# A STUDY OF DINITROPHENOL AND ITS RELATION TO CATARACT FORMATION*

WARREN D. HORNER, M.D.
San Francisco, Calif.

## INTRODUCTION

During the summer of 1935 there occurred a sporadic outbreak of cataracts, predominantly in young women, which could have been likened to an epidemic. This began about April, rapidly increased during the summer and fall, and gradually disappeared during 1936–37. Like an epidemic, too, it seemed to point to a common source, namely, dinitrophenol, which was taken for the rapid reduction of body weight. The number of persons who were affected—estimated at more than 164—probably exceeds the number of cataracts reported from any single toxic epidemic with the possible exception of that of ergot poisoning. A study of this unusual phenomenon is, therefore, of interest.

## EARLY HISTORY

Dinitronaphthol and dinitrophenol were shown to be accelerators of metabolism in dogs—by Cazeneuve and Lépine in 1885,[1] by Gibbs and Reichert in 1891,[2] and by later investigators.[3,4]

Dinitrophenol did not receive medical consideration until the first World War, when it was discovered that many of the explosives manufactured in Europe and in the United States produced toxic effects upon the workmen who handled them; these varied from malaise to death from poisoning. This discovery led to a series of studies by commissions and committees in the different countries, appointed to investigate

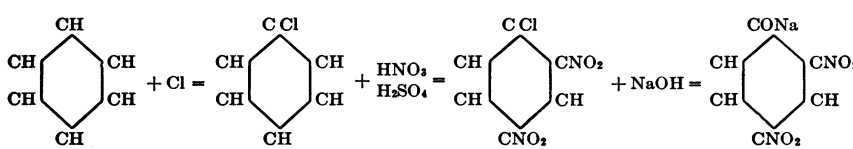
* From the Department of Ophthalmology, University of California Medical School. Candidate's thesis for membership accepted by the Committee on Theses.

health hazards in munition plants. The findings were reported by Magne, Mayer and Plantefol[5] in France, and by Roger Perkins[6] in America, the latter serving as a member of the American National Research Council.

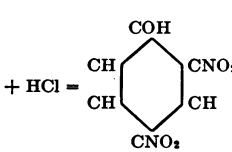
Dinitrophenol is particularly a French explosive. In combination with trinitrophenol (picric acid) and trinitrotoluol ("TNT"), it formed most of the filling mixtures used in shells and hand grenades.

## CHEMISTRY OF MANUFACTURE

Theoretically, dinitrophenol ($C_6H_3(NO_2)_2OH$) is a double nitration of phenol. It is, however, usually made from benzene by the formation of mono-chlor-benzene. The latter is treated with nitric and sulphuric acids to form di-nitro-chlor-benzene. Additional treatment with sodium hydroxid substitutes sodium oxid for the chlorine in the (1) position, the sodium being removed by the addition of hydrochloric acid, leaving the completed dinitrophenol. These reactions are evident from the following structural formulae:




BENZENE MONO-CHLOR-BENZENE DI-NITRO-CHLOR-BENZENE




or DINITROPHENOL 1-2-4

While there are six possible isomers, all of which are known, the ordinary or alpha-dinitrophenol is the isomer 1-2-4 with the OH in the (1) position and the $NO_2$ groups in the (2) and (4) positions. Further nitration of dinitrophenol yields trinitrophenol, or picric acid.

The finished dinitrophenol is a yellow solid having a faint odor of phenol. The melting-point, if the drug is pure, is 237° to 238° F. (114° to 115° C.). It may be sublimed, and carried off in aqueous vapor to the amount of about 2 to 3 grams to 2 kilograms of steam at 212° F. (100° C.)—important points in controlling the health hazards of workers. It is soluble in 21 parts of boiling water and in about 250 parts of water at 64° F. (18° C.). It is also soluble in alcohol, ether, and chloroform. The reaction is definitely acid, and crystalline salts, such as the sodium salt, $C_6H_3(NO_2)_2(ONa)$ $H_2O$, which was the usual form of administration in the later treatment of obesity, are readily obtainable.

## TOXICITY

The toxicity of dinitrophenol was established by André Mayer (quoted by Perkins[6]), a member of the Conférence pour l'Étude de la Toxicité des Explosifs, after a prolonged and elaborate series of experiments in animals and man were completed in 1918. I quote from a translation of his résumé:

"The long experience of the Service of Explosives in the manipulation of picric acid, of which hundreds of tons have been made and used without serious cases of intoxication, led to the idea that the nitrated phenols are not violent poisons for the human organism. Accordingly, when the manufacture of dinitrophenol was begun and the first cases occurred among the workmen, they were put down to impurities in the commercial products. This idea was shown to be incorrect. All the impurities which it was possible to extract, and even all the various compounds of benzene formed in the course of manufacture, were found to be less dangerous than dinitrophenol 1-2-4. This, then, is a toxic product, no matter how introduced into the animal organism, whether by ingestion, intravenously, subcutaneously, intraperitoneally, or even rubbed on the skin."

Following the recognition of the chief portals of entry (pointed out by the studies of Guerbet and others), quoted by

Perkins,[6] consisting of the skin, digestive tract, and respiratory tract, the various processes of manufacture, purification, and distribution were carefully checked to determine exposure hazards. Preventive measures followed, such as the placing of asbestos curtains about melting vats, modified gas masks, ventilators, cuffs above wooden shoes, washable gloves, sanitary eating regulations, rotation of service, medical observation, daily baths, and a change of clothing at the end of the day. The success of these measures is shown in the following table:

| *Period* | *Deaths* | *Tons of DNP. and Mixture "DD" Manufactured* | *Deaths Per 10,000 Tons* |
|---|---|---|---|
| May, 1916, to May, 1917..... | 31 | 19,100 | 16.3 |
| May, 1917, to May, 1918..... | 5 | 40,700 | 1.2 |

Considering the difficulty of enforcing safety regulations among three races, these results are remarkable. The workmen were Frenchmen, Chinese and Annamites, and black Senegalese, many of whom showed a great abhorrence of water, used either externally or internally. Moreover, the workers were either so alarmed by the printed warnings about personal danger that they refused to work and became neurasthenic, or, more often, they disregarded the warnings completely. Since women were not employed in dangerous tasks, few were exposed, and hence no cases of illness were reported among them.

## EXPERIMENTAL WORK

As the result of the animal experiments of Mayer, previously alluded to, dinitrophenol was proved to be a specific poison. Symptoms emphasized a definite exaggeration of the heat radiation activities, such as thermic polypnea in the dog and vasodilatation and sweats in the horse. Body temperature was considerably elevated, despite these protective reac-

tions, and in cases of fatal termination the temperature might reach 111° F. (45° C.). Rigor mortis set in immediately after death. The fundamental phenomenon appeared to be an increase of the general oxidation rate of the body. This was observed even in cold-blooded animals, and was not affected by nervous stimulation, muscular work, or the activity of any particular organ. Glycogen reserves were depleted by the intoxication, and fat metabolism was believed to be altered. Animals of the same species showed a remarkable variation in susceptibility to the drug, and tolerance to increasing doses was observed in nearly all animals.

## POISONING IN MAN

The symptoms of intoxication in man seemed to parallel those observed in animals. The subacute symptoms included gastro-intestinal disturbances, such as anorexia, nausea, vomiting, diarrhea, and colic. Icterus was rare. Loss of weight, sweats, especially at night, weakness, headaches, and dizziness were all recorded. These symptoms might rapidly disappear if the patient remained away from the factory for a few days. As had previously been observed in animals, susceptibility varied widely, since only a limited number of persons were affected, even under the worst working conditions. Alcoholism, lesions of the liver and kidneys, and a general lowered resistance among the workers made them poor risks.

