A British Medical Association Lecture ON INSULIN TREATMENT OF DIABETES:

WITH PARTICULAR REFERENCE TO
THE COMPLICATIONS OF DIABETES AND TO SURGERY
IN DIABETICS.*

BY

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THE death of a diabetic patient is never strictly a death from diabetes; it is a death due to some preventable complication of diabetes or to an intercurrent disease. Diabetics certainly die of pneumonia, tuberculosis, cancer, nephritis, apoplexy, and even of old age, and it is true that their resistance to any disease is lessened. Yet the main causes of death in diabetes down to the present time have been coma and gangrene.

How frequently coma is accountable for the fatal ending in diabetes can be realized from the figures given by Joslin¹ from his own clinic, where 66 per cent. of the deaths down to 1915 were due to coma, and from von Noorden's clinic, where the figure was 58 per cent. Von Noorden and Joslin show by their statistics how much more common coma is in young than in older diabetics. Fitz and Murphy,² in their analysis of the causes of death in diabetes, demonstrate that death from coma without some complicating infection is relatively rare at any age. Joslin has observed that nearly all diabetics who die in the first year of their disease die of coma. The explanation of this appears to be that on the discovery of the disease there is a great risk that the diet will be suddenly changed. If carbohydrates are restricted while protein and fat are simultaneously increased, coma may ensue forthwith.

Infections and an ill balanced diet constitute the chief dangers, therefore, of diabetes. The dangers of a diet containing an excessive proportion of fat are not even now sufficiently recognized. Since the introduction of insulin coma has become avoidable in practically every case. Infections more than anything else are responsible for serious diminution of carbohydrate tolerance in diabetes. These infections may be classified under two headings—general and local.

GENERAL INFECTIONS.

Pneumonia was responsible for 52 out of 887 deaths in Joslin's series, yet diabetics do not all die when they develop pneumonia—there were 13 recoveries. Influenza appears very fatal amongst diabetics when it comes in epidemic or pandemic form; sporadic cases stand a better chance of recovery. Tonsillitis, whooping-cough, dysentery, and erysipelas are dangerous complications; but diabetics may pass unscathed through measles, mumps, scarlet fever, variocella, and even whooping-cough. It is interesting to note that acute rheumatism very rarely attacks a diabetic patient.

Tuberculosis deserves more particular attention. Banting³ has said that tuberculosis in diabetics usually progresses rapidly and ends fatally. This is not invariably the case; not infrequently the phthisical diabetic will live many years as a chronic invalid. Diabetes may sometimes disappear when tuberculosis intervenes. The intervention is often insidious. Pyrexia is characteristically absent, hæmoptysis is rare, so that any loss of weight can be mistakenly attributed to diabetes. I have been surprised occasionally to find in chronic diabetics extensive signs of pulmonary tuberculosis which had been unsuspected. Suspicion of tuberculosis should be aroused whenever an unexplained improvement of carbohydrate tolerance is seen in diabetes. Allen suggests a reason for this increased tolerance, in that fasting and loss of weight will improve

the tolerance of the severest diabetic patients. The advent of insulin enables us to feed tuberculous patients with adequate diets, so that the diabetic consumptive is now no worse off than the non-diabetic in respect of nourishment.

LOCAL INFECTIONS.

Local infections are really more important than general. Septicaemia is a commoner cause of death, for example, than pneumonia. Joslin gave 6.9 as the percentage death rate from pneumonia of his fatal cases of diabetes; the figure for the general population of Massachusetts was 6 per cent. of the total deaths.

Other important local infections are boils, carbuncles, and gangrene. It may cause surprise to find gangrene mentioned among the local infections. The form of gangrene seen in diabetes is not as a rule the sudden complete blocking of a large vessel. When this occurs, as it does occasionally, the patient generally shows advanced arterio-sclerosis, and the case should be regarded as senile rather than diabetic gangrene. Such a patient may not survive amputation because of diabetes; thus diabetes may contribute to his death. But true diabetic gangrene is commonly caused by some local infection to which the soft tissues respond by a rapidly spreading necrosis. Comparatively slight injuries may lead to severe gangrene. Without insulin surgical intervention may do no good; with insulin treatment it may prove unnecessary; if insulin alone is not sufficient to check the progress of the gangrene it will contribute wonderfully to the success of an operation. Joslin⁴ considers that the majority of cases of gangrene are due to injuries occurring to unclean feet, and he has therefore laid down an almost surgical drill for the care of diabetic feet.

