1. *Acute Hepatic Inefficiency*.—Although the greater part of the liver may be removed or incapacitated without much change in the blood urea level, subnormal values of 5 to 10 mg. per 100 c.cm. have been recorded in severe and usually fatal conditions of acute yellow atrophy, acute necrosis due to arsenic, phosphorus, chloroform, and carbon tetrachloride, and in post-operative "hepatic shock." A corresponding rise in the amino-acid level of the blood usually accompanies this type of hypo-uraemia.

2. *Diuresis*.—Increase in the volume output of urine tends to lower the level of blood urea, and may explain the minimal values recorded in diabetes insipidus and other diabetic polyurias.

3. *Lipoid Nephrosis*.—This controversial condition has been associated with blood urea values of 7 to 12 mg. per 100 c.cm.

4. *Pregnancy*.—The hypo-uraemia of pregnancy is probably due to renal stimulation by the extra load imposed upon it.

UROTOXAEMIA

Pathologically, the chief interest of urea is in relation to the condition of "uraemia," the late manifestation of nephritis, and other forms of oliguria. It is difficult to isolate and identify the various signs and symptoms that have been included in the uraemic syndrome, but a distinction can be drawn between simple uraemia, or *urotoxaemia*, due entirely to retention of urinary waste products, and the uraemias complicated by extrarenal factors, notably: vascular hypertension, diffuse arteriolar and arterial disease, abnormal vasomotor sensitivity, and myocardial degeneration. The biochemical syndrome of a simple uraemia following total nephrectomy in man has recently been described by Thompson (1932). It was accompanied by the following changes in the blood during the last five days of life.

Composition of Blood in Simple Uraemia. Values in Milligrams per 100 c.cm.

	Average	Sixth Day	Eighth Day	Ninth Day	Tenth Day
Total non-protein N ...	20-40	215	218	210	268
Urea ...	20-40	250	240	224	272
Uric acid ...	2-3	—	11	12.8	13.3
Ammonia ...	0.1	—	—	—	130
Sodium chloride ...	450-500	412	379	363	361

The term "urotoxaemia" in many ways is preferable to "uraemia" and may be defined as the pathological condition due to retention of urinary solutes in the blood. The identification of these solutes is important and must precede any attempt at the rational treatment of the disease. Up to the present this identification has not been accomplished with any degree of certainty, but there is reason to suspect that urea is one, at least, of the active agents in urotoxaemia.

In the ordinary ways of life urea is non-poisonous. Doses up to 100 grams have been assimilated and excreted by healthy subjects, and smaller quantities are given repeatedly in the concentration test for renal function. But there is a profound difference between the effect of a transient acute hyperuraemia due to excessive ingestion and a sustained and increasing hyperuraemia due to abnormal retention. Hewlett, Gilbert, and Wickett (1926) have raised the blood urea level to as much as 245 mg. per 100 c.cm. in healthy subjects, and have reproduced many of the characteristic symptoms of urotoxaemia.

Although the analogy must not be pressed, the fact that all the dialkylbarbituric acid hypnotics are derived from urea suggests that the coma of urotoxaemia may be an autonarcosis following urea accumulation in the

central nervous system. The high diffusibility of urea makes such an accumulation probable, but whether the concentrations reached in severe hyperuraemia would be sufficient to affect the nervous system can only be decided by experiments similar to those conducted by Quastel (1932), who has shown that all narcotics have a specific inhibiting action on oxidations by the brain. A survey of the urea content of the nervous system after death from urotoxaemia should be of value. Unfortunately, even if urea were shown to be implicated in the development of the urotoxaemic syndrome there is no direct line of treatment available, since there is no means of inhibiting the ureagenetic activity of the organism and allowing the renal tissue time to recover. Perhaps future technicians may devise a method of aseptic vividiffusion, whereby the blood can be freed at intervals from diffusible waste products; perhaps when an adequate supply of amino-acids is at last available for research it may be possible to give the fasting subject the individual units he requires, and thus turn him from his fatal onslaught on the fabric of life.

THE TREATMENT OF GLAUCOMA*

BY

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Ever since the auditorium of medicine surrounded the Plane Tree at Cos the treatment of glaucoma has been that of dominant symptoms with scant regard to primary physiological disturbances. The pathological travesty of physiology has sufficed to illustrate gross structural defects of morbid anatomy, but the essential primary cause of physiological derangement has remained obscure, and while this obscurity persists the treatment of glaucoma must be empirical and can have no accurate scientific basis. It follows, then, that any study in disturbed intraocular pressure must include a consideration of the factors which control normal intraocular pressure.