Urinalysis proved of definite clinical value in determining the serious cases. Although unchanged dinitrophenol and various reduction products might be found in subjects displaying no clinical signs of intoxication, amino-2-nitro-4-phenol was always found in abundance in serious cases. This fact was made the basis of a specific test of urine, known as Derrien's test.[6,7,34] This involved an azoreaction, the positive tests being violet, wine color, or orange-red, whereas negative tests were either colorless or yellow. A positive Derrien reaction which became increasingly high or remained

high indicated an impending acute intoxication. Positive Derrien tests were later used to indicate neglect in the enforcement of preventive measures in a particular factory.

Acute poisoning usually followed as a sequel to subacute symptoms. The onset was sudden, with complaints of tiredness in legs and arms, painful constrictions at the base of the chest, and a burning thirst. Pallor, cyanosis, profuse sweating, agitation, and dyspnea occurred, together with a moderate elevation of temperature. The urine diminished in amount and the Derrien test became increasingly positive. Prompt removal from work and rest usually brought relief. The patient remained off duty until the urine became negative, with a minimum rest period of eight days. Fulminating intoxication was most marked among alcoholics and persons with kidney or liver diseases. In these cases, death might supervene within a few hours. The patient suddenly finds that he is unable to work or collapses on the way home. He is seized with colic and diarrhea. The temperature rises to 104° F. (40° C.) or higher, sweating is profuse, and the skin is stained yellow. Thirst is intense. The heart-beats remain regular, and the lungs exhibit only occasional scattered râles. The patient becomes frightened and excited, and general or partial convulsions appear. Unconsciousness, coma, and death follow in a few hours, the death resembling that occurring in uremic poisoning. Rigor mortis sets in immediately, a conspicuous feature previously mentioned in connection with experimental animals. This phenomenon was believed to be due to the extreme dehydration.

At postmortem no characteristic lesions were found. The acute edema of the lungs mentioned was believed to be secondary to toxic effects upon the vasomotor system. Microscopic lesions of the liver and kidney cells were inconstant, and typical changes were lacking elsewhere. The presence of dinitrophenol within the body was not characteristic, since it was also found in the bodies of workmen who had died from accidental causes. It is to be noted, in passing, that in all

these studies only one workman complained of poor vision. This man was working in a dinitrotoluene plant, and it is possible that he might have had an eye defect that was unrelated to the intoxication.

In 1928 Professor C. Heymans, of Ghent,[3,4] and others (quoted in [34]),[8,9] revived interest in the fever-producing and other properties of nitrated naphthols. These researches stimulated Tainter and his co-workers to study alpha-dinitrophenol.

## INVESTIGATIONS IN AMERICA

In 1931, Tainter and Cutting and their associates began an elaborate series of independent studies on the pharmacology of dinitrophenol. They confirmed much of the work cited in the French and Belgian reports, and made additional investigations as to certain possible clinical uses of the drug.[10-19]

Proved experiments showed that dinitrophenol was able to increase the consumption of oxygen in animals to as much as 12 times the normal amount.[14] The increased metabolism was noticeable within one minute after the injection, and varied with the size of the dose, which could be raised to a point where the animal died from the excessive heat production. The increase in metabolism was peripheral, and was due to direct stimulation of the cellular metabolism. The metabolic response was not prevented by destruction or curarization of brain or cord, or by removal of the thyroid or the suprarenal glands. Heightened oxidation was accompanied by a marked increase in the respiratory rate, probably due to a greater oxygen demand and to an increased carbon dioxid production. Pulse rate and blood-pressure were not raised so long as the circulatory and respiratory symptoms kept pace with the increased oxidation, and neither anoxemia nor acidosis developed. The drug decreased the supply of glycogen in the liver and muscles, raised the blood sugar, and increased the lactic acid content of the blood and muscles. The increased metabolism was primarily at the expense of

fats and carbohydrates. Experimental animals developed tolerance to the drug only when exceedingly high doses were given. The fatal dose for various species was determined at 20 to 30 mg. per kilogram of body weight. No specific antidote was found. In experimental animals death resulted from direct circulatory depression, high fever, acidosis, and anoxemia. Tainter and Cutting were unable to find any significant damage to important organs of dogs given daily, just short of fatal, doses of dinitrophenol for periods of six months.

## EFFECTS IN MAN

In human beings the action of dinitrophenol agreed closely with that observed in animals in equivalent doses. In July, 1933, Cutting, Mehrtens and Tainter[19] reported that nine patients had been given from 3 to 5 mg. of the drug daily for periods of from one to ten weeks. In six of these the metabolic rate was repeatedly determined and was found to be maintained at an average of 40 per cent. above normal. All these subjects lost weight without dietary restrictions. Changes in temperature, pulse rate, and respiration were not observed, although the amount of perspiration was increased. No undesirable symptoms were encountered, and the patients stated that they felt better and were more active than before taking the drug. These authors believed that preliminary results in patients indicated that dinitrophenol could satisfactorily increase metabolism, experimentally and therapeutically, and might "be useful in the treatment of obesity, hypothyroidism, and similarly depressed metabolic states."

Anticipating extended clinical applications of the drug, the authors carefully pointed out the dangers that may arise therefrom. They emphasized the point that continuous administrations in animals and man had not been made beyond three months and only in normal subjects. They had no assurance that toxic manifestations might not appear after

more prolonged dosage or in diseased conditions. They pointed out that excessive doses could cause a fatal hyperpyrexia, and warned against possible idiosyncrasies, such as unusual sensitivity or atypical response to the drug. They recommended that "dinitrophenol be used only as an experimental therapeutic procedure in carefully selected patients under close observation by the physician." This warning was repeated both as an editorial[25] in the same issue, and in a preliminary report of the Council on Pharmacy and Chemistry.[26]

In November, 1933, Tainter, Stockton, and Cutting[20] published a progress report covering 113 consecutive, unselected cases of obesity treated by dinitrophenol. The patients consisted of 98 females and 15 males. About one-half of the cases had received previous thyroid administration and had undergone dietary regimens until no further weight loss was effected, hence they represented the more unresponsive types of obesity.

The treatment was successful in 101 (89.4 per cent.) cases. An average loss of weight of between two and three pounds (0.9 to 1.3 kg.) a week was obtained by an average daily dose of 0.3 gm. The weight loss was shown by measurements to be predominantly from hips and abdomen. Those patients who were not on special diets at the beginning of the treatment were allowed to eat their regular fare without restrictions.

Individuals who had taken the drug continuously for four months showed no demonstrable evidence of cumulative or toxic effects. Certain side actions were observed in others; these will be mentioned further on. The drug was stopped in three cases because of unsatisfactory weight loss with average doses, and in nine other patients who showed undesirable reactions. The initial adult dose was fixed at 100 mg. of the sodium salt (equivalent to 75 mg. of dinitrophenol) given in capsules daily with meals. This dose was to be increased at weekly intervals as it became necessary to a point where two to three pounds of body weight a week were lost or until

symptoms of warmth and sweating became unpleasant. The danger of indiscriminate or careless overdosing was again stressed.

During 1933, Dodds and Robertson[27b] published three communications dealing with the clinical application of a related nitro-compound, 4:6 dinitro-ortho-cresol. This drug was claimed by these authors to be from three to five times more powerful than dinitrophenol, although its toxicity was no greater. They believed that dinitro-ortho-cresol was superior for weight reduction, since equal effects could be secured with one-third the dosage. These observers defined a safe dose as from 50 to 100 mg. a day, or 0.5 to 1.0 mg. a kilogram of body weight. The effect of the drug in therapeutic usage was best determined by making measurements of the basal metabolic rate. Discomfort or toxic symptoms did not occur when the basal rate was maintained between plus 30 and plus 50. Dodds and Robertson considered any rate above plus 50 dangerous. Experiments convinced these authors that metabolic stimulants of the dinitro-group were of no use in alleviating myxedema, a potentiality that had been suggested by Tainter.[20] Dinitro-ortho-cresol and mixtures containing this drug were used extensively in Europe in reducing "cures."

