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# Retinotoxic and choroidotoxic substances

## The Jonas S. Friedenwald Memorial Lecture

Albert M. Potts

*Four separate examples have been discussed with the object of showing, first, how the concept of toxic amblyopia is an irrelevant one for modern ophthalmic research. This is the more true since one large category of the classical toxic amblyopias is not toxic at all and further adds to the confusion. It is suggested that rigorous criteria for the causative role of a particular substance in toxic phenomena be adopted. It is further suggested that since the ever increasing number of toxic substances act by widely different mechanisms on different parts of the retina and choroid, and since our knowledge of these mechanisms can be obtained in some detail by modern experimental methods, each of these toxic entities be considered separately and on its own merits unless one is dealing with two effects which are experimentally demonstrable to be identical. Only if this type of procedure is followed, can we pursue a logical experimental course from toxic effect to mechanism to rational therapy.*

I am greatly honored that the Association has chosen me to participate in this function, the purpose of which is to keep green the memory of Jonas Friedenwald. That it is fitting and proper we do this need not be emphasized. There are few of us here today who have not recollections—few or many—of that unique personality, and no one who came in contact with him failed to profit by the encounter. Such selfless dedication to the advancement of the science of ophthalmology, such human kindness, and such total competence in achievement we shall wait a long time to see again.

One aspect of the science of ophthal-

mology which claimed Jonas Friedenwald's attention was the clarification of our ideas about eye disease as shown in the classification and description of disease entities. His emphasis was always on the dynamics of disease processes, as opposed to static descriptions of disease pictures, and he emphasized the scientific value of reformulation of known material in order to make further progress. An outstanding example of this is his Gifford Memorial Lecture on "Disease Processes Versus Disease Pictures in Interpretation of Retinal Vascular Lesions."<sup>1</sup>

My concern today is with another category of eye disease known for the last one hundred years as the toxic amblyopias. It is my contention that whether used as originally intended to denote "all amblyopias which are caused by the influence of a toxic substance,"<sup>2, 3</sup> or, as later defined, "disease of the lower visual neuron,"<sup>4</sup> this is a category manqué and has no significance for present-day ophthalmic science. It is more important that this be recognized,

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since, with the multiplication of organic syntheses in the field of pharmaceutical, industrial, and agricultural chemicals, the area is an increasingly significant one. Eye damage due to chemicals never before known is being recorded with increasing frequency, and it is imperative that our thinking be as clear as possible to allow a rational approach to the disease.

For proper orientation one should recognize the term "amblyopia" as a subtractive one created by the advent of ophthalmoscopy.<sup>5</sup> Any loss of vision for which there was no obvious ophthalmoscopic finding was designated *Amblyopia ohne Befund*. Thus, although retrobulbar damage is included in the category, retinal disease with diffuse or late changes and choroidal disease also find their way into the group. Thus, the term has no bearing on causative mechanism and only oblique bearing on the location of the lesion.

The word "toxic" in this context also has a meaning greatly different from today's usage. Seventy-five years ago an accurate knowledge of chemical poisons was just being acquired. As a result of contemporary advances in bacteriology much attention was given to bacterial toxins. Extrapolating from this, physicians of the era made the assumption that many still unexplained diseases were the result of "endogenous toxins," and ophthalmic entities, such as "diabetic toxic amblyopia" and "toxic amblyopia due to pernicious anemia," were created. De Schweinitz, in his monograph, wisely restricted his discussion to exogenous poisonous substances, but even here great caution must be exercised.

It is my contention that the use of the term "toxic amblyopia" is misleading. We are learning enough about toxic phenomena to demonstrate whether any given substance is truly responsible for eye damage. We are able to describe that damage as retinotoxic or choroidotoxic. We are often able to make progress in discerning the mechanism of the damage, and in rare instances, we can work out a rational therapy. These are the ideal bases for classifi-

cation of toxic eye phenomena. To illustrate these points I wish to present four specific cases which fall in the old category of toxic amblyopia but which represent four highly diverse entities. There are now many types of phenomena to choose from—one might have used the iodate, azide, and iodoacetate phenomena discussed by Dr. Noell in his lecture in 1959.<sup>6</sup> Our specific ones were selected because these are areas of experimentation or study in our own laboratory.

