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TEXT-BOOK OF OPHTHALMOLOGY

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BY
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diplopia

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One-eye

pp 6818

VOL. VI

INJURIES

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Injuries to the Lower Visual Neuron : Toxic Amblyopia

A heterogeneous collection of organic substances, some of them in common use industrially, therapeutically or in everyday life, may cause considerable visual damage by their action on the ganglion cells of the retina or the optic nerve fibres. These comprise alcohols, particularly methanol, certain halogenated hydrocarbons (methyl bromide and iodide, carbon tetrachloride, trichlorethylene), certain aromatic amino and nitro compounds (aniline, nitrobenzene, trinitrotoluene), and salicylic acid and its derivatives.

Clinically the toxic effects of all these substances are similar, a depression of vision being produced either by the development of a central visual defect (methyl alcohol, methyl bromide, trichlorethylene, carbon disulphide, barbiturates), a contraction of the peripheral field (carbon tetrachloride, salicylates) or a combination of both (aniline and its relatives). Frequently in the initial stages some cedematous disturbance is evident in the retina and at the optic disc ; some degree of atrophy is the usual termination. Pathologically, the action of such poisons is not understood. In the case of some there is evidence that a *vascular disturbance* is the initial cause, in others that the damage is essentially *neurogenic*, while in others both elements seem to be present, but whether as parallel or dependent phenomena is by no means clear. The same combination of vasotoxic and neurotoxic effects, it will be noted, is observed in the action of those inorganic poisons ¹ and toxins of vegetable origin ² which also attack the lower visual neuron.

THE ALCOHOLS

METHANOL

METHANOL (METHYL ALCOHOL, WOOD SPIRIT) [CH_3OH] may be ingested in one of three ways—through the stomach, the lungs or the skin. Most commonly it is drunk in cheap adulterated or fortified beverages. In this event a very small quantity may cause immense damage, especially when taken on an empty stomach (Hirschberg, 1912), for a teaspoonful may produce permanent blindness and 1 oz. may be fatal (Ziegler, 1921). It may also be absorbed by the inhalation of fumes in several commercial processes, for the alcohol is widely used as a solvent for shellacs and varnishes as well as in the manufacture of china-cement, rubber, and in other processes. In comparison with drinking, this method of poisoning is usually more chronic and insidious in its clinical effects but its occurrence has been amply authenticated in persons working with methyl alcohol in closed ill-ventilated spaces (de Schweinitz, 1896–1911 ; Patillo and Wood, 1899 ; Wood and Buller, 1904 ; Gruening, 1911 ; Tyson, 1912 ; Robinson, 1918 ; Ziegler, 1921 ; Koelsch, 1921 ; Humperdinck, 1941 ; and others). Cutaneous

¹ p. 6774.

² p. 6838.

absorption is rare, but cases of blindness have been recorded following the prolonged daily use of liniments, bay rum and toilet waters (Wood and Buller, 1904 ; Tyson, 1912 ; Ziegler, 1921).

The drinking of methanol is a relatively common cause of blindness ; thus Wood and Buller (1904) were able to collect 153 cases of blindness and 122 of death, and in one Berlin institution for tramps 130 cases were admitted in 1911. Similar tragic incidents continually recur wherein whole parties of people have been affected in this way, some dying, others becoming permanently blind and others escaping with much impaired vision—130 people from one party were taken to hospital, of whom 51 died and many became blind from complete optic atrophy (Mendel, 1912) ; 67 cases occurred in 3 days among a party of Russian prisoners of war (Opsahl, 1948) ; 48 cases in Poland (Kwaskowski, 1949) ; and so on. In times of war when potable spirit becomes expensive or controlled and environmental stresses may be great, the consumption of this cheaper alcohol increases ; thus in Denmark, Blegvad and Rønne (1920) found that an amblyopia hitherto unknown in that country became common during the first World War ; and in the first 5 months of this war Goldflam (1920) collected 100 cases in Warsaw. Potts (1952) considered that methanol poisoning accounted for 6% of blindness from all causes among American veterans of the second World War. Periods of prohibition have always added to the number of such incidents ; thus even before this restriction was enforced in the U.S.A., Jackson (1920) considered that it caused more blindness than all other toxic causes added together : Hubbard (1920) reported 52 cases in New York in 1918, and Cooper and his colleagues (1952) and Benton and Calhoun (1952) 132 cases of acute poisoning after drinking bootleg whisky in Atlanta, among whom 37 died. Blindness from this cause is relatively common in Scandinavia ; in January, 1948, there were 42 cases in Norway (Holst, 1950). Sporadic cases of chronic and secret addiction are still by no means unknown in England, sometimes among the most unlikely persons (Morgan, 1952).

Industry also provides its quota of poisoning. Up to 1912 about 100 cases of amblyopia and death from inhalation had been reported, occurring mostly in painters, lacquerers and polishers, to which number Baskerville (1913) added 64 from America ; further instances were contributed by Koelsch (1921).