## POPULARITY OF DINITROPHENOL TREATMENT

The popular response to dinitrophenol was immediate and overwhelming. It appealed to the imagination of both physician and patient. Here was a drug that would apparently banish the tired feeling that accompanied low metabolic states without inducing the deleterious symptoms that might result from equivalent doses of thyroid extract. Corpulent females could lose unwanted poundage without the necessity or inconvenience of dietary restrictions! In spite of repeated warnings[30-32] that were issued, dinitrophenol was used to an astonishing degree in the treatment of obesity. It is estimated that during the first fifteen months

following its introduction,[22] 100,000 persons took the drug for weight reduction. More than 1,200,000 capsules of 0.1 gm. each were dispensed from one clinic alone in San Francisco. This would correspond to about 4,500 patients. More than 20 drug houses offered to supply both dinitrophenol and mixtures containing the drug. Many of these remedies could be procured without prescription, and with no further directions than to take "one capsule three times daily after meals."

## TOXIC EFFECTS

It is not surprising that, under the circumstances, instances of toxic reactions began to appear in the literature. Gastro-intestinal symptoms, consisting of nausea, vomiting, and loss of appetite, were common. Skin lesions, however, were the most frequent, with an incidence of from 8 per cent. to 23 per cent.[20,34-41] These lesions included maculopapular dermatitis, urticaria, or angioneurotic-like swelling, accompanied by itching and burning. Although the majority of cases were mild, others were severe. Hitch and Schwartz's case[40] persisted for over ten months, and was complicated by polyneuritis, otitis media, and cataract. One case of alopecia was reported.[41] Skin tests were of no value in indicating individual hypersensitivity.[36,38]

## EAR COMPLICATIONS

Dintenfass[33] and Hitch and Schwartz[40] reported exudative otitis media occurring in two patients.

## AGRANULOCYTOSIS

In view of the similarity of dinitrophenol to benzene, bone-marrow changes might have been anticipated. Eight cases of agranulocytosis were reported, with three fatalities.[42-46,65,66] The smallest amount of the drug taken in these cases was 5.6 gm. over a period of fourteen days. In the other cases the average was 12 gm. over fifty-eight days.

### NEURITIS

Under this head are included aberrations of taste (loss for salt and sweet) and multiple regional involvement affecting particularly the feet and legs. Thirty cases were reported in the literature.[20,34,48,49,51,87] Symptoms appeared after an average of ten weeks, followed ordinary therapeutic doses, and persisted for weeks or months.

### CARDIOVASCULAR SYSTEM

Remarkably few changes in the cardiovascular system were reported. Electrocardiographic evidence of functional damage was offered by MacBryde and Taussig[50] and by de Châtel and Motika.[51] Poole and Haining[63] and Tainter and Wood[64] reported finding fragmentation of the heart muscle at autopsy in fatal cases. Tachycardia and a fall in blood-pressure were occasionally noted. Hypertensive patients showed a definite lowering of both systolic and diastolic pressures, but hypotensive patients exhibited little change.[21,41]

### LIVER FUNCTION

Jaundice and other symptoms of liver damage were reported by various observers.[50,53,55-57,63,116] Graham[54] has demonstrated that the liver is less able to withstand toxic substances when the glycogen content is low. Some investigators believe that this may be a factor in dinitrophenol patients. Simkins,[41] however, in a late analysis, concludes that in therapeutic doses the drug is rarely hepatogenic. This agrees with the findings of Koch, Lee and Tainter[52] and Schulte.[58]

### KIDNEY FUNCTION

Although instances of kidney damage have been reported,[55,59,63,64] most observers believe that this rarely occurs.

### MORTALITY

A total of nine deaths have been reported from the use of dinitrophenol and one from dinitro-ortho-cresol.[60-69] Three

patients died from overdoses. Three of the remainder had agranulocytosis. In the majority of cases death occurred within twenty-four hours after the onset of such toxic manifestations as dizziness, fatigue, dyspnea, high temperature, intense thirst, and excessive perspiration. As had been observed in animals, rigor mortis set in immediately after death.

## SUCCESSFUL WEIGHT REDUCTION

Interim studies had confirmed the potency of dinitrophenol as a slimming agent. Tainter, Stockton, and Cutting[24] obtained weight reduction in 165 of 170 unselected cases (97 per cent.). In a review of 290 cases in the literature, McGavack[70] showed a weight loss in 276 (95 per cent.). Simkins,[41] in his comprehensive clinical study of 181 unselected obese patients, recorded a lower figure (79.7 per cent.) in 59 cases. He found that the effectiveness of dinitrophenol as a reducing agent could be increased substantially by the addition of desiccated thyroid.

The amount of weight lost by patients receiving dinitrophenol therapy varied. Nineteen patients reported by Whalman[104] lost an average of 37.7 pounds per patient. Simkins[41] obtained only 11.1 pounds average loss in 47 cases. Individual losses varied from zero to 140 pounds in one series.[41] Other reports (Strang and Evans[71]) questioned the practical value of dinitrophenol in this regard, but proportionately few negative results are mentioned in the literature.

On July 6, 1933, the Council on Pharmacy and Chemistry of the American Medical Association recommended that dinitrophenol be not accepted for inclusion in "New and Non-official Remedies."[72] In arriving at this conclusion they pointed out that dinitrophenol as a new drug should await further study in laboratories and clinics before being put into general use as a remedy for obesity. They stated further that "to treat a mild chronic condition such as obesity with a

toxic agent capable of inducing serious injury and death appears to be unjustified." The Council recommended that restrictions be placed on the sale of the drug, and that its use be limited to selected patients and be supervised by properly trained physicians. The dangers of dinitrophenol had already received official recognition in Germany,[73] Canada,[74] and England.[75,76] The most drastic legal regulation of dinitrophenol to date has been enacted in California[77] (California Laws, 1939, C582). This makes it a felony for any person to sell, dispense, administer, or prescribe dinitrophenol for the purpose of human consumption. In order to procure the drug a prescription is obligatory in Connecticut, Florida, Nevada, North Carolina, and other states.

## CATARACTS

The development of cataracts following dinitrophenol therapy was first described by Horner, Jones, and Boardman[78] in July, 1935. In this communication we reported three cases of bilateral incipient cataracts occurring in women who had taken considerable quantities of the drug for weight reduction. One of us (Jones) had made careful medical records of these patients, which, together with an average age of thirty-eight years, made the development of cataracts from any other cause unlikely. All three patients showed similar powdery anterior subcapsular changes, denser posterior subcapsular opacities resembling brass filings, and rapid loss of vision. In other articles Boardman[79] reviewed two of these cases, and mentioned eight others that had come to his attention. In each report we stressed the point that the use of dinitrophenol be stopped, pending further study.

During the next two months, seven additional writers reported cases.[80-86] In October, 1935, Cogan and Cogan[87] reviewed the first 20 cases that had appeared in the literature. Other reports followed.[88-110] Rodin[91] reviewed 32 cases, particularly as to age, duration of treatment, and onset of lens changes. Whalman,[104] in October, 1936, in an excellent

paper, tabulated 27 cases, and in an appended note stated that since completing this paper his list of cases had been increased to 40. This is the largest series in the literature. Although a majority of the cataracts due to the drug have occurred in California, cases from nearly all sections of the country are on record.