The first is the phenomenon of methanol poisoning which has some curious historical background. Although methanol has been known for centuries, methanol poisoning is a twentieth century phenomenon and one that, in origin, belongs to our Western Hemisphere. Until 1895 only one case of methanol poisoning had been recorded in the world literature. Since that time, thousands of cases have occurred and for the first 16 years every one of these was from the North American continent. The explanation is a simple one, for until the end of the nineteenth century methyl alcohol was always obtained by dry distillation of wood. The resultant product was nauseous with much tar and resins and decidedly nonpotable. In 1890, however, a practical process was developed in the United States for rectification of wood alcohol to the point at which it was virtually tasteless and odorless. At first manufacturers vehemently denied the toxicity of their product and later made every effort to conceal its poisonous nature (Fig. 1). Further, the new material was cheap and sold at 50 cents per gallon, compared with \$2.50 per gallon for taxed grain alcohol. As the result of these factors, Wood and Buller<sup>7</sup> were able to report 275 cases of methanol poisoning in the *Journal of the American Medical Association* for 1904. The plea of the authors for substitution of a cheap denatured ethanol was never heeded, and the advent of synthetic methanol in the middle twenties brought to the market an even purer and cheaper poisonous product.

Each time we have become quite certain



Fig. 1. Label from commercial methanol bottle "Columnian Spirits." Notice the misleading words "pure refined spirits for domestic use."

that everybody knows not to drink methanol, we have become shockingly convinced that the contrary is true. Whether because of wartime restrictions, as in World War II, or economic factors in the postwar recessions, cases of methanol poisoning continue to crop up. As recently as this past month an account appeared of an epidemic of methanol poisoning, which claimed 7 lives in Grand Rapids, Michigan.<sup>8</sup>

This may give some notion of the magnitude of the problem but not of its complexity, for there have been unique difficulties in studying methanol poisoning. First, there is the difficulty of establishing the toxic dose for human beings. Wood alcohol, before being drunk by human beings, is usually mixed with various amounts of other fluids, such as water, fruit juices, or ethanol-containing liquids. This type of dilution is haphazard at best, but when one adds to this the difficulty of getting information from a habitual alcoholic, a semi-comatose individual, or a criminally liable supplier, on the dilution or the amount taken, the problem of establishing how much a patient drank is a serious one. Add to this the effect of ethanol intake on methanol poisoning and evaluation is most difficult indeed. Although it has been reported that 2 teaspoons (8 c.c.) of methyl alcohol may cause blindness and 1 ounce (30 c.c.) may cause death, the dose generally accepted as lethal is 75 to 125 c.c.; and

cases are on record of individuals surviving amounts up to 260 c.c. with no symptoms whatsoever.<sup>9</sup> This spread is more than one can legitimately expect of ordinary toxic behavior.

A second source of confusion lies in the difference in response between man and the ordinary experimental animals. Ingestion of a lethal dose of methanol in man is not followed immediately by any ominous symptoms. Inebriation is disappointingly small and may lead to further ingestion of the concoction in question. After a latent period of 24 or more hours (extremely high doses shorten this to 6 to 12 hours), there is the onset of dizziness, nausea, and abdominal cramps followed by dilated pupils, loss of vision, cyanosis, coma, and death. In a widespread epidemic, such as reported by Benton and Calhoun,<sup>10</sup> a third of the affected individuals die, another third have severe loss of vision, and a third show no final effects. A laboratory finding quite uniform in human beings is an uncompensated metabolic acidosis. The acid formed is not known, but has been demonstrated not to be acetone bodies, lactic acid, or formic acid.<sup>11</sup>

In marked contrast is the behavior of the ordinary experimental animal toward methanol. The fact that there are no detectable histologic changes was observed by Jonas Friedenwald in his very first piece of medical research during his days as a medical student.<sup>12</sup> Add to this the fact that in the ordinary laboratory rodent the LD<sub>50</sub> is 10 to 11 Gm. per kilogram roughly 10 times the figure quoted above for man.<sup>13</sup> In the laboratory animal there is no latent period, but immediate coma from which it never recovers. Moreover, no demonstration of acidosis or blindness in the animals has ever been made.<sup>14</sup> Thus, the literature collected on experimental animals since the time that methanol poisoning became a serious problem is a morass of misinformation.

Human experimentation is, of course, not possible because of the pressure for life-saving measures, and animal experimenta-

tion, until recently, was fruitless and misleading. How might one make a dent in this formidable barrier? In a last desperate effort we turned to the rhesus monkey as an experimental animal and found to our delight that the low dosage, the latent period, and the metabolic acidosis characteristic of methanol poisoning in human beings were exhibited by this animal.<sup>14</sup> With animal experimentation thus possible, new information began to be obtained.