The *general symptoms* of acute poisoning by wood-alcohol are headache, dizziness, nausea, vomiting, abdominal pain, cardiac weakness, marked prostration, delirium, convulsions, stupor, and finally death. In cases that recover, blindness is usually noticed on the second or third day when the stupor wears off. In the worst cases the blindness may be early, sudden, complete and permanent. In less severe cases there may be marked recovery at the end of 4 or 5 weeks ; this itself may be lasting or may be followed by gradual failure and ultimate loss of vision. In cases of more chronic or insidious absorption, or where the poison is drunk in

repeated small quantities or is absorbed by inhalation, headache and obscure nervous and gastro-intestinal symptoms may appear associated with a gradual deterioration of vision and the development of a dense central or paracentral scotoma (Fig. 6286).

Objectively there may be papillitis with considerable swelling and dilatation of the veins and also a good deal of retinal oedema in the early stages (Wagner, 1947; Rohr, 1947; Agg, 1949; Geserick, 1951). Alter-

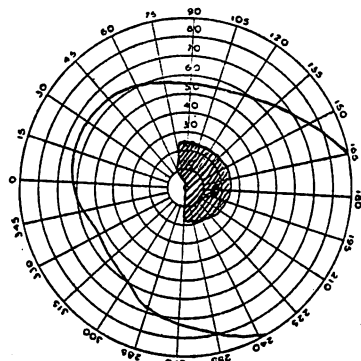


FIG. 6286.—METHYL ALCOHOL AMBLYOPIA.

Two and a half months after poisoning: 3/330, white.

natively, a chalky white pallor of the disc may rapidly develop; or in the more insidious cases the symptoms may be those of retrobulbar neuritis, often with an initial centrocaecal scotoma, followed by the gradual appearance of atrophy. The atrophy following this type of poisoning is usually profound, and the discs are typically excavated, resembling a glaucomatous cup (Gruening, 1910; Morrison, 1922; Shannon, 1932; Barazzoni, 1947). The pupils are usually dilated and may be inactive and pareses of the extra-ocular muscles with diplopia and ptosis may occur,¹ while a certain degree of hypotony may exist. Unilateral cases are occasionally seen; in these the prognosis is

often relatively good (Siegert, 1949).

A considerable amount of experimental work has been done on methyl alcohol poisoning in animals (Holden, 1899; Birch-Hirschfeld, 1901-20; Hunt, 1902; Kasass, 1913; Igersheimer and Verzar, 1913; Tyson and Schoenberg, 1914; Schwarzkopf, 1922; McCord, 1932; Scott *et al.*, 1933; McGregor, 1943; Fink, 1943; Röe, 1948; Marconcini, 1953; and others). It would seem that the ocular lesions are more difficult to produce than in man, but nevertheless there appears to be a special affinity for the tissues of the eye (Marinesco *et al.*, 1929), and although degeneration of the ganglion cells of the retina has been found by some authors, this finding has not been invariable. It is obvious that deductions from experiments on animals should be transferred to the manifestations of poisoning in the human subject only with reservations.

Pathological examinations on human subjects have been relatively few (Pick and Bielschowsky, 1912; Comora, 1920; Eleonskaja, 1925; MacDonald, 1929; Menne, 1938; Fink, 1943; Wagner, 1947; Röe, 1948; Müller, 1950). Initially the picture is that of an acute toxic oedema followed by profound and widespread degeneration of the ganglion cells of the retina (Figs. 6287-88), with degeneration of the fibres in the optic nerve, which in severe and chronic cases may extend up to the external geniculate body

¹ p. 6832.

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(Eleonskaja, 1925). Some controversy has arisen as to whether the changes in the retina or the nerve are primary (Uhthoff, 1886), but the view of Holden (1899), Tyson and Schoenberg (1914) and Birch-Hirschfeld (1920) that the injury to the ganglion cells is primary and that the degeneration in the nerve is an ascending secondary phenomenon seems substantiated by the findings of MacDonald in an early human case examined pathologically

FIGS. 6287-88.—THE RETINA IN ACUTE METHYL ALCOHOL POISONING (MacDonald).

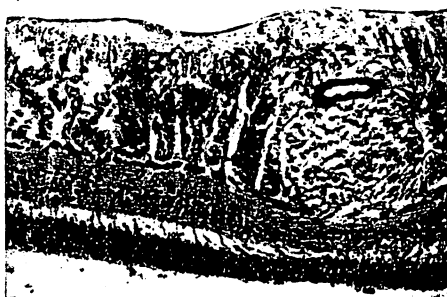


FIG. 6287.

FIG. 6287.—Autopsy 6 hours after death, showing marked changes about the vessel and degenerative debris under the internal limiting membrane. (Mallory's phospho-tungstic acid hæmatoxylin) ($\times 100$).

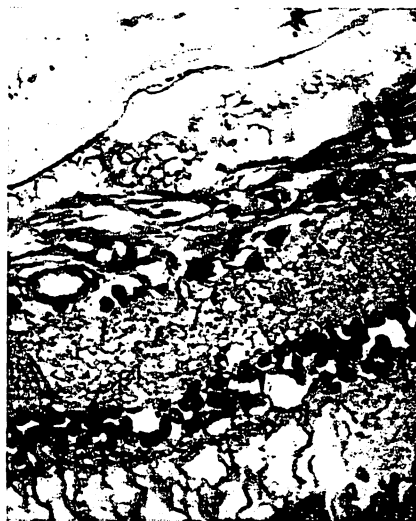


FIG. 6288.

FIG. 6288.—The same case as Fig. 6287, showing swollen ganglion cells and globules under the internal limiting membrane (H. & E.) ($\times 400$).