Boils and carbuncles are important examples of local infection; they will be considered later with other skin complications.

Many local infections present grave problems when they complicate diabetes, although they may not result even indirectly from diabetes. Gall stones, cholecystitis, and pericholecystitis may be suspected of being in some instances the precursors or exciting causes of diabetes. Seeing that we are often called upon to consider their treatment after diabetes has been established for some time, in practice they become complications. No one should hesitate to operate in such cases on account of the diabetes. Operation may distinctly improve the state of the pancreas. The patient should, if possible, be given a preparatory course of insulin; it need not be long—two or three weeks are often sufficient to bring the blood sugar to normal, to restore the patient to an adequate carbohydrate diet, and to repair his nutrition.

Appendicitis and perinephric abscess may be so acute as to permit of no delay for preparatory insulin. In such cases large doses of insulin accompanied by glucose should be started at once, before or after the operation. Coma and suppuration are very grave dangers in these urgent operations. As an illustration of the dosage I may quote the case of a diabetic woman of 73 who underwent an urgent operation for gangrenous appendicitis. Before the operation she was living comfortably on 20 units of insulin (divided into two doses) daily. After the operation the insulin was increased to 20 units four times in the day. This dosage kept the urine sugar-free, but her blood sugar three hours after a feed was as high as 222 mg. per 100 c.cm. of blood. During convalescence the insulin was reduced to 15 units twice a day.

Dental abscesses and pyorrhoea are chiefly dangerous by lowering the carbohydrate tolerance, and as such need treatment. In diabetes all bad teeth should be removed, and all pockets of pus must be cleared out. Without insulin, general anaesthesia brings the risk of coma, and infiltration of the gum with local anaesthetics may give rise to sloughing.

NON-INFECTIVE COMPLICATIONS.

Among complications other than the infections arterio-sclerosis takes an important place, especially in protracted cases. It seldom occurs in young diabetics, and when it does it should lead to a suspicion that congenital syphilis

*Delivered at a meeting of the North Lancashire and South Westmorland Branch at Calgarth, Windermere, on December 5th, 1925.

is the cause of both conditions. I have met with at least three cases of severe diabetes in young subjects where the existence of congenital syphilis was proved.

As a rule the arterio-sclerosis seen in diabetes is of the senile type. The diabetes may not cause arterio-sclerosis, but it is a singular fact that the blood pressure in diabetics under the age of 35 is usually below normal; at 35 it reaches to about normal, and then as the age of patients increases the pressure is found to become progressively supernormal. Further, those diabetics who have high blood pressure have almost always arterio-sclerosis, aortitis, or granular kidneys. Perhaps the old-fashioned dieting with protein excess causes the high blood pressure and vascular changes, or arterio-sclerosis of the pancreatic vessels may cause the diabetes. However this may be, it is well worth while treating such patients with insulin. I have seen the most remarkable diminution of severe anginal pains in a male diabetic of 74, and a woman of 69 who suffered from continual headache with high blood pressure, attacks of unconsciousness, transient aphasia and hemiplegia, albuminuria and retinitis, was greatly improved with insulin. Her blood pressure fell from over 200 to 150. Moreover, she lost her headache and giddiness. On the other hand, another elderly woman died of cerebral haemorrhage in spite of insulin treatment of her diabetes.

The arterio-sclerosis of diabetes affects the vessels of the lower extremities and the heart more frequently than the vessels of the brain; in other words, it is of the senile not the syphilitic type. It is noteworthy that acquired syphilis is rare in diabetics. They do not seem to acquire syphilis after diabetes has developed, perhaps because diabetes notoriously lessens sexual desire and produces impotence. Moreover, there are relatively few instances of the pre-existence of syphilis. In my workhouse experience, where syphilis is so frequent among other patients, I find diabetics are rarely syphilitic.