One of the first objects of study was the role of acidosis in methanol poisoning. From the report of Harrop and Benedict<sup>15</sup> in 1920 attention had been directed toward the role of acidosis and the possible therapeutic benefits of alkali in methanol poisoning. Other authors<sup>10, 16</sup> have claimed that acidosis is responsible for both loss of vision and loss of life. In a series of experiments we gave monkeys 6.0 Gm. per kilogram of methyl alcohol, an LD<sub>90</sub>.<sup>17</sup> When base was given to such animals in a quantity adequate to combat acidosis, most of the animals survived and all lived past the 20 to 24 hour period in which untreated animals died of acidosis. Such treated animals, however, did show eye and central nervous system symptoms. Retinal edema was seen consistently<sup>14, 18</sup> and at its peak the edema involved the entire retina and nerve head, leaving a rhesus equivalent of a "cherry red spot" at the fovea. Thus, this particular "toxic amblyopia" is not an amblyopia at all, for there are distinct ophthalmoscopic signs when observation is done at the proper time. The duration of eye symptoms, carbon dioxide-combining capacity, and administration of base are all shown in Fig. 2. Histologic evidence of eye damage is demyelination of the optic nerve (Fig. 3), and abolition of the b-wave of the electroretinogram occurs (Fig. 4).

Evidence of further damage to the central nervous system lies in the fact that despite adequate treatment with base some animals showed progressive weakness, lethargy, coma, and death.<sup>18</sup> The behavior of these animals was also unusual. Because of a peculiar loss of concerted action, such

an animal would be perfectly able to pick up a food pellet and examine it but would not have the intelligence to put it in his mouth and chew it. Such animals had to be fed by stomach tube to be kept alive. Similarly, when the leg of such an animal was caught in a chain, he was unable to perform the necessary coordinated movements to free his leg and the entanglement could remain for hours on end. Examination of the brain of such animals showed an unusual, bilaterally symmetrical, necrosis of the basal ganglia<sup>19</sup> (Fig. 5). We believed this finding was entirely new until we discovered that the same phenomenon had been described for methanol poisoning in human beings in the monograph of Orthner.<sup>20</sup>

On the basis of this work with our experimental test object, we were forced to conclude that methanol poisoning is a threefold disease. Methanol, like any other organic solvent, can cause death when given in large enough doses (10 Gm. per kilogram), and this is the factor responsible

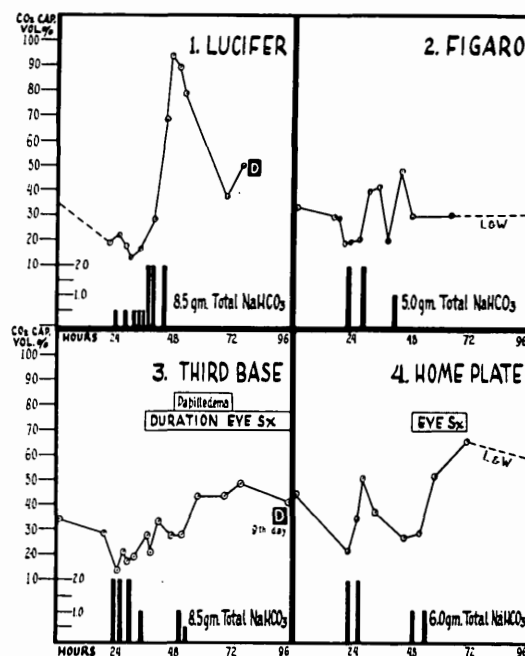


Fig. 2. Blood base (CO<sub>2</sub> capacity) and base given methanol-poisoned monkeys (6.0 Gm. per kilogram MeOH). (From Potts, A. M.: *Am. J. Ophth.* 39: 86, 1955.)

