Thirty grams of cortical tissue yield only 1 c.cm. of the final therapeutic preparation, and Levy Simpson⁴ tentatively suggests the dosage indicated in severely ill patients to be 50 c.cm. intravenously on the first day, and thereafter 20 c.cm. daily, until definite clinical improvement sets in. It is thus clear that effective treatment must severely strain the financial resources, not only of the individual patient, but even of the average institution—if, indeed, sufficient supplies of the preparation are to be had, apart altogether from the question of cost. We do not wish to deny the therapeutic value of cortical suprarenal extract, as this appears to have been definitely established^{3, 4, 5}; but it must be admitted that, though several striking temporary successes have been reported in this country,^{1, 4} as well as at least two cases where more lasting benefit was obtained, the results have been less good than those claimed by American workers.^{3, 5} Davidson,² after reviewing the literature and adding four cases personally known to himself, points out that, of thirteen cases treated in this country, nine are dead, though it is true that several showed initially a good response, and that death in some was not wholly due to suprarenal insufficiency. One patient of Davidson's, in a severe relapse, failed altogether to react to intravenous injection of 25 c.cm. of a reputable preparation, though he had previously shown some improvement under treatment with an earlier sample.

We feel, therefore, that the results so far recorded cannot be regarded as more than encouraging, and that, until the active principle has been identified and its synthesis established on a commercial scale, treatment with cortical suprarenal extract must remain of limited practical utility.

Summary

A case of Addison's disease is described, with reference to its clinical features and to the pathological changes found. These were of the nature of atrophy, combined possibly with some regeneration. The value of treatment with cortical suprarenal extract is discussed.

REFERENCES

- ¹ Benham, H. W., Fisher, M., More, I., and Thurgar, C. J. L.: *Lancet*, 1932, i, 125.
- ² Davidson, L. S. P.: Address to Aberdeen Medico-Chirurgical Society, reported in summary form in the *British Medical Journal*, 1932, i, 525, and amplified in personal communication.
- ³ Greene, C. H., Rowntree, L. G., Swingle, W. W., and Pfiffner, J. J.: *Amer. Journ. Med. Sci.*, 1932, clxxxiii, 1.
- ⁴ Levy Simpson, S.: *Quart. Journ. Med.*, 1932, N.S., i, 99.
- ⁵ Rowntree, L. G., Greene, C. H., Swingle, W. W., and Pfiffner, J. J.: *Journ. Amer. Med. Assoc.*, 1931, xcvi, 231.

ADDISON'S DISEASE AND ITS TREATMENT WITH CORTICAL EXTRACT *

BY

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There is no more fascinating chapter in the history of medicine than that dealing with the suprarenal glands, the influence of which—in contrast to their minute size—extends over every system in the body. As Sir Humphry Rolleston has pointed out, indications of the function of the suprarenal cortex were first given by "Nature's pathological experiments." Attempts to obtain an active extract of the cortex were for many years unsuccessful, and in consequence clinicians were tempted to explain hypofunction of the gland in terms of the more familiar medullary secretion (adrenaline). The recent production of an active extract of the cortex provides complete proof that it is essential to life. Pioneers in this work

are Hartmann, MacArthur, and Hartmann, Stewart and Rogoff, Swingle and Pfiffner. Substitution therapy with the extract of the last two was first carried out by Rowntree and Greene at the Mayo Clinic, and by myself at the London Hospital. Hitherto Addison's disease was nearly always fatal, usually within a period of months. With cortical extract life may be prolonged, as with desuprarenalectomized animals, for an indefinite period—possibly until old age. There are at least two active preparations now available—namely, eucortone and eschatin. I have used the former with success, and American workers have reported favourably on the latter.

ILLUSTRATIVE CASES

The following is a brief description of four cases,* three of whom were dying and one of whom was bedridden previous to treatment with cortical extract.

