \simeq$) one-thirtieth the amount needed to account for the electric response to x rays.

From these observations it can be concluded that any retinal fluorescence produced by x rays has a negligible effect toward the production of the x ray phosphene.

BLEACHING OF VISUAL PURPLE.—A third proposal was that x rays acted by directly breaking down the visual purple in the rods. Excised, dark-adapted retinae were irradiated for as much as an hour, but no bleaching of the visual purple was observed (Brandes and Dorn, 1897; Fuchs and Kreidl, 1896; Himstedt and Nagel, 1901). However, as Himstedt and Nagel pointed out, these experiments were done with near-threshold intensities, and near-threshold intensities of light produce no detectable bleaching in that length of time. It was also found (Gatti, 1897) that at low intensities, x-irradiation of light-adapted frogs had no effect on the course of regeneration of visual purple in their retinae.

"LIGHT ADAPTATION" OF THE RETINA WITH X RAYS.—Dark-adapted animal retinae were irradiated for up to half an hour in vain attempts to produce in them certain of the attributes of the light-adapted retina. One attribute was photomechanical adaptation—change in length of rods and cones and movement of pigment in the retinal epithelium cells (Birch-Hirschfeld, 1904; Gatti, 1897; Guglianetti, 1909; Lodato, 1897-98; Pergens, 1896, 1897); another was a change in the colour of the retina stained with triazide dye (Birch-Hirschfeld, 1904; Guglianetti, 1909); the third was a change in the oxidizing power of the retina (Guglianetti, 1909). Since all these tests were made with near-threshold intensities of x rays, negative results were to be expected.

QUESTION OF SUMMATION OF LIGHT AND X-RAY STIMULI.—Bossalino (1906b), while experiencing the phosphene from an x-ray beam, simultaneously illuminated his eye with light of just subthreshold intensity produced by a lamp shining through red, turquoise, orange, or yellow gelatin filters. The colour of the x ray phosphene was not affected by the light. He also repeated the experiment with the light intensity high enough to show the colour of the gelatins. The x rays had no effect on the apparent colour of the lights.

However, because the intensity of his x-ray beam must be assumed to be near-threshold, no conclusion can be drawn from his experiments. The first experiment is invalid because there is an appreciable range above absolute

threshold before an intensity is reached (still within the mesopic range) at which a light stimulus appears to have any colour other than a desaturated blue. So even if the subthreshold light summated with the near-threshold *x* rays, the result might still be in the blue-appearing range. In his second experiment the eye was partially light-adapted by the light stimulus which was at a high enough intensity to appear coloured. Therefore the *x* rays were probably so far below the then existing threshold that they could not be expected to have any effect on the eye.

Bossalino's experiments were ingenious and should be quite informative if repeated with sufficiently intense *x* rays.

Scotomata of the Fovea and of the Blind Spot.—Various experimenters have tried to determine whether cones responded to *x* rays by searching for an insensitive region of the retina, corresponding to the rod-free area of the fovea. Dorn (1898) found that 1·6 and 2·0 mm. diameter pencil beams failed to arouse a phosphene in only one retinal location, which corresponded to the head of the optic nerve. Godfrey, Schenck, and Silcox (1945), on getting the same results with a 1 mm. diameter beam, concluded that cones responded to *x* rays. However, they apparently believed that the rod-free area was about the same size as the optic nervehead—about 6 visual degrees wide, corresponding to 1·8 mm. on the retina. Present-day belief is that the rod-free area is not larger than ½ degree (0·15 mm.) in diameter. So only a beam of less than 0·15 mm. diameter would be small enough to show any insensitivity of that area, and no conclusions can properly be drawn from their results.

CONCLUSIONS

Site of Action.—It had been assumed by the above workers that since the retinal sensitivity to *x* rays increases during dark-adaptation, and since an increase in visual purple concentration is the only change occurring in the retina during dark-adaptation, then *x* rays must act on the visual purple. And, if they do not act indirectly, by producing fluorescence which affected the visual purple, then they must act directly on the visual purple. But, it has recently been shown that in dark-adaptation from room lighting levels the change in concentration of visual purple is negligible (Rose, 1948*; Lipetz, 1953; Rushton and Cohen, 1954*; Wald, 1954*), so that that argument collapses.