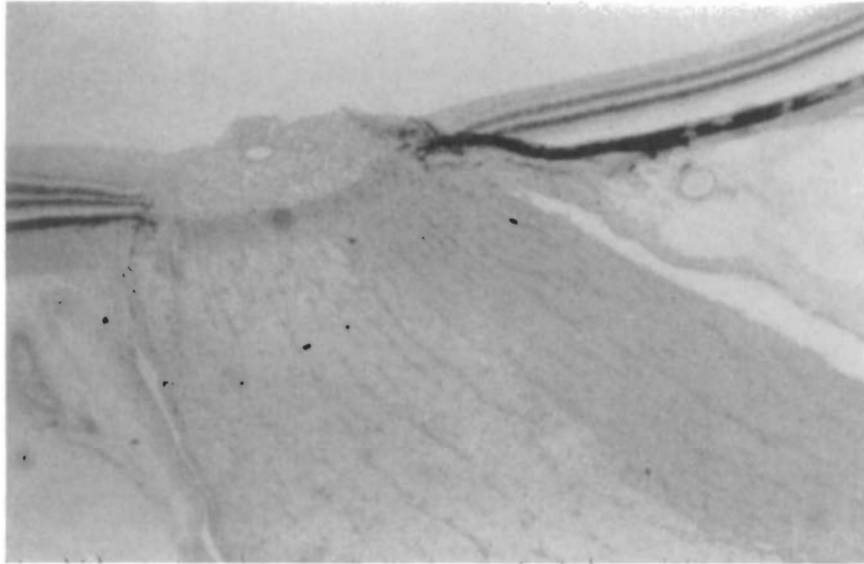


Fig. 3. Optic nerve of monkey showing demyelination. (From Potts, A. M., et al.: *Am. J. Ophth.* 40: 76, 1955.)

for the death of the lower laboratory animals used by us and by others. This may be considered as Disease I. In primates on lower doses of methanol Disease I is never manifested, but the typical acidosis, the nature of which is still unknown, may in itself be an adequate cause of death and constitutes Disease II. However, even when acidosis is combated, the eye effects and basal ganglion effects appear uninhibited and these central nervous system phenomena, the cause of which cannot be acidosis per se, constitute Disease III.

Now that the primate test object was available and behavior toward methanol had been delineated, a prime objective was investigation of various therapeutic agents for methanol poisoning. The number of substances suggested for treatment of methanol intoxication are legion. In addition to alkali treatment discussed previously, sodium thiosulfate,<sup>21</sup> pectin,<sup>22</sup> vitamins B<sub>1</sub>, B<sub>2</sub>, nicotinamide, and vitamin C,<sup>23</sup> potassium iodide,<sup>24</sup> ammonium carbonate,<sup>25</sup> massive infusions of 1 per cent sodium chloride,<sup>26</sup> and ethanol<sup>27</sup> represent just some of the recommended items.

The last item is of particular interest, for its mention goes back to the first extensive

report on methanol poisoning, that of Wood and Buller,<sup>7</sup> who mentioned the belief of Assistant Surgeon R. from his experience with 5 cases of poisoning that "methyl must be replaced by ethyl alcohol in order to combat collapse and sustain the patient's vitality." Our own experience with lower animals led us to doubt the validity of ethanol therapy.<sup>13</sup> However, we believed it necessary to evaluate ethanol on the primate test animal in its turn, and much to our surprise and delight we found that ethanol, when given early enough and in adequate dosage, completely combated all symptoms of methanol poisoning—both acidosis and central nervous system symptoms, including the ocular ones.<sup>28</sup> Because of the rapid oxidation of ethanol, the amount required proved to be formidable, corresponding to 0.5 Gm. per kilogram every 4 hours for 56 to 64 hours. For a man of 70 kilograms this translates to 3 ounces of 100-proof whiskey every 4 hours, a tolerated but not inconsiderable amount of ethanol. The results of a typical experiment on the monkey are shown in Fig. 6. A monkey given 6.0 Gm. per kilogram of methanol followed by the described dosage of ethanol showed no alteration in carbon

dioxide-combining capacity, and, in addition, no clinical signs of methanol poisoning for an indefinite period after the administration of methyl alcohol. After a recovery period of a month the same animal was given the same dose of methanol without ethanol added, and, as can be seen, he died in the usual 20 hour period in acidosis. This illustrative example is completely typical of the many similar experiments performed before and since.

Although these and further studies<sup>29</sup> allowed us to define an effective therapeutic regime for methanol poisoning, many inadequately answered questions remain. The effectiveness of ethanol in preventing all symptoms of methanol poisoning is suggestive evidence that the toxic manifestations are not those of methanol itself but an oxidation product, and that ethanol operates as a competitive inhibitor to methanol oxidation. Whether this inhibition is of alcohol dehydrogenase<sup>30</sup> or of the catalase system<sup>31</sup> is not yet firmly established, but exact definition of the nature, site, and rate of methanol oxidation will probably be necessary to show why this unusual disease is restricted to primates.