Case I (Previous Series).—This patient, M. S., aged 53, was the first to be treated in this country. She was semicomatose when I saw her in November, 1930. Twelve c.cm. of cortical extract a day were given intravenously for four days, and dramatic recovery followed. She has remained well ever since without receiving any more of this substance. The extract used in this case was made in Swingle and Pfiffner's laboratory.

Case VI (Previous Series).—This patient, E. G., aged 43, was in a moribund delirious condition when first seen by me in July, 1931. Dr. T. Thompson kindly permitted me to treat her with cortical extract. I gave 600 c.cm. of intravenous 5 per cent. glucose and 50 c.cm. of extract on the first day, with 20 c.cm. of extract on subsequent days. Remarkable improvement occurred on the third day, and within a few weeks she was walking about the ward. She maintains health on 5 c.cm. of cortical extract given daily, except on Sundays.

Case VII.—The next patient, J. H., aged 31, is my most recent case. She had been unwell for three years, and had been in bed for some months with weakness, anaemia, vomiting, inability to stand cold, wasting, and pigmentation. Five hundred c.cm. of 5 per cent. glucose in saline together with 35 c.cm. of cortical extract were given on the day of admission to hospital; subsequently she received 20 c.cm. of extract a day. Apparently these large quantities were insufficient, as the patient collapsed and went into crisis on the third day. Eight hundred c.cm. of glucose together with 75 c.cm. of cortical extract intravenously produced a rapid improvement, and she has since kept up reasonably good health on a daily maintenance dose of 20 c.cm. (Smaller quantities than this prove inadequate.)

Case VIII.—In this patient, G. M., aged 46 years, initial symptoms commenced after the birth of her last child five years ago, and were aggravated by the menopause two years ago. Twenty c.cm. of extract intramuscularly, given daily for a week, produced marked benefit. Apart from the diminution of pigmentation, increased strength, and recovery of appetite, there was a complete psychological change, intense depression and morbid introspection giving way to a cheerful optimism and a happy outlook. The maintenance dose during the last two months has been 10 c.cm. daily.

Failures.—Two of these have to be reported. The first, C. D., aged 42 (Case II of my previous series), remained well on 5 c.cm. of cortical extract a day for a period of one year. She then, without my knowledge, omitted the injection of extract every other day. After a few weeks she suddenly fell ill and died. The other failure, A. D., aged 35 (Case IX), gave one year's characteristic history, and had lost 6 st. in weight in four years. His condition on admission to hospital was not in any way disquieting, there being no vomiting, while the pulse was of good volume and slow—rate 68. On the third day he developed a sore throat, and within a few hours he went into crisis. An inability to converge the eyes, although quite conscious, was an interesting early sign. He received 600 c.cm. of saline and 50 c.cm. of cortical extract intravenously in the morning, and similar quantities in the evening, with the addition of glucose. In spite of this active treatment he died a few hours later with anuria, and blood

* Read in the Section of Medicine, British Medical Association Centenary Meeting, London, 1932.

* These were shown to the Section.

urea 0.125 per cent.; necropsy revealed almost total destruction of the suprarenal glands. This case illustrates the fact that every patient with Addison's disease is always in a potentially critical condition.

PRINCIPLES OF TREATMENT

The administration of cortical extract must be regarded as a substitution therapy comparable to that of insulin in diabetes mellitus. The extract can be given intravenously, intramuscularly, or subcutaneously, the former method being advisable in crisis, the latter only when small quantities are needed. The discomfort or pain of intramuscular or subcutaneous injection can be obviated by the addition of 1 per cent. novocain, or by very slow injection. Protein-like reactions have been recorded with intravenous injections (Benham *et al.*). This possibility calls for caution in patients who may have an allergic diathesis.