CAUSES OF GLAUCOMA

The following classification of the various causes of glaucoma will indicate how varied may be the methods of treatment, for in many examples the treatment is obvious, in others it is unknown, and for the more important types it is disputed.

Congenital.—(1) Buphthalmos; (2) aniridia; (3) glaucoma of facial naevus.

Hereditary familial glaucoma.

Trauma.—(1) Hyphaemia; (2) cataract; (3) capsular; (4) dislocation; (5) post-operative.

Inflammation.—(1) Hypopion (acute or organized); (2) acute iritis; (3) anterior synechiae; (4) peripheral synechiae; (5) ectasia of the cornea; (6) closure of corneal fistula; (7) iris bombe.

Accidental mydriasis.—(1) Following drops; (2) following third nerve paralysis.

Neoplasm.—(1) Innocent and parasitic cysts; (2) sarcoma of the uveal tract: secondary carcinoma; (3) glioma of the retina.

Degenerations.—(1) Primary glaucoma, acute and chronic; (2) absolute glaucoma; (3) post-cataract: (i) intumescent, (ii) hypermature; (4) detachment of the retina; (5) vascular: (i) thrombosis of central vein, (ii) after Coats's disease, (iii) after severe retinal haemorrhage; (6) capsulo-cuticular glaucoma.

Many of these examples are rare and demand specific treatment, ranging from simple puncture to removal of the globe; for general purposes the common type of glaucoma simplex merits more detailed discussion.

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TREATMENT OF GLAUCOMA SIMPLEX

This type has been defined as raised tension occurring in an eye, the cause of the tension being not immediately obvious. It is usually classified as: (1) acute or congestive glaucoma; and (2) chronic glaucoma (a) with acute exacerbations and (b) without acute exacerbations. The treatment is medical or surgical.

Acute Glaucoma

The medical treatment of acute glaucoma has assumed greater prominence within recent years, and there are few surgeons who care to operate on eyes which are in the acute or congested condition. It is now fully realized that most of these cases will respond to preliminary medical measures which aim at a temporary reduction of tension and vascularity, thus considerably assisting the technical manœuvres of subsequent operation, for in operations carried out in the acute stage excessive haemorrhage may obscure anatomical landmarks, and there is always the risk of injury to the lens. Such preliminary measures represent the ancient therapy of this disease, including as they do the use of leeches, massage of the globe, fomentations, and purgation. Miotics in present-day use are the salts of eserine and pilocarpine, which act by drawing the swollen iris away from the crowded angle of drainage in the anterior chamber and by presenting a larger area of iris stroma for absorption of the aqueous. More recent remedies in stubborn cases are the intravenous injection of hypertonic saline, according to the technique of Duke-Elder (50 to 100 c.cm. of 30 per cent. warm sterile saline solution). This raises the osmotic pressure of the ocular capillaries, and thereby attracts fluid from the turgid ocular media into the blood stream. Another recent method is that of Hamburger, who introduced laevo-glaukosan, of which the chief constituent is a high concentration of adrenaline. In primary glaucoma this has not found general acceptance, but in those cases of secondary glaucoma due to iritis, where dilatation of the pupil is desired without an increase of tension, it has been found to be of great benefit. Rauh has also used it as an alternative to enucleation in absolute glaucoma. To these measures must now be added the use of diathermy, which is still in the experimental stage. Law has used this form of physical therapy with success at Moorfields, especially in the alleviation of pain and sudden reduction of tension.