(who died on the third day and was examined 6 hours after death), wherein the degeneration in the retina was marked and no pathological change could be observed in the optic nerve.

The rationale of the poisoning is still obscure. It is known that whereas ethyl alcohol is rapidly and completely oxidized in the body, methyl alcohol is much less readily dealt with, remaining many days so that a cumulative effect is possible (Völtz, 1912). Tyson and Schoenberg (1914) found that there was a general acidosis due to the imperfect oxidation of the methyl alcohol, resulting in the formation of formaldehyde and formic acid in the blood-stream and tissues; this even gives rise to an increase in the acidity of the aqueous humour (Grignolo, 1913; Tyson and Schoenberg, 1914) where formaldehyde has been found in poisoned rabbits (Flury, 1928). By

some workers formaldehyde is considered the toxic agent (Flury and Wirth, 1936 ; Keeser and Vincke, 1940 ; Potts and Johnson, 1952), by others formic acid (Harnack, 1912 ; Kaplan and Levreault, 1945 ; R  e, 1946 ; Bogen, 1946). However that may be, it has been shown by Goldschmidt (1922) and Oguchi (1932) that the oxidative processes in the retina are much impaired and its respiratory activity lowered, so that the metabolism may be reduced by 40% to 50%. The former investigator concluded that the damage was greater when the retina was exposed to light, a view put forward also by Schanz (1920) and Schieck (1922), but not universally accepted (Schwarzkopf, 1922). It would seem probable that an interference with the activity of those enzymes in the retina which mediate glycolysis is the fundamental cause of the damage to this tissue, perhaps by a combination of methanol or one of its break-down products with the iron catalyst of the oxidase system, thus rendering it inactive (Rohr, 1947 ; Potts and Johnson, 1952 ; Gilger *et al.*, 1952). This process may be accelerated in the presence of acidosis, and initially brings about an cedematous reaction which may be reversible and from which visual recovery is possible, and eventually progresses to degeneration and death of the nerve cells with permanent visual loss. Whether the vascular and cedematous reaction is the essential cause of the damage leading secondarily to neuronc degeneration (Geserick, 1949), or whether the two phenomena are parallel effects of the same cause is disputable ; nor is it known how far the changes in the optic nerve are independent of or consecutive to those in the ganglion cells of the retina. Much of the intimate mechanism is not yet understood.

Treatment. In severe cases of poisoning the rapidity of the toxic action makes treatment of little avail. Gastric lavage should be carried out immediately and at intervals during the first few days, since there is evidence that the alcohol in the system is continuously returned to the stomach ; it has been said, indeed, that more may be recovered in this way in the second and third day after ingestion than during the first (Ziegler, 1921). Eliminative treatment by diaphoresis, hot-packs, pilocarpine, hot drinks and saline purgatives is also indicated to wash as much poison out of the system as possible. Acidosis should be overcome by the early and massive administration of alkalis, sodium bicarbonate being given by mouth or intravenously (500 ml. of 5% solution : Ziegler, 1921 ; R  e, 1946) ; unless given early, however, such treatment is useless (Siegert, 1949). Intravenous glucose has also been advocated (Kwaskowski, 1949) or intravenous novocaine (Aronov, 1949), and vasodilators such as Priscol (Fanta, 1948) or erythrol-tetranitrate (Montag, 1948). The administration of ethyl alcohol has been practised in the hope that, by competing for oxygen with the methanol, the formation of the toxic products of the oxidation of the latter would be delayed (R  e, 1949 ; Agner *et al.*, 1949), but this method of therapy would appear to be associated with some danger (Gilger *et al.*, 1952). Finally, good results have

been claimed from repeated lumbar punctures (Pincus, 1920 ; Zethelius and Wersen, 1920 ; Fanta, 1948 ; Kwaskowski, 1949).

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ETHANOL

ETHANOL (ETHYL ALCOHOL) [C_2H_5OH] is much less toxic than its lower homologue ; indeed, its deleterious effect on the lower visual neuron is usually

an adjuvant factor in association with the ingestion of other toxins such as those found in tobacco.¹ The older writers, however, satisfied themselves that cases of alcohol amblyopia occurred in heavy drinkers who are also non-smokers (*amblyopia potatorum*) (Hutchinson, 1887 ; Griffith, 1887 ; Connor, 1890 ; de Schweinitz, 1896). On the Continent of Europe the condition would appear to be more common than in Anglo-Saxon countries (44% of cases of amblyopia, Uhthoff, 1886 ; 27%, Sattler, 1923). The condition is always associated with a long history of alcoholism, and frequently with peripheral neuritis. There is no doubt that a recent deterioration of the physical and mental health enters largely into the ætiology, a matter in which malnutrition, usually owing to long-standing alcoholic gastro-enteritis, usually plays a prominent part. Indeed, it may well be that the condition is essentially a deficiency disease related to alcoholic pellagra and due essentially to lack of absorption of one or more of the constituents of the vitamin B complex (Keefer, 1931 ; Carroll, 1935-37 ; and others.)²

Little experimental work of value has been done on the question, largely owing to the difficulty in inducing a chronic poisoning in animals ; thus de Schweinitz (1896) kept a monkey constantly drunk for 6 months but found neither ophthalmoscopic nor histological evidence of ill-effects in its eyes. Rymowitsch (1896) and Friedenwald (1901), however, after chronically poisoning rabbits for one year, observed degeneration of the ganglion cells, without connective tissue overgrowth or cellular infiltration and unassociated with degeneration of the nerve fibres as revealed by Marchi's method of staining. Morax (1935) recorded a case wherein a woman was given an intravenous injection of 200 ml. of 33% alcohol for puerperal septicæmia and subsequently developed bilateral absolute central scotomata with optic atrophy.