An equally fascinating problem is the nature of the oxidation product which is the proximal toxic agent in methanol poisoning. On the basis of studies of *in vitro* enzyme inhibition<sup>13</sup> and electroretinography,<sup>32</sup> we were led to suggest strongly that formaldehyde is the substance in question. However, all attempts to date to reproduce the symptoms of methanol poisoning by administration of formaldehyde have been unsuccessful.<sup>33</sup> Identification of the actual toxic agent and measuring susceptibility of primate and nonprimate tissues to it will again be required for full understanding of why methanol poisoning is a disease of primates. Thus, although we have experimentally established an effective therapy for methanol poisoning, much remains to be done to acquire a full understanding of the disease.

A second retinotoxic phenomenon of in-

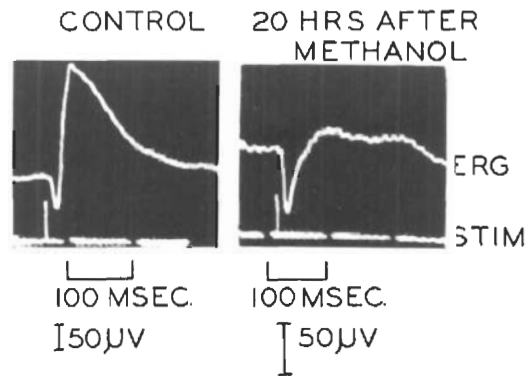


Fig. 4. Monkey electroretinogram before and 20 hours after administration of 6.0 Gm. per kilogram methanol. (From Potts, A. M., et al.: *Am. J. Ophth.* 40: 76, 1955.)



Fig. 5. Monkey methanol. Cross section through basal ganglia showing necrosis and hemorrhage into putamen. (From Potts, A. M., et al.: *Am. J. Ophth.* 40: 76, 1955.)

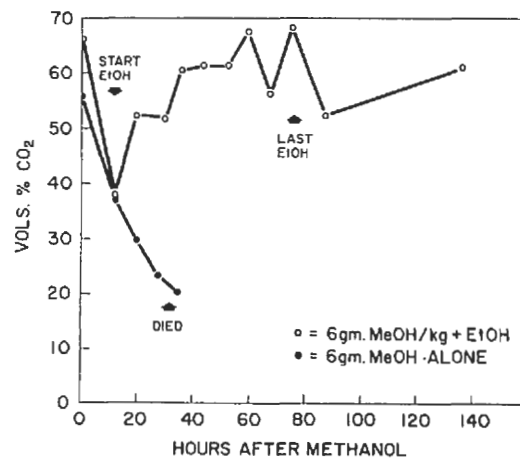


Fig. 6. Plasma CO<sub>2</sub>-combining capacity in monkey No. 2. (From Gilger, A. P., Farkas, I. S., and Potts, A. M.: *Am. J. Ophth.* 48: 153, 1959.)

terest is that caused by sodium glutamate. This is as yet known only in experimental animals. A report appeared in 1957 by Lucas and Newhouse<sup>34</sup> that administration of sodium glutamate to suckling mice caused degeneration of the ganglion cell

layer and failure of formation of the inner nuclear layer of the retina, leaving only the receptor cells intact. We had no trouble repeating these experiments. Fig. 7 shows the retina of a normal adult mouse and Fig. 8 shows that of a treated animal. We