Albuminuria is common in diabetes, but granular kidney is practically unknown until after the age of 50. Joslin considers deaths from uraemia rare in diabetes; yet in India, according to McCay,⁵ it is not infrequent. In pregnancy, at any rate, it would not always be easy to distinguish eclamptic from diabetic coma if it were not for the rarity of pregnancy in true diabetes. Renal complications of diabetes may be seen more often in future as modern treatment succeeds in prolonging life in this disease.

Cerebral arterio-sclerosis accounted for 33 deaths out of Joslin's 887, in the form of apoplexy or cerebral haemorrhage, hemiplegia, and paralysis. One must be especially careful to avoid excess of protein in dieting these cases. Insulin can be given without fear of ill consequences.

Heart disease appears usually in the guise of angina pectoris; valvular incompetence is rare, and we have seen that rheumatic fever scarcely ever attacks a diabetic. The myocardium suffers almost more severely than any other muscle from inability to utilize the sugar in the blood; thus it comes about that myocardial failure is responsible for so many of the unexpected deaths in acute disease (such as influenza and pneumonia) and after operations in diabetics. Insulin, in so far as it renders the blood sugar utilizable, is the only effective cardiac stimulant.

SKIN COMPLICATIONS.

Skin complications constitute a grave menace, first to the comfort of the patient, and secondly to his life. They may be divided into two main groups—the non-infective and the infective.

The non-infective group consists of those changes which are directly dependent on defective metabolism, and includes anhidrosis and xeroderma; pruritus, general and localized; urticaria; (eczema, generalized or confined to the genitalia); xanthoma; bronzed diabetes or haemochromatosis; (perforating ulcer). I have placed eczema and perforating ulcer in parentheses, as I question whether they are not always infective.

The dry, non-perspiring skin of diabetes requires special consideration as it contributes largely to the pruritus, eczema, and furunculosis to which diabetics are prone. An almost forgotten piece of research was published by

Rosenfeld⁶ (of Breslau) in 1906. He showed that by reducing the carbohydrate intake of healthy students the daily excretion of their skin fat could be brought to the same low level as that of a diabetic; and in this condition the hair follicles were made excessively susceptible to staphylococcal infection. The addition of fat to the diet did not increase the skin fat; the addition of carbohydrate immediately caused it to rise to normal, and therewith the skin became much more difficult to infect when cultures of staphylococci were rubbed into it. One lesson to be learned from this is to examine the blood sugar of all persons liable to boils; another is never to trust to the fasting treatment to cure the furunculosis of a diabetic. So long as a diabetic is not receiving enough insulin to metabolize such an amount of carbohydrate as will render his skin perceptibly greasy he will not be cured of the tendency to boils.

Pruritus is apparently connected in some way with the dryness of the skin; it resembles in some aspects the pruritus of persons who have senile and occasionally syphilitic skin atrophy. Or, like the urticaria which sometimes is so distressing, it may depend upon some chemical product of disturbed metabolism. Both conditions usually improve rapidly under insulin treatment.

Eczema is, I believe, invariably due to some secondary infection; the commonest is streptococcal or staphylococcal; but in women eczema pudendi is not infrequently associated with an epidermophyton infection—the fungus of dhotie itch, which may be present also in the cracked skin between the toes. There is no better culture medium for this fungus than a sugar-soaked skin.

Xanthoma, like xanthelasma, is in some curious way connected with fat metabolism. There is an excess of cholesterol present in the blood, and the xanthoma nodule consists almost entirely of cholesterol. These tumours disappear under insulin treatment or with a balanced diet, just as I have seen xanthelasma disappear in a young pregnant woman whose fat intake had to be greatly diminished during pregnancy on account of vomiting and acidosis. Her vomiting was cured and old-standing xanthelasma palpebrarum vanished when she was given almost fat-free diet.