The surgical treatment of acute glaucoma embraces the earliest of operations also, for the dramatic onset of this disease called for more urgent treatment than did the discovery of an increase of tension in chronic glaucoma. These operations include puncture of the globe, which nowadays is usually confined to the posterior segment and is used only as an emergency operation. Iridectomy, introduced by von Graefe in 1857, has long held pride of place as the classical operation for acute glaucoma, yet exactly how it diminishes intraocular pressure is not known; it is becoming less frequently employed. De Wecker followed up many of von Graefe's cases, and decided that successful results from iridectomy were due to a small accidental inclusion of iris tissue in the wound, which acted as a filter wick. Remembering that these operations were carried out on exquisitely painful eyes without an anaesthetic, accurate reposition of the iris must have been well-nigh impossible, a fact which strongly supports De Wecker's suggestion. Modern opinion inclines to the use wherever possible of permanent filtration operations, which aim at ensuring a channel of drainage between the anterior chamber and subconjunctival stroma, along which any excess of aqueous may be carried away and absorbed in the subconjunctival tissues. This may be achieved either by removing a piece of sclera and producing a permanent hiatus, as is

done in the Lagrange section and the Elliot trephine operation, or by interposing a strand of living iris tissue which acts as a drain, as is attained by the iridencleisis of Holth, which will be discussed later.

In a summary, then, the treatment of acute glaucoma is: (1) the patient is put to bed sitting up; (2) administration of aspirin or morphine for the pain; (3) application of leeches to the outer canthus; (4) local instillation of miotics; (5) the use of hydragogue cathartics; (6) application of electric eye warmer; (7) tension reduction by diathermy or saline; followed by (8) operation under subtenon or retrobulbar novocain anaesthesia.

Chronic Glaucoma

The non-operative treatment of chronic glaucoma depends on the old adage that a glaucomatous eye is a sick eye in a sick body. That it is associated with rheumatism and gout has long been known, but its relation to general vascular disease has not been quite so prominent. Duke-Elder has pointed out the importance of osmotic balance of the ocular capillaries and their influence on vitreous turgescence. Therefore the treatment of a case of chronic glaucoma must always commence with: (1) a medical investigation of the cardiovascular system with due attention to hyperpiesis and renal dysfunction; (2) the elimination of gross foci of sepsis; (3) the guarded use of miotics until such time as deterioration of vision is no longer controlled (Schleich has found that 40 per cent. of cases are kept stationary by miotics); and (4) coincidentally the use of prolonged local eye massage. Knapp is an advocate of this measure and has used it extensively. The indications for operation in chronic glaucoma consist in an increasing frequency of acute exacerbations, in an increase of relative scotomata and field loss, and in a persistent high tonometric tension.

The operative treatment of chronic glaucoma may be said to have commenced with the iridectomy of von Graefe in 1857, continuing with the cyclodialysis of Heine in 1905 and the iris inclusion of Holth in 1907, and terminating with the sclerectomy of Lagrange in 1906 and of Elliot in 1909. Harrison Butler postulates the ideals of an operation which cures chronic glaucoma—namely, that the filtration must be spread over a wide area, that it must be permanent and adequate but not excessive, and that there should be a minimum of trauma with no risk of late infection and with a good cosmetic result. To these may be added that it must be within the capacity of the average surgeon and not entirely the perquisite of the brilliant individual. In this country the operation of Elliot by trephining a disk of sclera $1\frac{1}{2}$ -2 mm. in diameter and so establishing drainage from the angle of the anterior chamber to the subconjunctival spaces is said to approach these ideals most closely, although there are strong advocates for the iris inclusion operation. The points of this latter procedure appear to centre on the question whether the iris remains a permanent filter or whether it is converted into cicatricial tissue.

THE PHYSIOLOGICAL BASIS OF TREATMENT

At the present day the treatment of chronic glaucoma is adequate, but the cause of the disease is unknown. Pathological scaffolding has erected many theories: that of Leber, which includes the obstruction of the angle of the anterior chamber and subsequent drainage; that of Priestley Smith, wherein an increasing lens in a small eye pushes the root of the iris forward and brings about a similar blockage; and that of Henderson, in which sclerosis of the pectinate ligament is a prominent feature. In 1909 Fischer stated that glaucoma was really oedema of the eyeball in which the hydrophilic colloids retain an increasing amount of water. Duke-Elder substantiates

this, and suggests that turgescence of the vitreous causes the lens to move forwards and so brings about obstruction. In recent research on the incidence of acute glaucoma he describes the close parallelism between the reactions of the iris to that of the skin, showing that when the iris is scratched there is a dilatation of the capillaries locally, followed by arteriolar dilatation of the whole of the iris with an increase of temperature and capillary permeability. This latter factor of capillary permeability initiates the rise of intraocular pressure by disturbance of osmotic equilibrium. The close resemblance which this bears to the triple response of Lewis will then be realized, for all three components are present in each reaction. It therefore seemed profitable, seeing that the response of Lewis was due to H-substance or histamine, to study the effect of this substance on the eye, and to discover the presence of this substance in the aqueous in cases of acute glaucoma.