The principal change in the retina during dark-adaptation has been shown to be a decrease in the number of photons which must be absorbed by retinal photochemicals in order to produce a response in the optic nerve. At maximum sensitivity, a single photon, absorbed in and disrupting a single molecule of photochemical, is sufficient to activate a photoreceptor cell. The neural cells require over 1,000 times as much energy for activation. The energy absorbed from *x* rays by the retina is not absorbed specifically in any particular cell or locus. Therefore it seems reasonable to expect the *x* rays to affect first the most energy-sensitive part of the visual system, that is, the *photochemical molecule.*

Photoreceptors Involved.—The visual response to *x* rays resembles in the following particulars the response of the rod-dominated retina to light:

(1) the rate of dark adaptation,
(2) greatest sensitivity in the peripheral retina,
(3) the *b*-wave type of retinal action current.

* See Additional References.

So it appears probable that the rods, of which the photochemical is visual purple, are excited by x rays.

The dark-adapted eye is dominated by rod activity, so any cone activity would be hard to detect. But the very fact that the x ray phosphene is seen in colours other than the greatly desaturated blue of rod-dominated vision, is evidence that the cones, which are known to be concerned in colour vision, are affected. The only cone photochemicals which as yet have been identified are the iodopsins, which differ from visual purple only in having a different protein attached to the carotenoid chromophore. And if visual purple is affected by x rays, they would probably be, also.

TEST OF THESE CONCLUSIONS.—An attempt was made to test the above-developed hypothesis that the x ray phosphene results from a direct action of the rays on the photochemicals of the rods and cones (Lipetz, 1953, 1955). The "phosphene" was detected objectively by measuring the discharge of nerve impulses at single ganglion cells on stimulation of the *in situ* frog retina with light and with x rays. These stimuli were found to evoke discharges indistinguishable in types and latencies. Stimulation with either x rays or light raised the response thresholds to both. Both thresholds dropped during non-stimulation.

A "fatiguing" or injurious action of x rays was found, in that x rays, but not light, produced a reversible drop in the ganglion cell action potential, and reversible immediate and cumulative rises in the thresholds. The threshold response was dose-dependent (dose being the product of intensity and duration of the stimulus) for up to 6 seconds of stimulus duration for light but only 2 seconds for x rays. It was suggested that these differences resulted from a reduction in the selective permeability of the retinal neurons, brought about by the ionizations from the x rays.

It was pointed out that these scotopic threshold responses to illumination are known to depend on the energization of visual purple by light.

X rays in doses of over 10^7r and high-energy particles in doses of over 10^7rep produced bleaching of the visual purple in the frog retina. This bleaching was only in small part caused by heating of the retina. Unlike light, bleaching doses of ionizing radiation also denatured the proteins of the retina. It was found that the ratio of bleaching dose to threshold visibility dose was 100 million to 1 for x rays and between 12 million to 1 and 200 million to 1 for light.

It was calculated that a threshold x-ray dose released in the visual purple from 2×10^{-3} to 8×10^{-3} erg/cm.^{2} of retina, which was from $\frac{1}{2}$ to 160 times the energy calculated to be released in the visual purple by threshold light. This accorded with the expectation that x rays, which act through ionizing particles having a higher average energy than the light photons, would be more wasteful of energy than light in energizing the visual purple molecules.

All the above findings are consistent with, but do not prove, the hypothesis that the x ray phosphene in the dark-adapted retina is produced through a direct action of the rays on the visual purple of the retina.

EFFECTS OF *X* RAYS ON THE VISUAL SYSTEM OTHER THAN THE PHOSPHENE

INDIRECT ACTION OF *X* RAYS ON THE VISUAL SYSTEM

Kektcheev and Anissimova (1939) and Kektcheev (1941) reported that *x*-ray irradiation of any portion of the body produced a statistically significant drop in the human absolute threshold for light for several subsequent days. However, this treatment could also cause a rise in threshold, depending on " the intensity and duration of the excitation, as well as the state of the subject ". These experiments need independent confirmation before the findings can be accepted.

Furchtgott (1952) found that whole body *x*-irradiation of rats with 370-470r produced a slight retardation for several days afterwards in their learning to choose between two grey cards on the basis of brightness. A low light level (about 0·1fc.) was used. He considered the results to be significant and the effect to originate from a change in the visual receptor system.

STIMULATION OF NON-VISUAL SENSATIONS IN THE VISUAL APPARATUS

Robertson (1896), who was completely blind from atrophy of the optic nerves, reported that *x*-irradiation produced in his right eye, but not his left eye, a pulsation which had nothing in common with the sensation of light. The pulsation may have been induced by the electric discharge rather than the *x* rays, since he found that the sparks of the induction coil gave a more intense sensation than did the focus tube.