FIG. 6289.—THE OPTIC NERVE, IN CHRONIC ALCOHOL AMBLYOPIA.

Showing papillo-macular degeneration (Juba, K. M. Aug.).

In so far as ethanol amblyopia may exist, it is characterized by a clinical picture resembling tobacco amblyopia³—a central scotoma for red and green in the early stages, a centro-cæcal scotoma for white in the later, eventually developing into optic atrophy. The pathology is also similar, being characterized by a primary neuronc degeneration affecting particularly the papillo-macular neurons and involving the ganglion cells and the nerve fibres (Nettleship and Edmunds,

1881 ; Samelsohn, 1882 ; Edmunds and Lawford, 1887 ; Uhthoff, 1901 ; Birch-Hirschfeld, 1902 ; Rönne, 1910 ; Juba, 1935) (Fig. 6289). Atrophy is rarely complete, normal fibres being present even in the most affected

¹ p. 6838.

² Vol. III, p. 3007 ; Vol. IV, p. 4111.

³ Vol. III, p. 3009 ; p. 6838.

areas, while the connective-tissue framework is consistently thickened and proliferated.

Treatment should involve cutting down or abstinence from alcohol, a similar restriction being placed on smoking if it is also indulged in, a complete overhaul of the general health, and, above all, the institution of a healthy and regular diet with an abundance of vitamin B in the form of yeast or otherwise (Carroll, 1935-37; Johnson, 1939); there is evidence that the administration of vitamin B₁₂ may give spectacular results. As in tobacco amblyopia, Bonnefon (1931) reported good results from the injection of vasodilatory drugs (intramuscular injections of 0.1 gm. acetylcholine).

The effects of alcohol on the higher visual functions¹ and the extra-ocular muscles² are discussed later.

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THE HALOGENATED HYDROCARBONS

Of the *monohalogenated hydrocarbons*,³ METHYL CHLORIDE [CH₃Cl] poisoning usually results in considerable visual disturbances, retrobulbar neuritis, diplopia and failure of accommodation (Roche and Bouchet, 1948; from the fumes of a refrigerator, Garde and Etienne, 1951). METHYL BROMIDE [CH₃Br] may give rise to acute visual symptoms when inhaled in quantity (as from a fire extinguisher or when used as a fumigant⁴) (Wyers, 1945; v. Oettingen, 1946). Vascular instability is probably an initial factor and the acute phase of intoxication may be followed by the appearance of neuro-degenerations among which there may be an aphasia, a transitory complete amblyopia, or a central scotoma which may persist for a few weeks or may last for years (Joquet, 1901; Duvoir *et al.*, 1937; De Jong, 1944; Clarke *et al.*, 1945; Roger and Simonin, 1948; and others).

METHYL IODIDE [CH₃I], in cases of acute intoxication, has also been reported as giving rise to visual disturbances with contraction of the fields (Hunter *et al.*, 1940; Garland and Camps, 1945).

IODOFORM

IODOFORM [CHI₃], if absorbed in large amounts, may give rise to complete amaurosis (Valude, 1893) or more usually to an amblyopia characterized by a loss of central vision with peripheral defects and without ophthalm-

¹ p. 6830.

² p. 6832.

⁴ p. 6695.

³ See also pp. 6832, 6833.

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Disturbances of the Higher Visual Functions

Many organic chemicals on ingestion produce disturbances in the higher visual functions. The narcotic chlorinated hydrocarbons (chloroform, trichlorethylene, etc.) or ethyl ether produces on inhalation a muzziness of vision as a preliminary to unconsciousness, an effect partly due to the occurrence of diplopia owing to ocular inco-ordination but largely to impairment of perception and judgment. In this class of substance, however, the most important from the practical point of view is ethyl alcohol.

ETHANOL (ETHYL ALCOHOL)

The disturbances of the higher visual functions following the ingestion of alcohol—even of the most reputable type—are well known; they are much more common than the organic lesions which may occur in the lower visual neuron¹ or the extra-ocular musculature.² It is important to remember that alcoholic intoxication is not a gradual process but comes on quickly when the concentration in the blood rises to a critical level which varies considerably between individuals (from 170 to 183 mgm. per 100 ml. blood) but is relatively constant for the same individual; a concentration achieved rapidly, however, is more potent than when acquired slowly, and even although an intoxicating level is maintained in the blood, time has a sobering influence (Mirsky *et al.*, 1941; Newman and Abramson, 1942).

Several visual effects become evident in alcoholic intoxication, all of which are depressant in type, but there is on the whole little direct correlation between the alcoholic concentration in the blood and the decrease in the efficiency of the visual functions (Newman and Fletcher, 1941). The visual acuity is lowered by an appreciable amount varying from 5 to 20% (Newman and Fletcher, 1940; Newman and Abramson, 1941) although the perception of objects in the peripheral field has been found to remain relatively good (Newman and Fletcher, 1940; King, 1943). Sensitivity to light is lowered

¹ p. 6821.