The dose of cortical extract must be judged largely from clinical experience. There are, however, some biochemical indications. A high blood urea is a warning of severe insufficiency, but a normal blood urea is no guarantee against the imminence of crisis. A low blood sugar may coexist with a satisfactory clinical state, but blood sugars below 0.6 per cent. suggest the need for very close observation. A high blood calcium or blood phosphate is also a warning indication. A marked degree of creatinuria occurs in severe cases, and R. H. Dobbs and myself have confirmed in two further cases the diminution or even disappearance of creatinuria under treatment with cortical extract. Failure to produce diminution suggests inadequate dosage. It is interesting to note in contrast that Bernhardt and myself, working at the Charité Klinik, Berlin, have found the creatinuria of myasthenia gravis unaffected by cortical extract. In crisis I advise very large quantities of extract—at least 50 c.cm. intravenously to commence with. Failure often means insufficient extract. Infection calls for immediate doubling of the maintenance dose of cortical extract. The functioning remnant of suprarenal gland is impaired by infection in the same way as the pancreas is in diabetes mellitus. In most cases the extract must be given daily for an indefinite period. In a physician with Addison's disease, treated by Dr. Hamilton Fairley, it was only found necessary to tide over a period of influenza, after which the extract was discontinued, the patient having remained well up to the present time (for six months). In my first patient (Case 1) no extract has been necessary for twenty months. Dehydration and oliguria are very important factors in crisis, and large quantities of intravenous glucose and saline are an essential part of the treatment.

SIGNIFICANCE OF CHANGES PRODUCED BY CORTICAL EXTRACT

In patients who respond adequately to cortical extract, nearly all the symptoms and signs of Addison's disease tend to disappear—namely, asthenia, anaemia, nausea, retching, vomiting, hiccups, yawning, lethargy, wasting, photophobia, conjunctivitis, involuntary cries and facial grimaces, hypersensitivity to cold, irritability, negativism, pessimism, delirium, and pigmentation. In a previous publication I have shown that both the deposition and the dissolution of pigment are affected. If this is correct, one must modify or supplement the views of Meirowsky, Bittorf, and Bloch. In any theory of pigmentation one must explain: (1) untreated cases, in which pigmentation was never present even at death (Rowlands, Rowntree, etc.); (2) cases in which pigmentation was the only sign for many years; (3) cases in which cortical extract caused a marked diminution of pigment but failed to save life.

Blood Sugar

Carbohydrate metabolism in Addison's disease is of great interest, and the physiologists and clinicians differ

as to both fact and theory. Stewart and Rogoff, Banting and Gairns, find that the blood sugar in de-suprarenal-ectomized animals is normal until just before death, when a fall may occur. Britton and Silvette, on the contrary, find in animals an early and marked fall in the blood sugar level, an increase in blood lactic acid, and a diminution in liver and muscle glycogen. They observe that all these variations return to normal on giving cortical extract. Greene and Rowntree state that they "agree with Wadi in considering that hypoglycaemia in Addison's disease is essentially a phenomenon of collapse."

In my experience (previously expressed) low blood sugar values are of common occurrence in Addison's disease, and there is a tendency to a still further fall at times of crisis. After treatment with cortical extract there is a relative rise from the low value of crisis, but, nevertheless, values over many months may remain chronically low in spite of a good clinical condition and the use of cortical extract therapy. Because of these and other supporting observations (see previous publications) I considered that the low blood sugar might be due to a diminished or absent secretion of adrenaline, and that normally adrenaline played some part in the maintenance of the blood sugar level. This view would explain why some patients showing signs of cortical insufficiency nevertheless maintain normal blood sugar values. Britton and Silvette find that not only can the blood sugar of de-suprarenal-ectomized animals be brought back to normal after some hours by cortical extract, but that by similar means the blood sugar of normal animals—particularly young growing ones—can be raised above normal within a few hours. I have previously reported negative results in man (normal Addison's disease, diabetes mellitus), observed over a period of three and a half hours, after injection of 10 c.cm. of cortical extract. I have since tried 20 c.cm. of extract in two patients with Addison's disease, and have found no elevation of blood sugar over a period of four hours. It is necessary to point out that if one used quantities equivalent to those employed by Britton and Silvette in animals, 200 to 1,000 c.cm. of cortical extract would be required. This may explain the different results. Britton and Silvette were unable to prevent or counteract insulin hypoglycaemia in animals by the administration of cortical extract. This tends to disprove any direct action of cortical extract on carbohydrate metabolism. In a previous publication I stated that if the relative rise of blood sugar seen in some cases in the third week of treatment was real, it would suggest a readjustment of metabolism rather than a direct action of cortical extract.