Kolle (1897) reported that after lengthy exposure to *x* rays normal subjects got a " shooting-star " light sensation which could be cut off by interposing a steel plate in the *x*-ray beam. The sensation was accompanied by headache, and supra-orbital and deep-seated pain in the globes of the eyes.

Foveau de Courmelles (1898) tested 204 blind children with *x* rays. He wrote (my translation):

> Two almost completely blind persons, a 15-year-old boy with ophthalmia, and a 21-year-old girl with atrophy of the globe and cyclitis on the left and iridocyclitis with calcareous cataract on the right, have indicated pain in the eyes during the putting into operation of a Crookes' tube; that pain continued throughout the duration of the experiment for the young lady, and ceased at once for the boy.

History of the Radium Phosphene

Giesel (1899) was the first to isolate a large amount of fairly pure radium salt. He soon discovered that if the radium preparation were brought right up to the eye, a very clear glow was perceived even with the eyelid closed. He attributed this to the becquerel rays from the radium and suggested that they caused the media of the eye to fluoresce. He successfully demonstrated this phenomenon at the Congress of Naturalists in Münich (and thereby probably obviated much controversy as to the " reality " of the phenomenon).

Himstedt (1900) borrowed the preparation and found that persons blinded by clouding of the cornea or lens could get a sensation of light from the radium; with Nagel he conducted elaborate experiments to determine the process by which the radium radiations affected the eye (Himstedt and Nagel, 1901). By 1903 strong radium preparations were more generally available, and in England Hardy and Anderson (1903) made the most thorough of the studies to date on the phosphene.

A few other studies showing the visibility of radium rays (Giesel, 1902; London, 1903a,b, 1904; Javal and Curie, 1904; Gjerts, 1904; Miethe, 1904) were made up to 1904. Only one study has since been published, a doctorate thesis (Thier, 1933) on the electrical response of the frog eye to radium rays.

" *Curing* " *Blindness with Radium.*—Newspaper misrepresentation of the work of London (1903a,b; 1904) created a popular belief that vision could be restored to the blind by merely putting radium against their eyes. Crzellitzer (1903) and Holzknecht and Schwarz (1903) denounced this belief, as did Greeff (1904a) in an official report. Later, Greeff (1904b) denounced both the belief and London. London (1904) replied that his own published articles clearly stated that radium did *not* restore vision, and invited Greeff to read those articles.

Javal and Curie (1904) used radium to produce a light sensation in partially blind subjects. Javal later announced that because of inaccurate newspaper reporting of their work he had received many pitiful letters from blind persons asking him to restore their sight with radium, and added that he had written in reply, " to end their chimaeric hopes ".

Characteristics of the Radium Phosphene

APPEARANCE.—The sensation aroused by radium has been described as a diffuse, general glow (Greeff, 1904a) that felt either as if the whole eye were filled with light (Himstedt, 1900; Himstedt and Nagel, 1901) or as if there were in front of the head a bright space with indistinct boundaries (Hardy and Anderson, 1903; London, 1903b). Thier (1933) has emphasized that this space appeared to be, not flat, but a concave or convex surface.

SIMILARITIES TO THE LIGHT PHOSPHENE

Dark-Adaptation.—Hardy and Anderson (1903) observed that sensitivity to the radium phosphene increased with dark-adaptation. London (1903b) showed that if one eye were dark-adapted and the other not, only the dark-adapted eye experienced the phosphene.

Regional Variations in the Retina's Sensitivity.—London (1903b) and Thier (1933) both noted that the light sensation produced by radium was strongest when localized in the periphery of the visual field. London further tested this by so placing two radium preparations of equal strength that, when one was viewed centrally, the other was viewed peripherally, and he found that whichever was viewed centrally appeared the weaker. This is also true for dim light sources.

Electrical Responses of the Eye.—Himstedt and Nagel (1901) tried to produce an action current in the frog eye with radium, as could be done with light, and attributed their lack of success to the weakness of the radium preparation they used. Waller (1903) wrote that he had succeeded at this, but gave no details.

Thier (1933) found that the excised, dark-adapted, whole eye of the frog showed an action current in response to exposure to radium much like that in response to light. He concluded that the reaction to the radium rays was localized in the retina for the following reasons:

(1) Halved eyes (from which cornea, lens, iris, and vitreous humour had been removed) reacted to the radium with nearly the same shape action current as did the whole eye.

(2) If the retina were removed, the eye no longer responded to the radium rays.

(3) An isolated retina gave an action current. This action current was negative in relation to that of the eye.

Differences between the Radium and Light Phosphenes

Colour.—Greeff (1904a) wrote of the radium phosphene as "sea-green", and Failla (1932) mentioned that it is greenish. This is in contrast to the desaturated blue colour of dim light.