² p. 6832.

on the average by some 30% and the threshold to brightness-difference is increased by some 50% (Lange and Sprecht, 1915 ; Jellinek and McFarland, 1940) ; recovery from glare is also retarded (Newman and Fletcher, 1941). The data as to colour vision are inconsistent. Colson (1940) found no change in colour vision although the intake of alcohol was pushed to the point of unconsciousness, but Peters (1942) found a constriction of the colour fields progressing to their complete extinction ; Pirittyi and Nagy (1951) concluded that the weakening of colour perception depended essentially on disturbed judgment rather than on impaired perception. A case of dyschromatopsia (mainly cyanopsia) has been recorded (Pergens, 1898). The more complex visual judgments, such as depth perception, are also grossly impaired (Newman and Fletcher, 1941 ; Newman *et al.*, 1942) and the reaction-time (as for reading) shows considerable deterioration (Rudin, 1904 ; Seward and Seward, 1936 ; Mead, 1939). The general inhibitory effect on visual perceptions is clearly demonstrated by the decrease in retinal rivalry and the parallel increase in unocular dominance which become evident after the ingestion of alcohol (Bárány and Halldén, 1947).

The ocular movements are usually affected at an early stage. The development of a general slowness and hesitancy of movement has been established by several observers and the ability to maintain fusion in the presence of lateral heterophoria almost invariably breaks down ; there is little change in the vertical phorias, but a fairly constant increase of esophoria and a decrease in exophoria. These changes in ocular deviation are usually small, averaging some 2 prism dioptres, but the failure of fusional ability and particularly the decrease in the power of suppression—part of the general breakdown of inhibition—make diplopia a relatively constant symptom (Powell, 1938 ; Colson, 1940 ; Charnwood, 1950).

The most important feature about the visual evidences of alcoholism, apart from the diplopia which is too subjectively obvious to be denied, is that the general depression of the visual functions is rarely recognized by the inebriated individual who, indeed, is too apt to imagine the reverse.

Sedatives such as the *barbiturates*,¹ CHLORAL HYDRATE [$C_2Cl_3H_3O_2$] and others, share the depressant effect of alcohol on the higher visual centres. This was elegantly shown by Bárány and Halldén (1947) by studying their effect on retinal rivalry. After their ingestion the less dominant eye suffers a preferential inhibition so that the rhythm of rivalry decreases, and central inhibition may eventually be depressed to such a degree that rivalry is replaced by simultaneous perception.

STREPTOMYCIN² [$C_{21}H_{39}N_7O_{12}$] has been reported as causing disturbances of perspective and coloured vision (xanthopsia) associated with euphoric states (Eiselt and Kloubek, 1948 ; Weigelin, 1949).

CARBON DISULPHIDE³ [CS_2] poisoning may be associated with curious phenomena of *dyschromatopsia*, sometimes transient and sometimes of considerable duration,

¹ See also pp. 6821, 6833.

² See also pp. 6829, 6837.

³ See also pp. 6827, 6833, 6834, 6836.

manifested most often as yellow vision (xanthopsia) (Changarnier, 1886), but sometimes green (chloropsia) or red vision (erythropsia) (Bruce, 1884 ; Mattei and Sédan, 1924).

ASTEROL DIHYDROCHLORIDE (6-(β -diethylaminoethoxy)-2-dimethylamino-benzothiazole dihydrochloride) [$C_{15}H_{23}N_3OS \cdot 2HCl$], a substance used medically in the treatment of fungus infections (ringworm, etc.), has been associated with the production of convulsive seizures in children followed by a state of lethargy and confusion in which visual hallucinations are a prominent feature ; nystagmus and mydriasis may also be present (Hitch, 1952).

The visual disturbances, involving dyschromatopsia, hallucinations, etc., which follow the ingestion of certain alkaloids of vegetable origin (digitalis, mescal, caffeine, etc.) are discussed elsewhere.¹

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Muscular Disturbances

Muscular disturbances of the most varied types may follow the ingestion of many organic chemicals—palsies of the extra-ocular muscles, nystagmus, and paresis or spasm of the intra-ocular musculature resulting in mydriasis or miosis and anomalies of accommodation which may induce refractive changes of some size.

THE EXTRA-OCULAR MUSCLES

Paralyses of the extra-ocular muscles involving diplopia are not a common toxic manifestation of poisoning by organic chemicals.

Among the *hydrocarbons*, PETROL fumes have been noted to produce this effect (Plummer, 1913) ; so also has METHYL ALCOHOL² [CH_3OH] (Wood and Buller, 1904). The nuclear palsies ascribed to ETHYL ALCOHOL³ [C_2H_5OH] have been described in a previous volume under the heading of thiamine deficiency (Wernicke's acute hæmorrhagic encephalopathy).⁴

Among the *halogenated hydrocarbons*,⁵ the monohalogenated members of the series are the most toxic in this respect ; ptosis, ocular palsies and diplopia have been reported after the inhalation of both METHYL CHLORIDE [CH_3Cl] (Baker, 1927-30 ;

¹ p. 6848.

² See also pp. 6736, 6816.

³ See also pp. 6737, 6821, 6830.

⁴ Vol. IV, p. 4111.

⁵ See also pp. 6732, 6823, 6833.