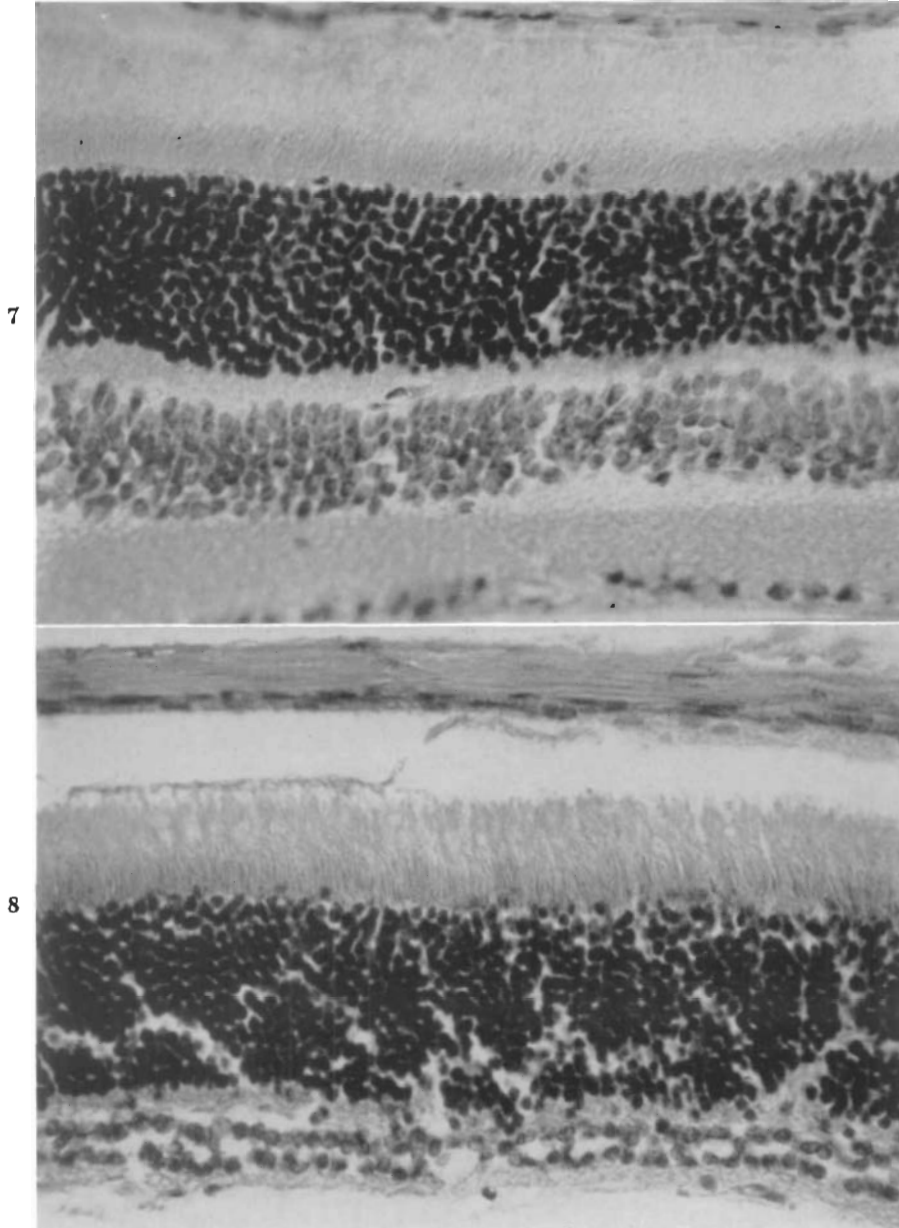


Fig. 7. Retina of normal adult mouse, 34 days old. (From Potts, A. M., Modrell, R. W., and Kingsbury, C.: *Am. J. Ophth.* 50: 900, 1960.)

Fig. 8. Retina of glutamate-treated mouse. (From Potts, A. M., Modrell, R. W., and Kingsbury, C.: *Am. J. Ophth.* 50: 900, 1960.)

were able to demonstrate that such treated animals, possessing only receptor cell layers in the retina, showed an electroretinogram which possessed only an a-wave. The b-wave was entirely lacking (Fig. 9). Since there is good evidence that the ganglion cell layer does not participate in generation of the electroretinogram,<sup>35, 36</sup> this evidence leads to the inevitable conclusion that the cells in the intermediate cell layer are responsible for generation of the b-wave, and that the a-wave only is a function of the receptors.

Looking back to the methanol experiments, the loss of the b-wave in our monkeys suggests that the intermediate cell layer is involved by methanol. In investigating the mechanism of this unusual effect, we were impressed by the fact that in our hands the glutamate effect was demonstrable only in newborn animals. We could produce the effect in newborn rats as easily as in mice, but results with rabbits were negative. In surveying developmental biochemical phenomena, we were impressed by the newer concepts of repression of enzyme formation by products of this specific reaction in question. This phenomenon had been demonstrated in numerous instances for microorganisms and was known to occur in mammalian tissues as well.<sup>37, 38</sup> To explore this hypothesis five of the enzymes involved in glutamate and glutamine metabolism were examined. The enzymes were: (1) glutamyl synthetase which manufactures glutamine from glutamic acid and ammonia, (2) glutamyl transferase which transfers other amines to glutamine replacing the ammonia, (3) glutaminase I which hydrolyzes glutamine to glutamic acid and ammonia, (4) "glutaminase II," a system which accomplishes the same result as glutaminase I but achieves this by transamination followed by deamination, and (5) the glutamic oxaloacetic transaminase.<sup>39, 40</sup> Our experiments showed that there was no measurable glutaminase II in rat retina and that there was no difference in content of glutamyl synthetase and glutamyl transferase between experimental