Localization and Shadowing of the Radium.—Himstedt and Nagel (1901) found that interposing a lead sheet 1 cm. thick between the radium and the eye cut off the light sensation. If various shaped openings were made in the sheet, the light sensation aroused by the emergent radiations was the same no matter what the shape of the opening. The intensity varied with the size of the opening, but it always appeared that the whole eye was filled with light. With x rays, as with light, the phosphene is limited in extent and changes in shape when the opening is changed, so it is apparent that the two phosphenes differ in mechanism from the radium phosphene.

The radium phosphene was found to be stronger in that part of the visual field corresponding to the location of the radium, and was strongest when the axis of vision was directed at the radium (Himstedt and Nagel, 1901; London, 1903a,b; Hardy and Anderson, 1903; Thier, 1933). Hardy and Anderson explained this directionalized brightness as a pinhole " lens " effect of the orbital bones on the beta particles from the radium.

Experiments on the Mechanism of the Radium Phosphene

Lack of Direct Effect of Radium on the Central Visual System

Effect on the Brain.—A strong radium preparation was found to produce a light sensation, even when placed at the back of the head (London, 1903a,b; Hardy and Anderson, 1903; Thier, 1933). London believed this was a direct effect on the brain, but Hardy and Anderson demonstrated that the phosphene occurred only when the axis of greatest radiation density from the radium preparation cut one or the other eyeball. They concluded that there was no stimulation of the brain and that the phosphene originated solely in the retina.

Effect on the Optic Nerve.—Even though the optic nerve was still in good condition, no radium phosphene was aroused in a freshly eviscerated eye, while it was aroused in the subject's normal eye (London, 1903b). This showed that the radium phosphene was elicited *via* the retina.

IMPORTANCE OF THE RETINA FOR PERCEPTION OF THE RADIUM PHOSPHENE.—The ability of radium rays to arouse a sensation of light in blinded persons was tested many times (Himstedt, 1900; Javal and Curie, 1902; London, 1903a,b; Greeff, 1904a). The experimenters all concluded that the radium phosphene could be perceived only if the eye were capable of perceiving light and still *had intact some retina* and the central visual pathway.

FLUORESCENCE OF THE EYE MEDIA.—All parts of the eye, and in particular the refractive media, were found to fluoresce when exposed to radium (Himstedt and Nagel, 1901; Exner, 1903; Hardy and Anderson, 1903). Thier (1933) showed that this effect was produced solely by the beta rays from the radium. All these experimenters believed, as did the discoverer Giesel (1902), that this fluorescence was the basis of the radium phosphene, and in all probability, it *is* the basis of the beta particle phosphene.

ACTION OF THE BETA PARTICLES.—Hardy and Anderson (1903) found that the radium phosphene was considerably dimmed by closing the eyelid or holding a lead sheet over the eye so as to stop all the beta particles. Deflecting the beta particles away from the eye by a strong magnetic field reduced the phosphene to about one-fifth its previous brightness.

Thier (1933) found that the action current in a halved frog eye was much reduced when the beta particles were prevented from reaching the eye.

These observations prove that the greatest portion of the radium phosphene is produced by the beta particles. They probably act on the eye by inducing fluorescence in the ocular media, as described above.

ACTION OF THE GAMMA RAYS ON THE RETINA.—Hardy and Anderson (1903) found that even after the beta particles were prevented from reaching the eye, radium still caused a dim phosphene. When a piece of lead 4 cm. thick and 2 mm. wide was moved between the radium and the eye, a bar of shadow was perceived to move across the background glow. Hardy and Anderson concluded that the shadow must have been produced on the retina itself by the gamma rays. This showed that the gamma rays can act in a manner similar to *x* rays, and is the probable explanation of the shadows observed by Miethe (1904).

Their work was corroborated by Thier (1933) who found that gamma rays alone were sufficient to produce an action current, though a weak one, in exposed frog eyes.

BLEACHING OF VISUAL PURPLE BY RADIUM.—In an attempt to determine whether radium acted on the visual purple to produce the phosphene, dark-adapted retinae were exposed to radium, but with no effect on the visual purple (Hardy and Anderson, 1903; Greeff, 1904a; Birch-Hirschfeld, 1904). The latter also found no change in the photo-mechanical adaptation of the retina. These failures with near-threshold intensities of radium radiations were to be expected, since near-threshold intensities of light, also, have no effect.