Kegel, McNally and Pope, 1929 ; Jones, 1942 ; Florentin, 1944 ; Roche and Bouchet, 1948) and METHYL BROMIDE [CH_3Br] (Joquet, 1901) ; the latter may also give rise to nystagmus (De Jong, 1944). CHLOROFORM [CHCl_3] and several other allied anæsthetics produce initially on inhalation a bilateral internal strabismus which gradually passes into a divergent strabismus, a phasic variation which may be repeated (Högyes, 1883) ; the convergence is presumably a central stimulation which gradually or intermittently disappears as narcosis becomes deeper. Nystagmus occurs more rarely (Howie, 1944), an effect also seen after the inhalation of DICHLORETHANE (ETHYLENE DICHLORIDE) [$\text{CH}_2\text{Cl}.\text{CH}_2\text{Cl}$] (McNally and Fostvedt, 1941). DICHLORO-ACETYLENE [$\text{ClC}:\text{CCl}$], probably formed as a degradation product in the interaction between soda lime and trichloroethylene in a closed anæsthetic machine, has apparently caused paralysis of the IIIrd, IVth and VIth nerves, together with involvement of the Vth, Xth and XIth (Humphrey and McClelland, 1944). The vapour of this substance produces a generalized encephalitis in rabbits (Carden, 1944).

Among *nitro-compounds*, PYRIDINE [$\text{C}_5\text{H}_5\text{N}$], a coal tar derivative and a constituent of tobacco smoke (Vohl and Eulenberg, 1871), widely used in the dyeing and chemical industries, may on inhalation produce a symptomatology resembling Wernicke's acute polio-encephalitis.¹ In chronic industrial poisoning, cases involving facial paresis, conjugate deviations of the eyes, ptosis and horizontal nystagmus, as well as anisocoria, a loss of the palatal reflex and ataxia, have been reported by Ludwig (1934), and others showing slighter nervous symptoms by Holtzmann (1936) and Teisinger (1947).

In CARBON DISULPHIDE² [CS_2] poisoning ocular motor palsies are rare, but have been noted in workers who have been exposed to the fumes for many years (Little, 1887 ; Golesceano, 1907 ; Roger and Roger, 1950 ; van Leeuwen and André, 1950). A spasmodic diplopia was reported by Galezowski (1878).

The *barbiturates*³ have occasionally given rise to muscular palsies—VERONAL either on acute poisoning or on habitual ingestion, may produce irregular ocular palsies of the nuclear type associated with cerebellar derangements. LUMINAL may occasionally have the same effect (Collier, 1930) as also may EVIPAN (Palmer, 1936).

The barbiturates also tend to abolish nystagmus in the primary position of the eyes but produce a coarse nystagmus on lateral gaze when taken in large doses (Kisch, 1943 ; Bender, 1946 ; Bender and O'Brien, 1946 ; Bender and Brown, 1948 ; Bender and Gorman, 1949). This has been noted with VERONAL as well as with SULPHONAL (Oppenheim, 1917 ; Wilbrand and Saenger, 1921), and the more recently introduced preparations such as MYANESIN (TOLSEROL) (3-ortho-toxoly-1,2-propanediol) (Bender *et al.*, 1951). Animal experiments indicate that the action of these drugs is essentially on the brain-stem (Berger and Bradley, 1946 ; Kaada, 1950).

SALICYLIC ACID (ORTHO-ONYBENZOIC ACID) [$\text{C}_6\text{H}_4\text{OH}.\text{COOH}$] in large doses has given rise to nystagmus (Lewin and Guillery, 1913), and THIOURACIL [$(\text{NH})_2\text{CS}.\text{CO}(\text{CH}_3)_2$] to a gross nystagmus in all planes (Prowse, 1950).

THE INTRA-OCULAR MUSCLES

The PUPILLARY AND CILIARY MUSCULATURE is affected by several organic chemicals, the most notable of which are the halogenated hydrocarbons and the sulphonamides.

METHYL CHLORIDE [CH_3Cl] (Florentin, 1944), METHYL BROMIDE [CH_3Br] (De Jong, 1944), METHYL IODIDE [CH_3I] and METHYLENE CHLORIDE [CH_2Cl_2] (Hellwig, 1922 ;

¹ Vol. IV, p. 4111.

² See also pp. 6827, 6831, 6834, 6836.

³ See also pp. 6829, 6831.

Garland and Camps, 1945) all cause a marked dilatation of the pupil; in the case of methyl chloride a failure of accommodation may be marked (Roche and Bouchet, 1948). In narcosis with these substances the pupillary reactions follow a definite routine which has been most fully studied with CHLOROFORM [CHCl_3] (Budin and Coyne, 1875; and others). Initially in the stage of excitement there is mydriasis, to be followed by miosis, and in deep anaesthesia a mydriasis again develops indicating a dangerous depth of narcosis. Cats and rabbits do not develop the miosis (Nakazawa, 1910). These changes are of central origin; the mydriasis occurs after extirpation of the superior cervical ganglion (Spallitta, 1893) and is presumably due to central inhibition of the constrictor centre.

In chronic CARBON DISULPHIDE [CS_2] poisoning, paralysis of the intra-ocular musculature may occur—a weakness in the response to light (Offret, 1906) and in accommodation (Galezowski, 1878; Golesecano, 1907; Haas and Heim, 1910; Bashore and Staley, 1938; Warnecke, 1941) or absolute rigidity of the pupils (Quarelli, 1937).