## EUROPEAN CASES

Vannas,[111] in Finland, in December, 1935, reported the first "dinitro-cataract" in Europe. This cataract followed the use of dinitro-ortho-cresol[27] as a "reducing cure," and is the first case on record due to this drug. Vannas was also the first author to have made a histologic study of this type of cataract. Other cases were reported from the Netherlands (Van der Hoeve and Polak Daniels[112]); from Finland (Helminen[113] and Lindberg[122]); from Switzerland (Vogt[114,115]); from France (Onfray and Gilbert-Dreyfus[116] and Sedan[117]); from Brazil (Oneto, Gallino and Natale[118]); from Italy (Ciotola[119]); from Sweden (Ploman[120]), and from Denmark (Måhlén[121]).

## RÉSUMÉ OF CASES

From these case reports it became apparent that dinitrophenol cataracts presented certain new and characteristic features:

(1) They occurred in young women who were physically normal save for varying degrees of obesity, and who were all in an age group in which senile cataract does not occur. (2) The cataracts were bilateral, and appeared either during or following periods of "slimming" treatment with dinitrobodies. (3) An interval of months or years might elapse between the time the last dose was taken and the onset of blurred vision. (4) The lens changes were strikingly similar, and could be demonstrated by the biomicroscope at a time when vision for distance and reading was still normal. (5) After a gradual onset, the lens changes progressed with startling rapidity until vision was obscured. (6) Treatment

was without effect in staying their progress. (7) Surgical extraction of the lens was uniformly successful in restoring vision.

## LENS CHANGES

The earliest lens changes consisted of faint gray, striated, powdery, downy, or lace-like opacities situated just beneath the anterior lens capsule. The capsule remained transparent, but was often described as appearing "dry" or "pebbly," due to the presence of water vacuoles beneath it. The cortex was either clear, or contained small, whitish, discrete, cornmeal-like granules. The nucleus was unaffected. The most spectacular finding, however, occurred in the posterior lens. Here, in the subcapsular region, was a dense, saucer-shaped, granular deposit with a golden, sometimes silvery, luster. This deposit resembled brass filings, cloth of gold, hammered copper, or silvery or polychromatic crystals. The adjoining vitreous was normal. The cornea, aqueous, iris, and fundi were normal. Certain exceptions were observed. An aqueous flare was mentioned by Cogan and Cogan[83] and Whalman.[104] Fine, dust-like opacities were described on the posterior cornea (Allen[85]) and on the lens (Oneto and others[118]). McDannald[106] observed scattered areas of atrophy in the pigmented layer of the uvea in both the operated and the unoperated eye of one patient. Swett[101] described a patient with a conjunctival slough and symblepharon which accompanied an extensive desquamative dermatitis and mucous membrane involvement. Ultimately one eye was lost. Frost[102] reported one case with partial, secondary optic atrophy, with final vision of 20/50, field defects, and pale discs.

Visual impairment during these early stages was slight, and might be improved by glasses. These patients showed a characteristic increase in hyperopia. After an interval of weeks, vision suddenly and rapidly grew worse. The opacities became intumescent, invaded the cortex and finally the nucleus, so that the whole lens grew opalescent, silky-gray or

pearly, sometimes with the speed of a traumatic cataract. Lamellar dissolution[122] and fine striation were also described.

Late stages showed varying disintegration of the whole lens into sector-like fragments separated by dark intervening, spoke-like bands. The lens swelled early in the process, the anterior chamber became shallow, and tension increased, occasionally to the stage of acute secondary glaucoma. Helminen[113] encountered four such cases, Hessing[107] three, Horner[100] four, Whalman[104] two, and other cases are mentioned in the literature. Welton[108] observed an unfortunate patient who developed cataracts, bilateral glaucoma, panophthalmitis, and phthisis bulbi. Another patient living in the vicinity of San Francisco lost her vision from a similar secondary glaucoma.

The increase of hyperopia, often 2 or 3 D., mentioned above, is remarkable, since this is opposite to the usual behavior of a swollen lens. As the lens approached complete opacification, however, the refraction changed toward emmetropia or even myopia. Helminen[113] described early loss of accommodation, which he considered to be a precursor of beginning cataract.

In a minority of instances the lens opacities became arrested and vision was retained. Lindberg[122] described two patients who showed water slits beneath the anterior capsule, no golden reflex, and a series of white, isolated granules lying in front of the supranuclear layers both in front and behind the lens. Three years after stopping dinitrophenol corrected vision remained at 6/5 partly. One patient of mine with stationary lens changes had a greatly weakened accommodation (plus 2.25 addition at age forty-six). Whedon[103] recorded speck-like opacities and a golden reflex in one patient. Five months later scarcely any trace of the opacities could be found in the lenses or the capsules. Bedell[128] and Hessing[107] add four cases which did not progress.

The interval which elapsed between the onset of blurred

vision and complete lens opacification varied between seven days and five months, with an average of two and one-half months. The early changes progressed much more slowly than the later ones, as is illustrated by the earliest case which I saw (Case 3[78]). This patient presented characteristic lens findings, but retained a vision of 0.8 plus for more than two and one-half months, only to become blind (hand movements) within the next eight days!

### ONSET

Cataracts appeared after an average of fifteen months' treatment in 27 patients (Rodin[91]). In 67 per cent. of these, treatment had already been stopped before lens changes occurred. This interval between the termination of the drug administration and the appearance of cataract symptoms varied from a month to a year, with an average of seven months.

### DOSAGE

The length of time that dinitrophenol was taken and the amount of the drug consumed varied widely. Rodin[91] found that in 29 cases the duration of treatment varied from three months to twenty-four months, with an average of eleven months. The amount of drug taken, as estimated by Rank and Waldeck,[99] varied from a minimum of 9 gm. to a maximum of 126 gm., the average being 73 gm. Neither the length of treatment nor the total dosage seemed to have any bearing upon the occurrence of these cataracts. Individual susceptibility appeared to be a more important factor.

### AGE AND SEX

Only three males are believed to have acquired cataracts from the use of dinitrophenol. Cogan[87] and Rundles[88] reported one case each, whereas the third came to my attention in San Francisco.

The average age in 32 cases was forty-five years. The youngest was thirty, the oldest, sixty-seven (Rodin[91]). Of

these, 70 per cent. were in the third and fourth decade. Two patients aged twenty-five years have been reported. Hessing[107] mentions a mother and her daughter who were operated upon for cataract at about the same time.

## INCIDENCE

In a paper published in 1937[100] I estimated that the incidence of cataract in patients who had taken dinitrophenol was probably between 0.1 per cent. and 1 per cent., and that the total number of patients so affected would range between 60 and 100.

There are only a few reports of extensive clinical studies of dinitro-bodies to be found in the literature. The data available show that Tainter, Stockton, and Cutting[24] (1935) reported 1 case in 170 treated patients; Hill[90] (1936), 1 in 68; Simkins[41] (1937), 1 in 159; Måhlén[121] (1938), 1 in 66 of Berglund's 73 cases who received dinitro-ortho-cresol. These average 0.86 per cent., which is within the estimate previously given. Since the interval between the discontinuance of the drug and the occurrence of cataract may be as long as one year, some of the patients treated in these four series may have acquired cataracts at a later time. This figure is, therefore, more likely to be minimum than maximum. My previous estimate of the number of persons affected proved much too low. I have recently collected a total of 177 cases from the literature up to January, 1941. Of these, 164 followed the use of dinitrophenol, whereas 13 had been taking dinitro-ortho-cresol. These figures are probably again too low. It is certain that additional cases have occurred which have failed to be reported in the medical journals. Other cases may have been presented as case reports before local medical societies. Since relatively few of the proceedings of the latter are published, such patients are lost sight of. An additional number of isolated cases has resulted from the use of patent slimming nostrums. Five of these were reported as late as 1938,[109] but are now more likely to be mentioned in

the *Journal of the American Medical Association* in the section devoted to the investigation of patent medicine frauds.[139]

## TREATMENT

Medical treatment failed to cause regression or to prevent the progress of any of these cataracts. Although a few "arrested" cases have been reported, which are discussed under the head of "Lens Changes," with one exception these were not attributed to the treatment. Local measures, such as hot compresses, ethyl morphine hydrochloride, or subconjunctival injections, proved useless. General therapy, consisting of forced fluids, calcium salts, cevitamic acid (Vitamin C), and lens antigen, was equally ineffective.