Blood Pressure

Excision of the medulla and the sympathetic nervous system in animals produces no fall in blood pressure (Cannon), neither does adrenalectomy—except perhaps terminally (Swingle, Stewart, Elliot, Marshall and Davis). Tumours of the medulla or of the cortex may be associated with hypertension (Neusser, Orth, Wiesel, Bergstrand, Labbé, Tinel, and Doumer, Oppenheimer and Fishberg).

Adrenaline raises the low blood pressure of Addison's disease. Does cortical extract? In an earlier publication I pointed out that "a belated rise of the pressure normally occurs during the third week, but this may not be consistently maintained even with a satisfactory general condition. Temporary or terminal relapses are associated with a fall of blood pressure. The delayed rise of blood pressure following treatment with cortical extract would not appear to be a direct effect of a cortical hormone, but was probably an expression of readjusted metabolism. Further, I was unable to show any rise of blood pressure in normal individuals in Addison's disease, or in essential hypotension, following the injection of cortical extract."

Looking through my data I find that failure to maintain the relative elevation of blood pressure seen in the third week was associated with a reduction in the dose of cortical extract. The effect of giving much larger doses over a long period must be observed. It is interesting to note that my first patient (Case i) now has a blood pressure of 120 mm., although pigmentation and subnormal temperature persist. In Case vi the pressure rose from 85 to 110 mm. two months ago and has since been maintained near that level. Case viii has always had a blood pressure within the lower limits of normal.

Effects on Sexual Characteristics

The cortex has a striking influence over sexual and secondary sexual characteristics. This was clearly indicated many years ago in the classical paper of Bulloch and Sequeira on cortical tumours. Hypertrophy or neoplasia of the cortex may produce precocious and excessive sexual development, hermaphroditism, masculinization of the female, etc. (Bulloch and Sequeira, Glynn, Fordyce and Evans). Robert Hutchison has shown that tumours of the medulla have, on the contrary, no effect on sexual characteristics.

In Addison's disease amenorrhoea, absence of libido, impotence, and atrophy of the testis may occur. Cortical extract administration usually results in a return to normality. In young adults (Case iv, previous series) infantilism may occur. In a patient with a pituitary tumour and loss of secondary sexual characteristics (previously described by Rowlands and myself) I tried the effect of 20 c.cm. of cortical extract intramuscularly daily for ten days. After the first few days there was a return of libido and the occurrence of four nocturnal erections within a week, manifestations which had been completely absent in the previous twelve months. This was not associated with any improvement in the general condition, although the patient was less susceptible to cold and the subnormal temperature (97.0° F.) was inconsistently maintained at a half-degree-higher level. There was no influence on a negative metabolic rate of -40, estimated on four occasions by Dr. C. E. Brunton. Corey and Britton have shown that a precocious maturity of sex glands in young albino rats can be produced by injections of cortical extract.

Other Changes

These I do not propose to consider in any detail in this paper. Subnormal temperature is raised to normal in Addison's disease, although it may remain subnormal in spite of general improvement. I believe, however, that a persistent subnormal temperature indicates inadequate dosage. Basal metabolism, where subnormal, tends to approach normal levels. Growth in young adults (Case iv, previous series) may be impaired. This is true of young adrenalectomized rats, and may be counteracted by adequate dosage of cortical extract (Hartmann, Brownell, and Crosby). Impaired renal function in Addison's disease may be corrected by cortical extract. I regard failure of renal function in Addison's disease as similar to that occurring in diabetes mellitus and intestinal obstruction, and as being due to: (1) dehydration, (2) toxæmia, (3) superadded acute fall of an already low blood pressure. If the toxæmia produces sufficiently severe structural changes in the kidneys, complete recovery of renal function may not be possible (Case vii).