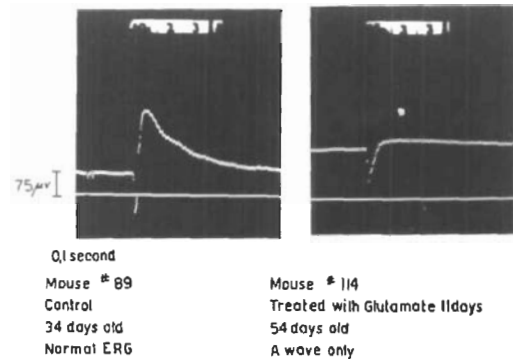


Fig. 9. Effect of glutamate on mouse ERG. (From Potts, A. M., Modrell, R. W., and Kingsbury, C.: *Am. J. Ophth.* 50: 900, 1960.)

Table I. Glutamyl synthetase and glutamyl transferase activity of rat retinal homogenates (as  $\mu\text{M}$  of glutamyl hydroxyamic acid produced/100 mg. wet tissue/30 min. incubation)

	Glutamyl transferase	Glutamyl synthetase
Untreated	7.1	12.0
Treated	7.0	12.0

Table II. Glutaminase I activity in rat tissues (as  $\mu\text{M}$  ammonia liberated/100 mg. wet tissue/30 min. incubation)

	Retina	Brain	Liver
Untreated	20.5	76.9	10.3
Treated	12.3	79.1	14.3

and control animals (Table I). There was, however, a marked decrease in glutaminase I in the retina of the experimental animal as compared with the control (Table II). It should be mentioned that recent and as yet unpublished results indicate an increase in transaminase content of the same retinas used in the experiments.

Some have raised the question of how much glutamate actually reaches the retina after injection of our dosage levels. It has been shown by Himwich and colleagues<sup>41</sup> that the blood-brain barrier of the young rat is permeable to glutamate, as demonstrated by chemical analyses. How-



first description of tobacco amblyopia occurs in Mackenzie's "Treatise on Diseases of the Eye," which appeared in London in 1830.<sup>49</sup> In the same decade in France, Sichel,<sup>50</sup> described a similar entity resulting from excessive use of ethyl alcohol. During the century from 1830 to 1930, the notion of what constituted tobacco-alcohol amblyopia subtly changed from any loss of vision occurring in a drinker or a smoker to the very specifically defined bilateral centrocecal scotoma containing one or more nuclei described by Traquair.<sup>48</sup>

In the hundred year span literally thousands of papers were published on the subject, but even from early times there were murmurs of discontent which were brushed aside by the strong and righteous personalities decrying the use of tobacco and alcohol. For example, the paper on tobacco amblyopia by Jonathan Hutchinson in the *Lancet* of 1863 was discussed by a Mr. Ernest Hart, who analyzed Hutchinson's 40 cases and from the clinical information was able to refer all but 17 to causes remote from tobacco. Of the 17 cases he showed 2 patients with precisely the same train of symptoms, one of whom was a confirmed smoker, the other of whom had never smoked. He noted that "in nearly all these cases the persons were very moderate smokers; in none did the cessation from smoking improve even temporarily the condition; that the atrophy supervened at the end of a lifetime during which the patients, affected, had been in the habit of smoking moderately without suffering from it; and in one case it was noted that the eyes had been worse five years ago than they were now notwithstanding that the patient had smoked as much as half an ounce a day during that time."<sup>51</sup>

In his thesis at the University of Paris, Dr. Martin,<sup>52</sup> quoted two physicians of Constantinople, a Dr. Hubsch and a Dr. Dickson, who pointed out that in that city "everybody smokes from morning till night; men smoke a lot, women a little less than the men, and children acquire the same habit from the age of seven or eight years

on; I have never been able to attribute amaurosis to the abuse of tobacco, the number of smokers is immense, the number of amaurosis limited."

A very admirable and rigorous statistical study was done by Usher and colleagues,<sup>53</sup> who examined a series of 1,100 cases from the Royal Aberdeen Infirmary from 1895 to 1927. As controls they used 500 pipe smokers unaffected by tobacco, part from the surgical wards of the same Infirmary, and the rest from rural districts where all men over 21 were questioned to avoid false selection. It was noted that the diagnosis was preponderately among men, for of the 1,100 cases only 27 were women. There was no significant difference in the amount of tobacco smoked between the experimental and the control subjects. Neither was there any difference in the strength of tobacco on the basis of nicotinic content. Although most individuals were pipe smokers, 21 of the 1,100 subjects smoked less than 1 ounce of tobacco per week, 3 smoked cigars only, 4 smoked cigarettes only, and 5 used snuff only. Although figures on consumption of alcohol were not complete enough for statistical validity, about 25 per cent of the patients were total abstainers. The authors concluded that there was no evidence that excessive smoking in itself will cause tobacco amblyopia.