## SURGICAL CONSIDERATIONS

Operative treatment was successful in a high percentage of patients. The technique was not difficult, and the results were, in general, probably better than the average of an equal number of senile cataract extractions, because of the fact that the eyes were in healthier, younger bodies.

While the technique varied with the preference of the operator and the age of the patient, the majority of the cataractous lenses were removed by one of the procedures applicable to the extraction of soft cataract, with preservation of a round pupil.

As a reasonable cross-section of surgical experience in this type of cataract, I have analyzed the combined operative reports of three surgeons who have published their findings in a substantial series of cases, namely, Hessing,[107] 25 cases; H. Barkan and others,[94] 20 cases, and my own,[100] 17 cases. In a total of 62 cataract extractions, a Graefe incision was made in 42 (67.7 per cent.), while a keratome was used in 20 (32.2 per cent.). There was a peripheral iridectomy in 30 cases (48.4 per cent.), no iridectomy in 18 (29 per cent.), and a full iridectomy in 14 (22.6 per cent.). Extracapsular extractions were done in all cases (100 per cent.). The compli-

cations that occurred consisted of iris prolapse, 1 case; secondary glaucoma, 2 cases; iritis, 3 cases; vitreous loss, 3 cases; postoperative bleeding, 4 cases; and secondary cataract, 12 cases. Further comment concerning secondary cataract will be made further on. Vision of 15/20 or better was obtained in 86 per cent. of the series, and the average visual result for the 62 patients was 17/20 plus at the preliminary or the final refraction.

The surgical treatment of cataract due to dinitrophenol thus presented no particular difficulties. Certain peculiarities, however, are worthy of mention. The lenses were usually soft, sometimes lardaceous, and less often, firm, as in senile extractions. The lenses were delivered in fragments, rather than *en masse*. Lens débris present postoperatively was unusual, since most of the fibers were opaque and could be removed completely at the time of operation. Intracapsular extractions were seldom employed since, because of the taut, swollen nature of the lens, they would appear to be performed only with difficulty and were regarded as unnecessary. Acute secondary glaucoma was treated, in a minority of cases, by Graefe or other basal type iridectomy. The majority of operators proceeded as in a soft cataract extraction, disregarding the swollen lens by a bold incision. The results were equally good in relieving tension and better as regards the cosmetic result.

In the great majority of cases secondary cataract developed eventually as demonstrated by a late analysis of my own series of cases. Prior to this I have not seen any comment in the literature concerning this point. In 17 out of 19 eyes of which I have follow-up records, 15 discissions were either performed or advised, a startling incidence of 88 per cent. Many of these operations were necessary two years or more following the original extraction. This figure is the more remarkable when it is compared with an incidence of only 5 needlings in 32 cases of senile extracapsular extraction (15.62 per cent.) which I performed during the same period. The

explanation for this phenomenon lies, I believe, in the preponderant number of young lenses that we encountered in making these extractions. The formation of secondary cataract is in keeping with the proliferative activity of the capsule, which suggested to older writers the expression "regeneration of the lens" (Milliot; and Textor, 1872; quoted by Duke-Elder[138]). Duke-Elder states that this phenomenon "occurs preferentially but by no means exclusively in younger patients and concerns especially the subcapsular epithelium." Youth is, therefore, more of a factor than inflammatory reaction: (1) Since they occurred long after the operation, and (2) because the average reaction in these cataracts was no greater, and in most cases less, than in senile extracapsular extractions.

## ETIOLOGY

The etiology of cataracts following the use of dinitrophenol is not understood. There is even a lack of agreement in the classification of this form of lens. Although some American authors speak of dinitrophenol cataract as a new type, others in Europe and America, mindful of the early posterior lens changes, use the term "complicated cataract," a concept introduced by Becker in 1876, but later amplified, particularly by the slit-lamp studies of Vogt in 1919. Duke-Elder[141] considers dinitrophenol cataract under the head of "toxic cataract." European writers often combine dinitrophenol and dinitro-ortho-cresol under the collective term "dinitro-bodies," and designate the lens opacities as dinitro-cataract. Moreover, the relationship of cataract to the ingestion of dinitro-bodies remains unconfirmed.

In favor of such an etiologic relationship one may point out that, following treatment with these drugs, too many cataracts occurred in women who were too young to develop senile cataracts and too healthy to develop lens changes due to other causes. It may be admitted further that dinitro-bodies are toxic substances capable of causing death or severe

poisoning in man and animals; that susceptibility to these substances varies remarkably; that in carefully controlled dosage, without side reactions, there is an unnatural stimulation of metabolism and an increase in oxidative processes within the body. Is it not possible that toxic effects or the increased oxidation may affect the delicate metabolism of the lens, a subject about which we know so little? These statements, while true, and the questions, while reasonable, are unanswerable in the present state of our knowledge.

Against such an etiology one may say that similar cataracts have been reported in healthy young women who had not taken dinitrophenol (Horner[100]) (Barkan and Bettman[130]), and such cataracts have been seen by ophthalmologists in such conditions as diabetes and goiter, as was emphasized by Bedell.[128] If there is a toxic etiology, why should lens changes appear only once in about 116 patients, and why should they occur as late as a year after the drug has been eliminated from the system? Why did not cataract develop in munitions workers who were constantly exposed to dinitrophenol during the first World War? Why have not experimental animals that were given dinitrophenol developed lens changes? Here, too, are statements which are true, and reasonable questions that must for the present remain unanswered.

Although many of the contributors to the literature of dinitro-cataract have offered suggestions as to the mechanism involved, the majority of these are merely speculative, and not supported by experimental evidence. There are relatively few reports in the literature of investigations covering this phase of the problem. These will be reviewed, together with the suggested explanations of various authors previously mentioned.

Our knowledge of the etiology of cataract in general is gradually increasing, but even in the types which we can produce experimentally, such as follow the use of naphthol or thallium, we are still unable to say why these changes take place.

## ANIMAL EXPERIMENTS

Tainter and his co-workers[135] have been unable to produce pathologic eye changes in any of the common laboratory animals by dinitrophenol, administered under a variety of conditions. White rats, for example, which are generally susceptible to cataract formation, have been fed diets containing up to fatal concentrations of dinitrophenol from the time they were weaned until death occurred about two years later, without showing any pathologic eye changes.

Other feeding experiments have been carried out by Helminen[113] and Basile[137] with rabbits; Sohr,[131] with guinea-pigs; Nordmann and Reiss,[125] with rabbits and rats, and by Ciotola,[119] with rats, rabbits, and dogs. All these workers achieved equally negative results. Ciotola injected dinitrophenol directly into the anterior chamber and vitreous of animals without producing cataracts.

Krause,[134] in commenting upon the toxic substances that may injure the lens directly or indirectly, points out that in rats thallium poisoning results in cataract formation whereas in man the optic fibers are destroyed. This observer believes that this indicates a difference in the metabolism of species, and that it may explain the failure to induce cataract formation in rats by giving them dinitrophenol.

## DINITROPHENOL AND LENS METABOLISM

The effect of dinitrophenol upon the lens metabolism was studied by Field, Tainter, Martin and Belding.[127] These workers postulated that if such lenses were unusually responsive to dinitrophenol, the ordinary therapeutic dose might stimulate its respiration to such a degree that products of metabolism would accumulate faster than they could be carried off and nutritional opacities would result. Their results proved this assumption to be false. The oxygen consumption of the lens was low in the mean, as compared with striated muscle and rabbit retina, whereas in optimum

concentrations it was again lower than muscle and about equal to that of the retina. Whether the lens would deteriorate from this heightened respiratory rate was not determined, but it was regarded as possible.