NEED FOR STRONGER AND CHEAPER EXTRACT

The present advance in the therapy of Addison's disease must be regarded as the starting-point and not the end of our efforts. At present the average daily maintenance dose is derived from no fewer than fifteen oxen, or from as much cortex as would be present in the adrenal glands of thirty normal men. In severe cases it is difficult or

impossible to give adequate amounts of cortical extract, because of both the bulk and the enormous cost. I am sure that many failures or disappointing results in attempting cortical extract therapy are due to insufficiently large quantities of extract being used. It is a great problem as to whether a voluntary hospital—and in some cases the national insurance—should be asked to provide £10 or more a week for an indefinite period for the maintenance of a patient with Addison's disease. In the past approximately 300 patients have died every year in this country with Addison's disease. In addition, there must be some thousands of people with minor manifestations of the disease, hitherto unrecognized, that, with the incentive of a potent therapy, will be sought for and found by competent observers. The potency of cortical extract prepared in the laboratory is far greater than that prepared on a large scale by any commercial firm. Research by experts must be applied to this aspect of the problem.

Although adrenaline can produce many effects of cortical extract such as raising the blood pressure, basal metabolic rate, blood sugar, and temperature, and also diminishing pigmentation, I regard this as of greater theoretical than practical importance. Whatever supplementary measures we use in the treatment of Addison's disease, cortical extract will always remain our chief therapeutic weapon for the majority of patients. A more concentrated product is also essential for research purposes, and I believe that many of our puzzling and indefinite clinical and biochemical results will assume a more enlightening aspect when adequate quantities of extract are used. At present we must be very tentative about our conclusions, because of this possible fallacy.

CONCLUSIONS

The problems of Addison's disease well illustrate both the value and limitation of animal experiments, and observations on man provide important supplementary knowledge. I would readily admit that in many ways our new knowledge might be considered to have rendered "confusion worse confounded." My revered teacher Sir Frederick Gowland Hopkins once told me that when all the facts began to contradict one another and new observations appeared to make matters worse, we were on the verge of important discoveries that would clarify everything. I hope this may be so. In the meantime I would suggest that the considerations I have mentioned justify the tentative acceptance of the following postulates:

1. There are several internal secretions of the suprarenal cortex (as in the pituitary gland) which are unevenly represented in potency in the cortical extract at present available.
2. There is a relationship, at present ill defined, between the cortex and medulla, which parts of the suprarenal gland, although of different embryology and morphology, may have been woven so closely together not merely as a purposeless whim of nature.
3. Although the cortex and not the medulla is essential to life, the absence or diminution of adrenaline plays a part in the symptomatology of Addison's disease.

I wish to record my sincere thanks for the help and constructive criticism of my chief, Dr. Robert Hutchison; and for the invaluable co-operation of Dr. J. R. Marrack, clinical pathologist of the London Hospital.

BIBLIOGRAPHY

- Banting, F. G., and Gairns, S.: *Amer. Journ. Physiol.*, 1926, lxxvii, 100.
 Benham, H. W., Fisher, M., More, I., and Thurgar, C. G. L.: *Lancet*, 1932, i, 125.
 Bergstrand: Quoted by Oppenheimer, B. S., and Fishberg, A. M. Bittorf, A.: *Arch. f. Pharm. u. Therap.*, 1914, lxxv, 143.
 Bloch, B.: *Zeit. f. Physiol. Chem.*, 1917, xcvi, 226.
 Britton, S. W., and Silvette, H.: *Amer. Journ. Physiol.*, 1931, xciv, 15, 33.
 Idem: *Ibid.*, 1932, c, 693, 701.