A transient myopia following treatment by one or other of the SULPHONAMIDES¹ has been recorded by Gailey (1939), Mattson (1939), Landsberg (1939), Lagrange and Laudat (1939), Fänge (1939), Heinonen (1939), Saba (1940), Hornbogen (1941), Blankstein (1941), Friedman (1941), Paez Allende (1941), Vázquez-Barri re (1941), Garcia Miranda (1942), v. Fieandt (1942), Granstr m (1949), Mehlhose (1949), Klinvanskaya (1951) and many others. The large number of reports from all over the world following the general adoption of these drugs shows that this complication of sulphonamide therapy is common. As a rule the myopia does not occur when the drug is taken initially, but during a subsequent period of dosage, suggesting that a sensitivity develops. In many cases the element of ciliary spasm seems to be the causal factor and it usually rectifies itself on cessation of the drug; according to Varga (1950) it is relieved by the administration of oxygen; and Mehlhose (1949) believed that a lesion of the nature of a localized encephalitis developed in the central nervous system determined, perhaps, by allergic sensitivity. That the myopia is not invariably of muscular origin, however, is indicated by the fact that atropine does not always abolish the refractive error (F nge, 1939). Hornbogen (1941) thought that the phenomenon might be due to oedema of the lens, which in Blankstein's (1941) view might be caused by an unequal distribution of the drug between this tissue and the aqueous. The mechanism of the refractive change, however, is by no means clear.

A similar myopia due to a temporary paralysis of accommodation has been recorded after the administration of DISULPHONE (Belousova, 1951; Lukomnik, 1951).

AMMONIUM THIOGLYCOLATE, sometimes applied to the hair as a cold permanent wave, has apparently given rise to a total internal ophthalmoplegia which recovered after 4 weeks (Halbron, 1949).

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¹ See also pp. 6796, 6829.

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Sensory Disturbances

A trigeminal sensory paralysis has been found to follow the inhalation of TRICHLORETHYLENE (ETHYLENE TRICHLORIDE) [$\text{CHCl}_2\text{CCl}_2$],¹ the vapours of which form an industrial hazard; the vapour has been employed as an anæsthetic ("trilene"), but fatalities have occurred after its use (v. Oettingen, 1937; Hunter, 1944). This peculiar action on the trigeminal was first described by Plessner (1916); it affects the sensory branch of the nerve, not the motor division, and although it may occur without any general symptoms of poisoning, a considerable period of time is necessary for its development. The anæsthesia is preceded by a phase of coldness and dryness in the mouth and nose associated with a loss of smell and taste,

¹ p. 6825.

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THE ALDEHYDES

THE ALDEHYDES are a group of substances widely used as solvents for oils, resins, cellulose, and other organic materials as well as in inorganic syntheses. Either in the form of vapour or liquid they have an intensely irritant action on the eyes and respiratory tract, the lower members of the series, which are more water-soluble, having the greater irritant effect on the mucosæ, while the higher, which are more fat-soluble, affect more particularly the lungs. Their narcotic action is less evident than is the case with many other solvents. The addition of a halogen atom to the molecule increases the irritant effect, but the addition of three enhances the narcotic effect (chloral hydrate). On exposure to the vapour in low concentration an immediate and intense ocular irritation results in profuse lacrimation; higher concentrations lead to lethal pulmonary irritation.

Their action is complex. In addition to their solvent properties, which endow them with great penetrant powers, they produce rapid necrosis of the tissues by combining avidly with the amino groupings in the protein molecules, thus inducing denaturation and precipitation. In addition, they are powerful reducing agents, being oxidized in the tissues to formic acid in the process, and in this way also they inhibit enzyme systems. Moreover, they tend to act as antigens to produce aldehyde-protein antibodies so that a specific sensitization is developed particularly by the skin, making repeated contacts more potent in their irritant effects.

FORMALDEHYDE (METHYL ALDEHYDE) $[HCHO]$ is used extensively in such industries as plastics and rubber and is usually encountered domestically in its commercial aqueous solution (40%), FORMALIN (FORMOL), commonly used as a preservative and disinfectant. An ocular lesion is caused by dilutions from 1 in 1,000 to 1 in 2,000 (Gepner, 1894; Flury and Zernik, 1931). Hisatomi (1939) recorded a case wherein a 26% solution was splashed into the eye causing an oedematous thickening of the cornea with folds in Descemet's membrane associated with iritis; but the condition rapidly resolved. Experimentally in the cornea of the rabbit, a drop of formalin causes immediate coagulation of the surface epithelium without much opacification; the chemical spreads rapidly throughout the entire thickness of the stroma in which the corneal corpuscles are killed and fixed *in situ* to

appear as minute white dots, while subsequently a swelling and oedema of the tissue gradually develops. About the end of a week after contamination there is an abortive attempt at vascularization. Within a month the cornea is normal although some epithelial disturbance remains for some time—a remarkable recovery in view of the gross initial changes (Carpenter and Smyth, 1946; Mann *et al.*, 1948). A considerable reaction of the same type is caused by intracorneal injection (Hughes, 1948).