The definitive experimental investigation of this condition was carried out by Dr. Frank Carroll, who recognized the similarities between nutritional amblyopias and the described tobacco-alcohol amblyopia.<sup>54</sup> Carroll repeated the controlled-diet experiments used by Spies in the study of alcoholic pellagra.<sup>55</sup> Twenty-five patients were hospitalized and allowed to continue smoking and drinking to the same degree as before admission. Eleven patients received a supplement of brewer's yeast, 5 received B complex and house diet, 5 received B complex and diet inadequate for all other vitamins, 5 received inadequate diet and synthetic B<sub>1</sub>. All of the patients recovered vision partially or completely, and the results were at least as good as with any

25 previous patients who simply stopped smoking and drinking.

It is perhaps worth noting that in his discussion Dr. Carroll quotes a personal communication from Jonas Friedenwald on the subject of "diabetic amblyopia." This entity, too, popular with ophthalmologists in the past, occurred in a woman with diabetes who had never used tobacco or alcohol. The typical bilateral scotomas improved rapidly and completely only on administration of vitamin B complex. In this area, too, we feel the progressive influence of the man to whom this lectureship is dedicated.

An interesting side light in this area is the rather remarkable disappearance in this country of the disease by whatever name we wish to call it. We mentioned the 1 per cent figure in Edinburgh up to 1929. Carroll,<sup>56</sup> in a series of cases from the Massachusetts Eye and Ear Infirmary, reported in 1935 that the incidence was 0.3 to 0.5 per cent and that "many older ophthalmologists feel that this condition is seen less frequently in this country now than formerly." In 20 years there has been no record of a case at the University Hospitals of Cleveland and I have not seen one in Chicago since going there. The explanation for this may well lie in a publication by Figueroa and co-workers<sup>57</sup> from the University of Illinois. The authors pointed out that a sharp (10 times) drop in alcoholic pellagra occurred in 1942 as found in the Boston City Hospital and in the Cook County Hospital. Similarly, in their study from 1948 to 1949 in screening 16,000 inmates of the House of Correction in Chicago, 56 per cent of whom were alcoholics, only 2 cases of pellagra and 2 cases of vitamin B<sub>1</sub> deficiency were found. The authors attribute this remarkable change to the fact that, as a wartime measure, all cereals in this country were fortified with vitamins and that even a person with severe, chronic alcoholism ate large amounts of bread, some stew, doughnuts, occasionally sandwiches, or spaghetti. The conclusion was that the vitamin supplement in the cereal products accounted for lack of alcoholic

vitamin deficiency, and this is almost certainly the explanation for the disappearance of tobacco-alcohol amblyopia in the United States.

On this basis one might believe that the subject would have disappeared from discussion and that I am simply wasting my time. This is not the case. A well-known textbook of ophthalmology,<sup>58</sup> published in 1954, bears a complete account of tobacco amblyopia and individual papers continue to appear.<sup>59-61</sup> The most recent of these was published in 1960. Thus, in addition to our objection to the irrelevance of the concept of toxic amblyopia, there is need for some touchstone to decide whether an effect described as toxic is truly due to the substance to which it is attributed. For this purpose I would like to suggest three postulates for toxic etiology somewhat parallel to Koch's postulates for bacterial etiology of a disease.

1. The clinical signs of the disease must be reproducible in experimental animals by administration of a purified chemical preparation. This must be repeatable, employing dosages comparable to those giving similar signs in human beings.

2. A. The response to the suspected substance in animals and human beings may show the normal scatter of random distribution, but one must not get the same effect from doses which differ by several orders of magnitude. B. In cases of chronic poisoning this stipulation must hold true for equal blood and tissue levels of the toxic agent.

3. Cessation of dosage (or lowering of blood and tissue levels of the agent) must be followed by remission of clinical signs (except those due to irreversible cell death).

Thus, by these criteria methanol poisoning is due to a toxic substance and tobacco-alcohol amblyopia is not. The latter is a vitamin deficiency disease.

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