- Bernhardt, H., and Levy Simpson, S.: To be published.
 Bulloch, W., and Sequeira, J.: *Trans. Path. Soc. London*, 1905, lxvi, 189.
 Cannon, W. B.: *Lancet*, 1930, i, 1109.
 Corey, E. L. and Britton, S. W.: *Amer. Journ. Physiol.*, 1931, xciv, 33.
 Idem: *Ibid.*, 1931, xcix, 33.
 Elliot, T. R.: *Journ. Physiol.*, 1914, xlix, 38.
 Fordyce, A. D., and Evans, W. H.: *Quart. Journ. Med.*, 1929, xxii, 557.
 Glynn, E.: *Journ. Obstet. and Gynaec.*, 1921, xxviii, 23.
 Greene, C. H., Rowntree, L. G., Swingle, W. W., and Piffner, J. J.: *Amer. Journ. Med. Sci.*, 1932, clxxxiii, 1.
 Hartmann, F. A., MacArthur, C. G., and Hartmann, W. E.: *Proc. Soc. Exper. Biol. and Med.*, 1927, xxv, 69.
 Hartmann, F. A., Thom, G. W., Lockie, L. M., Greene, C. W., and Bowen, B. D.: *Journ. Amer. Med. Assoc.*, 1932, xcvi, 788.
 Hutchison, R.: *Quart. Journ. Med.*, 1907-8, i, 33.
 Labbé, M., Tinel, J., and Doumer: *Bull. et Mém. Soc.*, 1922, xli, 982.
 Levy Simpson, S.: *Proc. Roy. Soc. Med.*, 1930-1, xxiv, 497.
 Idem: *Journ. Physiol.*, 1931, lxxii, 4.
 Idem: *Quart. Journ. Med.*, 1932, i, 99.
 Marshall, E. K., and Davis, D. M.: *Journ. Pharm. and Exper. Therap.*, 1916, viii, 525.
 Meirowsky, E.: *Munch. med. Woch.*, 1911, lviii, 1005.
 Neusser: Quoted by Orth, J.
 Oppenheimer, B. S., and Fishberg, A. M.: *Arch. Int. Med.*, 1924, xxxiv, 631.
 Orth, J.: *Sitzung. d. k. Preussischen Akad. d. Wissensch.*, 1914, ii, 34.
 Rogoff, J. M., and Stewart, G. N.: *Science*, 1927, lxvi, 327.
 Rolleston, H. D.: *West London Med. Journ.*, 1925, xxx, 105.
 Rowlands, R. A.: Personal communication.
 Rowlands, R. A., and Levy Simpson, S.: *Proc. Roy. Soc. Med. (Section of Medicine)*, 1929, xxiii, 16.
 Rowntree, L. G., Greene, C. H., Ball, R. G., Swingle, W. W., and Piffner, J. J.: *Trans. Assoc. Amer. Phys.*, 1931, xli, 123.
 Rowntree, L. G., Greene, C. H., Swingle, W. W., and Piffner, J. J.: *Ibid.*, 1931, xcvi, 231.
 Rowntree, L. G., and Snell, A. M.: Mayo Clinic Monographs, 1931.
 Stewart, G. N.: *Arch. Int. Med.*, 1929, xliii, 733.
 Swingle, W. W., and Piffner, J. J.: *Science*, New York, 1930, N.S., lxxi, 321.
 Wadi, W.: *Klin. Woch.*, 1927, vii, 2107.
 Wiesel: Quoted by Oppenheimer, B. S., and Fishberg, A. M.

CARE OF THE LUNGS IN ANAESTHESIA*

BY

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This subject may be described with truth as a vast one. In the course of a surgical operation under general anaesthesia the widespread effects of the drugs employed, the altered state of the entire physiology of the body, and the immediate and remote consequences of the actual operation are problems which must receive the constant attention of the surgeon and of the anaesthetist during their work. Since the lungs are affected in greater or lesser degree by these bodily disturbances, the anaesthetist must regard his responsibilities as being wide in their scope and profound in their detail.