By previous animal experiments it was found that histamine injected into the anterior chamber of the eye—the intraocular pressure all the while being kept constant—produced a rise of intraocular pressure, which was not brought about by an equal amount of normal saline. When injected into the blood stream there occurred a fall of blood pressure due to peripheral vasodilatation, and a coincident rise of intraocular pressure, provided the capillaries maintained their tone. Friedenwald has shown that the histological findings of animal eyes into which histamine had previously been injected conformed in close degree to the pathological findings of eyes removed for acute glaucoma. There appeared, then, to be a close relation between the effects of histamine on the eye and the clinical picture of acute glaucoma. If histamine could be detected in the aqueous of these cases a further link would be established.

The method of detection chosen was the production of a flare by intracutaneous injection: colour reactions and methods of biological assay were not considered suitable. Four cases of primary acute glaucoma were taken and equal amounts of aqueous and saline were injected on to the flexor surface of the forearm. The next day 0.1 c.cm. of 1 in 1,000,000 histamine solution was injected in order to prove that the patient would react to histamine if present. In no case was a flare produced by injection of the aqueous, although all cases reacted to an injection of histamine. At the present, therefore, a vasotoxic substance has not been detected by these experiments, whereas Friedenwald claims to have produced a wheal by the injection of the aqueous in a similar case; his patient, however, had been subjected to an operation a week previously.

It is proposed to extend these experiments, as it is realized that no final conclusion can be based on such a small number of cases, and the possibility that acetylcholine may be the vasotoxic agent.

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PRIMARY THROMBOSIS OF THE
AXILLARY VEIN

WITH REPORT OF A CASE

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This condition, although rare, is easily recognized, and there are a small but increasing number of cases reported in the current literature. It is interesting that in 1875 Sir James Paget¹ reported a case of axillary thrombosis. This was described, with others, in an article entitled "Gouty Phlebitis," but from his careful description it would appear that this was a genuine case of primary thrombosis. In 1920 Cadenat² was only able to collect twenty-seven reported cases of this condition. In this connexion the use of the term "primary thrombosis" is limited to those cases in which no obvious cause, such as a mass of malignant glands in the axilla, is present.

The characteristics of this lesion are as follows:

- (a) The right arm of a healthy male adult is affected, the age period ranging generally between 20 and 30 years.
- (b) The immediate history nearly always includes recent trauma, or some exceptional effort, with the arm in the abducted position.
- (c) The affected arm is swollen from the fingers to the level of the base of the axilla. This swelling is generalized, regular, and does not pit on pressure.
- (d) The skin is slightly cyanosed. Dilatation of the superficial veins can be seen over the pectoral region and the antero-lateral chest wall.
- (e) A firm, tender cord is palpable in the vicinity of the axillary vein.
- (f) Pain and tenderness are usually present.
- (g) There is no pyrexia or constitutional disturbance, and the individual appears to be healthy in all other respects.

Wilson³ reports two cases in which complete paralysis of the arm was present. Nerve involvement has not been observed in this country, apart from one case reported by Willan,⁴ in which a definite tumour was present in the axilla. In one of Wilson's cases occlusion of the artery had also occurred, so is not comparable with the condition here described. The diagnosis presents no difficulty. The treatment consists of rest and elevation of the arm; later gentle massage may be given with benefit. There is only one recorded case in which embolism occurred. This was a case quoted by Ruge⁵ in which Schepelmann explored and removed the thrombus. The prognosis is uniformly good. Complete functional use, with subsidence of the swelling, occurs within periods varying from a fortnight to several months. It is evident, then, that operative interference is unnecessary and dangerous. Slight residual symptoms, such as occasional aching pain and oedema after marked effort, may persist for some time, but are negligible. In one case described by Firth and Mackay,⁶ after involvement of the right arm, a similar condition was observed on the left side some months later. This also completely subsided.

CASE RECORD

The following case was seen by me recently:

A healthy male, aged 27, went to bed normal in every respect. On awakening the following morning he found his right arm heavy and swollen. On examination the limb was slightly cyanosed, swollen from the fingers to the level of the base of the axilla, and did not pit on pressure. A few days later a non-tender, indurated cord was felt in the axilla,