### PERMEABILITY OF THE CAPSULE

Studies were made by Borley and Tainter[129] to determine the effect of dinitrophenol upon the permeability of the lens capsule. This question had been brought up by Vogt[115] and others in connection with glaucoma, which sometimes occurred in dinitro-cataracts. Two possibilities had been suggested by Krause[123] for other types of cataract in 1934, namely, a decrease in the permeability of the capsule which might prevent normal exchange of metabolites, and an increase which might allow foreign materials to penetrate into the lens, or essential elements in the lens to escape. Borley and Tainter found no basis for assuming that dinitrophenol altered the permeability of the capsule either *in vitro* or *in vivo*.

### VITAMIN DEFICIENCY AND DINITROPHENOL

Tainter and Borley[132] could not produce cataracts in animals that were suffering from deficiencies of vitamin A, $B_2$, or C by feeding them dinitrophenol in maximum tolerated doses. This potentiality was investigated in order to determine whether possible vitamin deficiency in patients undergoing weight reduction with dinitrophenol might predispose the lens to cataract formation.

### LACTOSE CATARACTS AND DINITROPHENOL

Borley and Tainter[133] included dinitrophenol in various cataract-producing lactose diets in white rats in order to determine whether the addition of the drug affected the lens changes in any way. They found that the added dinitrophenol did not alter the average time of appearance, progression, nor the magnitude of the lens opacities. They also

demonstrated that dinitrophenol from three different manufacturers produced no variation in their results. Ciotola[119] in 1937 had also certified as to the purity of the dinitrophenol with which he had obtained negative animal experiments. He later observed the development of cataract in a patient who had taken the drug from this same source. The contention of Dally[142] that impurities in dinitrophenol, especially dinitronaphthol, were the cause of cataract has been disproved repeatedly. By other experiments[133] it was demonstrated that dinitrochlorbenzene, a possible impurity of commercial dinitrophenol, would not produce cataract in animals. In the original munitions experiments (Mayer, quoted in [6]) the French considered that certain common impurities, such as mononitrochlorbenzene and chlornitrophenol, were less toxic than the dinitrophenol itself.

## Oxidation Reduction Potential

Nordmann and Reiss[125] investigated the effect of dinitrophenol upon the oxidation reduction potential of the aqueous and lens in rabbits. After four injections of the drug, the potential of the aqueous was increased by 17 per cent. and that of the lens by 37 per cent. The rise persisted after cessation of the treatment.

## Other Suggestions as to the Etiology

Krause[134] believes that dinitro-cataracts may be caused in part by interference with the creatine and adenosine-phosphate processes in the lens.

H. Barkan, Borley, Fine and Bettman,[94] in discussing the etiology of dinitro-cataracts, refer to the rôle of vitamin C in normal and cataractous lenses. While cevitamic acid was used by Josephson[81] in the treatment of an early case of dinitrophenol cataract, a specific relationship to vitamin C is unproved. Barkan and others suggest the possibility of a disturbance of the nutrition of the lens or an altered pH

toward the acid side as a potential factor. No estimation of the pH of dinitrophenol cataract has, to my knowledge, appeared in the literature. In naphthalene cataracts, Reiss and Nordmann[136] have found that only lenses removed during the initial stages of opacity showed the expected increase in acid content. Mature cataracts revealed a shift toward alkalinity, averaging 7.8, from the range (pH 7.1 to 7.5) of normal rabbit lenses.

I have seen no previous comment as to the possible rôle of lactic acid in the production of these lens changes. Dinitrophenol, by increasing oxidation, raises the lactic-acid content of the blood. Since it is known that the lactic-acid content of the aqueous always exceeds that of the blood, it is conceivable that during treatment it might rise to such heights as to be harmful to the lens epithelium. Changes in the lens during treatment might continue to progress after the drug was discontinued. No estimation of the lactic-acid content of the aqueous during the administration of dinitrophenol has apparently been published. Biozzi[124] has produced cataracts in animals by inducing experimental asphyxia, which he explains by the uncompensated acidosis that prevails during asphyxia.

Müller[140] attributes lens changes to the increased oxidation by dinitrophenol.

Jackson[126] believes that it is conceivable that this drug breaks through the protective function of the lens capsule, which is to preserve transparency. Toxic effects upon the subcapsular epithelium would disturb its important functions of growth and nutrition, and might explain the special distribution of these opacities and their characteristic late appearance.

Cogan and Cogan[83] also suggest damage to the lens epithelium as an etiologic factor, but believe this to be the result of tissue anoxemia.

Onfray and Gilbert-Dreyfus[116] are of the opinion that cataracts may be an expression of liver damage by dinitrophenol

and a disturbance of water metabolism. They connect the latter with the frequency of glaucoma in these cases.

## RÉSUMÉ OF ETIOLOGY

We conclude our remarks upon the etiology of cataract formation following the use of dinitrophenol with the same paragraph with which we started, *i. e.*, that the etiology of cataract following the administration of dinitrophenol is not known and its cause and effect relationship is undefined. We have reached an impasse in this problem, since the drug is no longer being administered to humans, and all attempts to produce cataract by giving it to animals have been unsuccessful.

## SUMMARY

1. The pharmacologic properties of dinitrophenol are traced in four phases: (*a*) as a laboratory curiosity in 1895; (*b*) as a health hazard in the munitions industry (1914–18); (*c*) as a metabolic stimulant with possible clinical applications (1933); and (*d*) as a potent drug in the treatment of obesity (1934–35) which exhibited certain unfortunate side reactions.

2. The majority of these reactions were trivial, a few were fatal, and a middle group, affecting the skin and blood, were severe, but the most serious of all was the development of cataract.

3. Cataract occurred with recommended dosage of the drug and without demonstrable reactions.

4. A total of more than 177 cases of cataract developed following either dinitrophenol or dinitro-ortho-cresol, with an estimated incidence of 0.86 per cent. Of these, 98 per cent. occurred in women who averaged about forty-five years of age.

5. The cataracts were all of a type, were bilateral, developed rapidly, with visual loss, and might occur at any time up to a year after the drug had been discontinued.

6. Medical treatment was without effect, but surgical extraction proved successful with excellent visual acuity in a large percentage of cases.

7. Late secondary cataract was of frequent occurrence after these extractions, as was shown by a reported incidence of 88 per cent. in one series.

8. All attempts to produce experimental cataracts in laboratory animals by various and repeated administrations of dinitrophenol have been unsuccessful.

9. Dinitrophenol does not alter the permeability of the lens *in vivo* or *in vitro*, nor does it increase the oxygen consumption of the lens inordinately, as compared with other tissues. It does not hasten or otherwise affect the artificial production of lactose cataracts in animals.

10. The cause of cataracts following the treatment of obesity with dinitro-bodies is unknown, and its relation to the ingestion of these substances is unproved. The argumentative strength of the premise, *post hoc ergo hoc*, cannot be denied, however. The latter has been used successfully to obtain monetary damages in medicolegal actions filed by some of these patients.

11. Since these compounds found wide-spread and generally enthusiastic acceptance because of the beneficial results they produced, it is regrettable that they had to be discarded because of the secondary reactions. Additional studies are, therefore, needed to determine whether related products might not be developed that would retain the metabolic potency with a lessened amount of untoward effects, or even their complete absence. Some attempts along these lines have proved at least partially successful,[143] and others will doubtless be made. The chief deterrent to these studies is the necessity of being certain that the animal experiments can safely be used as guides to the potential clinical toxicity of the compounds elaborated.