Formerly, post-operative lung disorders were summed up by many as "ether bronchitis" or "ether pneumonia"; more recently research has been devoted to the subject of "post-operative massive collapse of the lungs," and during the last year or two attention has been drawn to the therapeutic value, and the prophylactic wisdom, of insufflations of carbon dioxide gas when mixed with air or with oxygen.

In this paper the difficulties which an anaesthetist may look for are summarized, but it is hoped that subsequent papers from physicians and physiologists may open our eyes still further to certain risks and wise precautions concerning which these workers are more qualified to show the way. Perhaps I may group the problems which have to be considered under the following general headings: (a) the anaesthetic agent; (b) the method of administration; (c) the operation itself; (d) the patient's general condition; (e) the patient's respiratory system; (f) the process of infection.

ANAESTHETIC AGENT

Of the anaesthetic agents which are available for inhalation, nitrous oxide, ethylene, ether, and chloroform are the drugs most commonly employed. They provide examples of different chemical and physical states—namely, gaseous oxide of nitrogen, gaseous hydrocarbon, liquid oxide of a hydrocarbon, and liquid halogen compound of a hydrocarbon. Ether vapour has an irritant effect on the mucous membrane of the respiratory passages, but sound technique renders this ill effect negligible. Impurities such as ketones and peroxides are harmful,¹ and should be avoided by employing only the purest ether. It is essential that the ether should be well vaporized, for a cold fog of ether droplets is particularly irritating. Sir Francis Shipway was the pioneer who drew attention to the importance of administering warmed ether gas, and his apparatus is one of the most important items in an anaesthetist's armamentarium. The proportion of ether vapour in the inhaled mixture of gases should be as low as is practicable, for the higher concentrations are very pungent; indeed, experiments on dogs² have shown that massive doses of ether produce petechial haemorrhages and oedema of the lungs. In lesser concentrations, narcotic drugs paralyse the vasomotor control of the blood vessels of the lungs, and physiological friends have suggested to me that this factor may be of importance in determining a considerable degree of damage to the lung tissue.

Salivation and profuse secretion from the upper air passages and the lungs are controlled by pre-operative administration of atropine, but the local injury to the epithelial cells, and the paralysis of the ciliated epithelium, should be prevented as far as possible by using only pure ether, warmed, thoroughly vaporized, and well diluted with air or oxygen. When these precautions have been taken, it is a common experience to find that the lungs of patients who have suffered from subacute bronchitis for a week or more prior to operation clear up rapidly after the administration of ether.

It may be of interest to remark that, in addition to the local effects of ether on the lungs, Graham³ showed that while ether checked phagocytosis in the body, olive oil administered by the rectum, or lecithin injected subcutaneously, restored the opsonic index to normal. Cutaneous vaso-dilatation and sweating should be dealt with by covering the body adequately with blankets and by the use of atropine, lest these indirect effects of ether predispose to lung disease. In long operations it has been realized that the dangers attaching to the prolonged administration of ether should be avoided by the employment of morphine or basal narcosis, together with nitrous oxide or ethylene with oxygen, and as little ether as possible.

Chloroform, in the weak dilution which is necessary for safety in inhalation anaesthesia, is not pungent to the nasal and oral mucous membrane, but experimentally it has been shown that strong chloroform vapour is destructive in its action on animal cells.⁴ Although the more serious risks of chloroform anaesthesia are due to the damage to the cardiac nerves, the heart muscle, and the liver, the frequency of post-operative pneumonia following chloroform anaesthesia is noteworthy, and perhaps the vasomotor disturbances in the lung tissues are more considerable than has been generally recognized.

Nitrous oxide and ethylene are gases which are comparatively inert in their local effects on the respiratory epithelium. The absence of poisonous effects is emphasized by the excellent results which have been obtained by Magill and Rowbotham⁵ in anaesthesia for the prolonged multiple operations which are entailed in plastic surgery of the face. Furthermore, they are the anaesthetic agents of choice in chest surgery.

* Read in opening a discussion in the Section of Anaesthetics at the Centenary Meeting of the British Medical Association, London, 1932.