CONCLUSIONS

The Beta Particle Phosphene.—The finding that when beta particles were prevented from reaching the eye the radium phosphene dimmed to one-fifth of its previous brightness shows that the beta particles are responsible for almost all of the usually observed radium phosphene. Since the beta particles are not sufficiently energetic to penetrate through the eye to the retina, they cannot be affecting the retina directly and so must be affecting it indirectly by producing fluorescence in the eye. This is confirmed by the finding that absorbers inserted in the path of the radium radiations did not produce recognizable shadows but merely dimmed the phosphene. A further confirmation is the finding that beta particles caused all parts of the eye to fluoresce strongly and with a colour like that of the phosphene.

The Gamma Ray Phosphene.—Even when beta particles were screened from the eye, a weak phosphene was observed from the extremely penetrating gamma rays. Sharp shadows in the phosphene could be produced by thick absorbers in the path of the rays. Since the gamma rays can easily penetrate to the retina, and since they have not been found to produce noticeable fluorescence of any part of the eye, it is probable that they act, as do the *x* rays, by breaking down the photochemicals in the rods and cones.

EFFECTS OF RADIUM ON THE VISUAL SYSTEM OTHER THAN THE PHOSPHENE

NON-VISUAL SENSATIONS.—Failla (1932) mentioned that with a tube of as little as 10 mg. radium held close to his eyes, he saw a " greenish glow, accompanied, in my eye at least, by a peculiar sensation ".

" FATIGUING " ACTION.—Himstedt (1900) found that after a radium preparation and a dummy packet had been placed ten to fifteen times in random sequence on the two closed eyes, many persons could no longer distinguish on which eye the radium packet had been placed. He suggested that the cause was a prolonged after-glow of the fluorescence in the ocular media, since that afterglow would reduce the contrast of the immediate radium phosphene. Exner (1903) tested this on excised animal lenses, but did not see any afterglow, though the lenses fluoresced strongly during the irradiation.

Thier (1933) demonstrated objectively on the opened frog eye that repeated exposures to radium reduced the ability of the retina to respond to radium or light. This effect was greater for the (more heavily ionizing) beta particles than for the gamma rays. The mechanism of this effect is not known.

Summary of Conclusions

On the basis of a critical review of the literature, evidence and arguments are presented that the most probable mechanism of the *x* ray phosphene is the breakdown of the photochemicals in the rods and cones of the retina by the ionizing action of the rays.

It is concluded that the radium phosphene consists of two phosphenes;

one caused by the beta particles from the radium, and a much dimmer one caused by the gamma rays from the radium. The beta particles act by producing fluorescence within the eye. The gamma rays (like the x rays) probably act by breaking down the photochemicals in the rods and cones.

The scattered literature was made accessible for this review by the University of California's Inter-library Loan Service The major portion of this study was done as part of a doctorate thesis (Lipetz, 1953). Much of this work was done while the author was a predoctoral fellow in the biological sciences of the Atomic Energy Commission. The preparation of this paper was aided by a Fellowship from the National Foundation for Infantile Paralysis.

SOURCE MATERIAL

ON THE *X* RAY PHOSPHENE

Reviews.—Comprehensive reviews of the literature of the x ray phosphene were made by Dor (1897), Birch-Hirschfeld (1910), Apatoff (1910), Nagel (1911), Tschermak (1929), and Gifford and Barth (1934). Ronchi (1951) reviewed the work of Bellucci (1951), and his article was in turn reviewed by Genaud (1952). A review by Desjardins (1931) is rather garbled; those of Birch-Hirschfeld (1904), Guglianetti (1909), and Rohrschneider (1930) are especially well presented.

Bibliographies.—All the literature dealing with x rays is listed by Glasser (1933) for the year 1896, by Phillips (1897) for the period up to March, 1897, by Barker (1899) for some of the papers up to 1898, and by Gocht (1911) in a monumental work covering all the German literature and some of the other European and American literature for the period up to 1910.

ON THE RADIUM-RADIATIONS PHOSPHENES

Reviews.—The literature on the phosphenes produced by radium radiations is reviewed by Birch-Hirschfeld (1904, 1910), Nagel (1911), Desjardins (1931), and Thier (1933). None of these lists is very complete.

BIBLIOGRAPHY OF THE *X* RAY AND RADIUM PHOSPHENES

CONSIDERABLE effort has been expended towards making this bibliography complete*. Grouped with each piece of original work under the first author's name are all the known reprints, translations, and rewritings, and the more complete abstracts, arranged as far as possible in order of appearance. Where a work is listed that has not been read in the original, this is indicated by an asterisk and the reference source listed as well.

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