Clinical cases in man have been few. The vapour causes a severe but transient reaction (Andreae, 1899, in a chemist; Würdemann, 1932, in disinfecting establishments; v. Oettingen, 1939, in industry), while a drop on the cornea has produced an extreme degree of chemosis and a keratitis resulting in permanent opacities (Andreae, 1899; Sager, 1906; Carpenter and Smyth, 1946). An intense reaction involving corneal infiltration and severe iridocyclitis with turbidity of the aqueous and vitreous opacities following the lodgement of two minute fragments of a gramophone record in the cornea, was attributed by Velicky (1951) to the formaldehyde in this material: removal of the foreign bodies brought rapid resolution.

Exposure of the eye to the vapour of other aldehydes has caused severe and painful reactions with swelling of the lids, blepharospasm, lacrimation and conjunctival injection; after lavage of the eye this has usually rapidly subsided. Droplet contamination may produce a necrotic lesion of the cornea—ACETALDEHYDE (ETHANAL) [CH_3CHO] (Carozzi, 1925–30; Flury and Zernik, 1931; McLaughlin, 1946), ACRYL ALDEHYDE (ACROLEIN) [$\text{C}_3\text{H}_3\text{CHO}$], used as a military poison gas (Lewin, 1900; Carozzi, 1925–30; Flury and Zernik, 1931; Prentiss, 1937; Jacobs, 1944; McLaughlin, 1946),¹ BUTYL ALDEHYDE (BUTANAL) [$\text{C}_4\text{H}_7\text{CHO}$] (McLaughlin, 1946), CROTON ALDEHYDE [$\text{C}_3\text{H}_5\text{CHO}$] (Homburg, 1883; McLaughlin, 1946), PYRUVIC ALDEHYDE [$\text{C}_3\text{H}_3\text{O}_2\text{CHO}$] (Carpenter and Smyth, 1946), and FURFURAL (FURALDEHYDE, FURAL) [$\text{C}_4\text{H}_3\text{O}_2\text{CHO}$] (Flury and Zernik, 1931; Lehmann and Flury, 1943).

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THE KETONES

THE KETONES are widely used in a large number of industries, particularly those dealing with plastics, rubbers, dyes and paints. They have a relatively low order of toxicity resembling in type that of the aldehydes,

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HYDROCYANIC ACID AND THE CYANIDES

HYDROCYANIC (PRUSSIC) ACID [HCN] (and CYANIDES which can liberate the CN radical, particularly potassium cyanide) is the most rapidly acting known poison. It produces death through asphyxia by inhibiting oxidative processes in the cells throughout all the tissues. The supply of oxygen through the blood is unimpaired and, indeed, since the oxygen is unused in cyanide poisoning, the venous blood is as red as the arterial; the cells of the tissues, however, are prevented from utilizing oxygen since the cyanide enters into a reversible combination with their oxidative enzymes, particularly those of the cytochrome system which are concentrated on their surfaces, an action similar to that of AZIDES¹ (see Warburg, 1911-29; Brinley, 1929; Clark, 1937; Quastel, 1939; Binkley *et al.*, 1944; Albaum *et al.*, 1946; and others).

The symptoms of acute poisoning are dramatic; after swallowing cyanide the victim falls down within a few seconds, usually with a loud cry, and rapidly dies in convulsions. After smaller doses the convulsive stage is preceded by a period of vertigo, dyspnoea and unconsciousness. Hydrocyanic acid is very volatile, boiling at 25.7° C, and accidental inhalation of the vapour—a misadventure which killed Scheele, the discoverer of this substance (1872)—leads to a progressive vasodilatation with flushing of the skin and a feeling of warmth followed by prostration, nausea, vomiting, dyspnoea, unconsciousness and respiratory paralysis. Between the years 1933 and 1948 in the United States alone, 248 people died by accidental cyanide poisoning, and suicides totalled more than 3,000 (Chen and Rose, 1952).

In chronic poisoning few ocular symptoms appear; Souwers (1878) noted a sluggishness of the pupil and swelling of the upper lid. In acute poisoning mydriasis may be maximal, there may be photophobia (Müller-Warneke, 1878), a hemianopia may occur (Tatham, 1884) or amaurosis. In the eye itself morbid changes are seen only in the retina of those dying of poisoning. Clinically the picture of diffuse oedema is found with the cherry-red spot at the macula and blurred margins of the disc characteristic of complete anoxia, resembling that following occlusion of the central artery. Histologically, the vulnerable lower neuron is particularly affected, the ganglion cells and the nerve fibres showing degenerative and atrophic changes (Alagna, 1946).

Nitrites may be used in the treatment of cyanide poisoning in order to bring about the conversion of some of the hæmoglobin to methæmoglobin which in turn combines with the cyanide. The most recent recommendation is the inhalation of amyl nitrite together with the intravenous injection of 10 ml. of 3% sodium nitrite and 50 ml. of 25% sodium thiosulphate (Potter, 1950; Wolfsie, 1951; Chen and Rose, 1952). The last authors stated that of 44 cases in the literature treated sufficiently early in this

¹ p. 6595.

way, 43 recovered ; resuscitation, however, must be immediate so that facilities are rarely available unless in factories where the risk is recognized and expected.

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C V Mosby Saint Louis Mo. 1954:6816-6821.

METHANOL

/RETROBULBAR

/NEURITIS

EYE

/OPTIC NERVE OK

optic nerve in a patient with severe visual loss from methanol
poisoning may appear normal indicating the presence of retrobulbar
neuritis.