## CONCLUSIONS

1. Dinitrophenol has been demonstrated to be a potent metabolic stimulant and an efficient oxidizer of excess body fat.

2. Such physiologic actions are highly desirable, and can be utilized in a number of abnormal body states.

3. The occurrence of toxic reactions, particularly cataract, formation, contraindicates further therapeutic use of this drug until these are understood and can safely be eliminated.

4. Should this prove infeasible, some other less toxic substitute may be developed through the knowledge that has accumulated in the study of dinitrophenol.

## REFERENCES

1. Cazeneuve, P., and Lépine, R.: Compt. rend. Acad. d. sc. **101**: 1167, 1885.
2. Gibbs, W., and Reichert, E. T.: Am. Chem. J. **13**: 289, 1891.
3. Heymans, C., and Bouckaert, J. J.: Arch. internat. de pharmacodyn. et de thérap. **35**: 63, 1928.
4. Heymans, C.: J. Pharmacol. & Exper. Therap. **51**: 144, 1934.
5. Magne, H.; Mayer, A.; Plantefol, L., and others: Ann. de physiol. **7**: 269, 1931; **8**: 1, 1932.
6. Perkins, R. G.: Pub. Health Rep. **34**: 2335, 1919.
7. Bolliger, A.: M. J. Australia, **1**: 367, 1934.
8. Koelsch, F.: Zentralbl. f. Gewerbehyg. u. Unfallverh., n. F. **4**: 261, 1927.
9. Leyman: Concordia, **9**: 55, 1928.
10. Cutting, W. C., and Tainter, M. L.: Proc. Soc. Exper. Biol. & Med. **29**: 1268, 1932.
11. Tainter, M. L.; Boyes, J. H., and De Eds, F.: Arch. internat. de pharmacodyn. et de thérap. **45**: 235, 1933.
12. Tainter, M. L., and Cutting, W. C.: J. Pharmacol. & Exper. Therap. **48**: 410, 1933.
13. Tainter, M. L., and Cutting, W. C.: J. Pharmacol. & Exper. Therap. **49**: 187, 1933.
14. Hall, V. E.; Field, J., 2nd; Sahyun, M., and others: Am. J. Physiol. **106**: 432, 1933.
15. Cutting, W. C., and Tainter, M. L.: J.A.M.A. **101**: 2099, 1933.
16. Cutting, W. C., and Tainter, M. L.: Proc. Soc. Exper. Biol. & Med. **31**: 97, 1933.
17. Tainter, M. L.: Proc. Soc. Exper. Biol. & Med. **31**: 1161, 1934.
18. Cutting, W. C.; Rytand, D. A., and Tainter, M. L.: J. Clin. Investigation, **13**: 547, 1934.
19. Cutting, W. C.; Mehrtens, H. G., and Tainter, M. L.: J.A.M.A. **101**: 193, 1933.
20. Tainter, M. L.; Stockton, A. B., and Cutting, W. C.: J.A.M.A. **101**: 1472, 1933.
21. Stockton, A. B., and Cutting, W. C.: J.A.M.A. **103**: 912, 1934.
22. Tainter, M. L.; Cutting, W. C., and Stockton, A. B.: Am. J. Pub. Health, **24**: 1045, 1934.
23. Tainter, M. L.; Cutting, W. C., and Hines, E.: J. Pharmacol. & Exper. Therap. **55**: 326, 1935.

24. Tainter, M. L.; Stockton, A. B., and Cutting, W. C.: J.A.M.A. **105:** 332, 1935.
25. Editorial. J.A.M.A. **101:** 213, 1933.
26. American Medical Association. Council on Pharmacy and Chemistry: J.A.M.A. **101:** 210, 1933.
27. a. Dodds, E. C., and Pope, Sir W. J.: Lancet, **2:** 352, 1933.
b. Dodds, E. C., and Robertson, J. D.: Lancet, **2:** 1137; 1197, 1933.
28. Ehrenfest, E., and Ronzoni, E.: Proc. Soc. Exper. Biol. & Med. **31:** 318, 1933.
29. Dunlop, D. M.: Brit. M. J. **1:** 524, 1934.
30. Quick, A. J.: J.A.M.A. **102:** 1419, 1934.
31. Editorial. J.A.M.A. **103:** 1950, 1934.
32. Toxicity of Dinitrophenol (Current comment). J.A.M.A. **101:** 1080, 1933.
33. Dintenfass, H.: J.A.M.A. **102:** 838, 1934.
34. Anderson, H. H.; Reed, A. C., and Emerson, G. A.: J.A.M.A. **101:** 1053, 1933.
35. Hirsch, S.: J.A.M.A. **102:** 950, 1934.
36. Frumess, G. M.: J.A.M.A. **102:** 1219, 1934.
37. Jackson, H., and Duvall, A. I.: J.A.M.A. **102:** 1844, 1934.
38. Matzger, E.: J.A.M.A. **103:** 253, 1934.
39. Noun, M. H.: Arch. Dermat. & Syph. **32:** 288, 1935.
40. Hitch, J. M., and Schwartz, W. F.: J.A.M.A. **106:** 2130, 1936.
41. Simkins, S.: J.A.M.A. **108:** 2110; 2193, 1937.
42. Hoffman, A. M.; Butt, E. M., and Hickey, N. G.: J.A.M.A. **102:** 1213 1934.
43. Bohn, S. S.: J.A.M.A. **103:** 249, 1934.
44. Davidson, E. N., and Shapiro, M.: J.A.M.A. **103:** 480, 1934.
45. Silver, S.: J.A.M.A. **103:** 1058, 1934.
46. Imerman, S. W., and Imerman, C. P.: J.A.M.A. **106:** 1085, 1936.
47. Wohl, M. G. and Ettelson, L. N.: J. Pharmacol. & Exper. Therap. **55:** 439, 1935.
48. Nadler, J. E.: J.A.M.A. **105:** 12, 1935.
49. Epstein, E., and Rosenblum, H.: J. Lab. & Clin. Med. **20:** 1118, 1935.
50. MacBryde, C. M., and Taussig, B. L.: J.A.M.A. **105:** 13, 1935.
51. de Châtel, A., and Motika, J.: Deutsch. Arch. f. klin. Med. **176:** 700, 1934.
52. Koch, R. A.; Lee, R. C. H., and Tainter, M. L.: California & West. Med. **43:** 337, 1935.
53. Haft, H. H.: J.A.M.A. **101:** 1171, 1933.
54. Graham, E. A.: J. Exper. Med. **21:** 185, 1915.
55. Koelsch, F.: Zentralbl. f. Gewerbehyg. u. Unfallverh., n. F. **4:** 261, 1927.
56. Sidel, N.: J.A.M.A. **103;** 254, 1934.
57. Warthin, A. S.: Bull. Internat. A. M. Museums, **7:** 123, 1918.
58. Schulte, T. L.: J. Pharmacol. & Exper. Therap. **59:** 419, 1937.
59. Rabinowitch, I. M., and Fowler, A. F.: Canad. M.A.J. **30:** 128, 1934.
60. Goldman, A., and Haber, M.: J.A.M.A. **107:** 2115, 1936.
61. Masserman, J. H., and Goldsmith, H.: J.A.M.A. **102:** 523, 1934.
62. Death after Slimming Treatment. Lancet, **1:** 489, 1934.
63. Poole, F. E., and Haining, R. B.: J.A.M.A. **102:** 1141, 1934.
64. Tainter, M. L., and Wood, D. A.: J.A.M.A. **102:** 1147, 1934.
65. Dameshek, W., and Gargill, S. L.: New England J. Med. **211:** 440, 1934.
66. Silver, S.: J.A.M.A. **103:** 1058, 1934.
67. Lattimore, J. L.: J. Kansas M. Soc. **35:** 388, 1934.
68. Leutsker, R. J.: U. S. Nav. M. Bull. **33:** 394, 1935.
69. Purvine, R.: J.A.M.A. **107:** 2046, 1936.
70. McGavack, T. H.: California & West. Med. **44:** 77, 1936.
71. Strang, J. M., and Evans, F. A.: J.A.M.A. **104:** 1957, 1935.
72. American Medical Association. Council on Pharmacy and Chemistry: J.A.M.A. **105:** 31, 1935.

73. Germany: Reichsgesundheits-Bl. **9:** 1078, 1934.
74. J.A.M.A. **103:** 1243, 1934 (Canada News).
75. Dekrysil Treatment. Lancet, **1:** 652, 1934.
76. Dinitrophenol Compounds in Obesity. Lancet, **1:** 746, 1934.
77. New California Law. J.A.M.A. **114:** 881, 1940.
78. Horner, W. D.; Jones, R. B., and Boardman, W. W.: J.A.M.A. **105:** 108, 1935.
79. Boardman, W. W.: California & West. Med. **43:** 118, 1936; Ann. Int. Med. **9:** 195, 1935.
80. Shutes, M. H.: Am. J. Ophth. **18:** 752, 1935.
81. Josephson, E. M.: Science, **82:** 222, 1935.
82. Kniskern, P. W.: J.A.M.A. **105:** 794, 1935.
83. Cogan, D. G., and Cogan, F. C.: J.A.M.A. **105:** 793, 1935.
84. Lazar, N. K.: J.A.M.A. **105:** 794, 1935.
85. Allen, T. D., and Benson, V. M.: J.A.M.A. **105:** 795, 1935.
86. Glowacki, B. F.: J. Michigan State M. Soc. **34:** 535, 1935.
87. Cogan, D. G., and Cogan, F. C.: New England J. Med. **213:** 854, 1935.
88. Rundles, W. Z.: J. Michigan State M. Soc. **34:** 777, 1935.
89. Mann, W. A., Jr.: Arch. Ophth. **15:** 116, 1936.
90. Hill, H. E.: J. Indiana State M. A. **29:** 67, 1936.
91. Rodin, F. H.: California & West. Med. **44:** 276, 1936.
92. Spaeth, E. B.: Am. J. Ophth. **19:** 320, 1936.
93. Veasey, C. A.: Am. J. Ophth. **19:** 332, 1936.
94. Barkan, H.; Borley, W. E.; Fine, M., and Bettman, J.: California & West. Med. **44:** 360, 1936.
95. Mengel, W. G.: Am. J. Ophth. **19:** 512, 1936.
96. Lehrfeld, L.: Am. J. Ophth. **19:** 513, 1936.
97. Differential Diagnosis of Cataract Due to Dinitrophenol. J.A.M.A. **107:** 60, 1936.
98. Loomis, E. A.: Am. J. Ophth. **19:** 515, 1936.
99. Rank, R. T., and Waldeck, E. A.: Wisconsin M. J. **35:** 629, 1936.
100. Horner, W. D.: Arch. Ophth. **16:** 447, 1936.
101. Swett, W. F.: Am. J. Ophth. **19:** 796, 1936.
102. Frost, A. D.: Arch. Ophth. **16:** 458, 1936.
103. Whedon, E.: Arch. Ophth. **16:** 459, 1936.
104. Whalman, H. F.: Am. J. Ophth. **19:** 885, 1936.
105. Davis, W. T.: M. Ann. District of Columbia, **6:** 246, 1937.
106. McDannald, C.: Arch. Ophth. **17:** 944, 1937.
107. Hessing, E. E.: Arch. Ophth. **17:** 513, 1937.
108. Welton, C. B.: Illinois M. J. **73:** 72, 1938.
109. Cataracts from "Weight Controls." J.A.M.A. **111:** 188, 1938.
110. Lewis, A. C.: Am. J. Ophth. **21:** 788, 1938.
111. Vannas, M.: Acta Soc. med. fenn. duodecim (Ser. B, fasc. 2, art. 4), **22:** 1, 1936. Abstr. Zentralbl. f. d. ges. Ophth. **38:** 516, 1937.
112. Van der Hoeve, J., and Polak Daniels, A.: Nederl. tijdschr. v. geneesk. **80:** 126, 1936.
113. Helminen, T.: Acta ophth. **15:** 490, 1937.
114. Vogt, A.: Schweiz. med. Wchnschr. **67:** 873, 1937.
115. Vogt, A.: Klin. Monatsbl. f. Augenh. **99:** 669, 1937.
116. Onfray, R. and Gilbert-Dreyfus: Bull. Soc. franç. d'opht. **50:** 114, 1937.
117. Sedan, J.: Ann. d'ocul. **176:** 191, 1939.
118. Oneto, J. A.; Gallino, J. A., and Natale, A.: Arch. de oft. de Buenos Aires, **12:** 731, 1937. Abstr. Am. J. Ophth. **21:** 476, 1938.
119. Ciotola, G.: Boll. d'ocul. **16:** 531, 1937.
120. Ploman, K. G.: Hygiea, **99:** 688, 1937. Abstr. Zentralbl. f. d. ges. Ophth. **41:** 691, 1938.
121. Måhlén, S.: Acta ophth. **16:** 563, 1938.
122. Lindberg, J. G.: Acta ophth. **16:** 556, 1938.

123. Krause, A. C.: The Biochemistry of the Eye. Baltimore, Johns Hopkins Press, 1934.
124. Biozzi, C.: Arch. f. Ophth. **133:** 423, 1935.
125. Nordmann, J., and Reiss, P.: Compt. rend. Soc. de biol. **123:** 233, 1936.
126. Jackson, E.: Am. J. Ophth. **19:** 431, 1936.
127. Field, J., 2nd; Tainter, E. G.; Martin, A. W., and Belding, H. S.: Am. J. Ophth. **20:** 779, 1937.
128. Bedell, A. J.: Arch. Ophth. **16:** 457, 1936.
129. Borley, W. E., and Tainter, M. L.: Arch. Ophth. **18:** 908, 1937.
130. Barkan, H., and Bettman, J. W.: Am. J. Ophth. **21:** 165, 1938.
131. Sohr, H.: Arch. f. Ophth. **138:** 332, 1938.
132. Tainter, M. L., and Borley, W. E.: Arch. Ophth. **20:** 30, 1938.
133. Borley, W. E., and Tainter, M. L.: Am. J. Ophth. **21:** 1091, 1938.
134. Krause, A. C.: Am. J. Ophth. **21:** 1343, 1938.
135. Tainter, M. L.: J. Pharmacol. & Exper. Therap. **63:** 51, 1938.
136. Reiss, P., and Nordmann, J.: Compt. rend. Soc. de biol. **128:** 111, 1938.
137. Basile, G.: Ann. di ottal. e clin. ocul. **67:** 223, 1939.
138. Duke-Elder, Sir W. S.: Text-book of Ophthalmology. St. Louis, Mosby, 1941, v. 3, p. 3236.
139. American Medical Association. Bureau of Investigation: J.A.M.A. **106:** 1587, 1936.
140. Müller, H. C.: Ber. ü. d. Zusammenk. d. deutsch. ophth. Gesellsch. **51:** 370, 1936.
141. Duke-Elder, Sir W. S.: Text-book of Ophthalmology. St. Louis, Mosby, 1941, v. 3, p. 3154.
142. Dally, P.: Concours méd. **57:** 3491, 1935; Arch. Soc. d. sc. méd. et biol. de Montpellier, **17:** 109, 1936.
143. Wesson, L. G.: J. Am. Chem. Soc. **62:** 3466, 1940.

---

# RECONSTRUCTION OF THE EYELIDS

WENDELL L. HUGHES, M.D.
Hempstead, Long Island, N. Y.

This candidate's thesis for membership was presented to the Committee on Theses and accepted by them. Because of its length and the elaborate illustrations it is being published separately in the form of a monograph.

BERNARD SAMUELS, *Editor*