The infective skin complications are, in addition to eczema: impetigo and ecthyma, folliculitis, furunculosis, carbuncles, whitlows, and, in my opinion, perforating ulcer. The latter may, indeed, start from a corn or callosity on the sole of the foot; but there is practically always a breach of the skin through which infection takes place. The treatment of all these conditions is the same. Prevention should be aimed at by keeping the skin exquisitely clean, by frequent (daily) change of linen worn next the skin; wool should be avoided, and the earliest signs of skin infection should be reported to the doctor. Above all, resort should be had to insulin when infection appears, even though dieting without insulin has kept the diabetes sufficiently under control.

EYE COMPLICATIONS.

These are common in diabetics of all ages, but after the age of 50 von Noorden⁷ estimated that some ocular trouble was present in 80 per cent. of cases. Retinitis and cataract are the most frequent. As yet we are not sufficiently experienced to state with certainty that by means of insulin these and other eye complications can be averted. I can only say that in several cases where retinitis has been present it has not improved under insulin treatment, but I am unable to distinguish diabetic retinitis from retinal arterio-sclerosis. Operations for cataract are rendered much safer by the use of insulin in good time beforehand.

SURGERY IN DIABETES.

Treves,⁸ in his *System of Surgery*, in 1896 wrote that "diabetes offers a serious bar to any kind of operation, and injuries involving open wounds, haemorrhage, or damage to the blood vessels are exceedingly grave in the subjects of this disease. A wound in a diabetic patient will probably not heal, while the tissues appear to offer the most favourable soil for the development of putrefactive and pyogenic bacteria. The wound gapes, suppurates, and sloughs. Gangrene very readily follows an injury in

diabetes, and such patients show a terrible proneness to a low form of erysipelas and cellulitis." That was a true picture of pre-insulin surgery, but now it need never be seen. As Lawrence⁹ says, "with insulin to aid us operations can be undertaken with practically the same safety as in normal individuals." In general, minimal operative intervention is indicated in diabetic patients, yet it must be radical enough in gangrene and infection to rid the patient of a focus likely to diminish carbohydrate tolerance. Surgeons and physicians sometimes delay surgical procedures in diabetics which in non-diabetic patients would be resorted to early and with favourable results. Yet early recognition of surgical complications is of the utmost importance in diabetics. Suppurative conditions, acute appendicitis, suppurative cholecystitis, pelvic suppuration, strangulated hernia, and, above all, gangrene, brook less delay than in normal individuals. Joslin¹⁰ has remarked that the complaints of diabetics to-day are one-quarter surgical, and if surgical delays are dangerous in ordinary circumstances, in diabetics they are disastrous.

The two principal dangers of operation are coma and sepsis. Both these dangers can be done away with if insulin is administered adequately and persistently. Many diabetics do not require insulin while in their usual health; dieting alone suffices for them, but when any operation becomes necessary insulin may be urgently needed to render them fit for it. After operation they may be able to dispense with further insulin and resort to simple dietetic measures once more. It is not the case that when a patient begins insulin it must be continued during the whole of a lifetime. A sufficient degree of carbohydrate tolerance may be re-established by the very operation which rendered insulin temporarily needful.

Operation cases are of two sorts—emergencies without time for preparatory insulin, and deliberate operations which allow time for preparation with insulin.

In emergency operations, where glycosuria is present without acetone or diacetic acid, 20 units of insulin may be injected before the anaesthetic is begun. It may be objected that there is danger in administering insulin without first determining the blood sugar. In the majority of cases of true diabetes the history of thirst, polyuria, and either obesity or emaciation, will distinguish the case from one of renal glycosuria with a low blood sugar. The probabilities of encountering renal glycosuria are not actually great. Moreover, glucose should always be at hand for oral, rectal, or intravenous administration in any event, since there is a chance that the dose of insulin given to a patient without previous blood sugar estimation will prove too large and produce symptoms of hypoglycaemia. This possibility would never deter me from giving insulin before an emergency operation. Hypoglycaemia is a less evil than an operation on a diabetic without insulin. As soon as possible the blood sugar should be estimated in order to regulate subsequent dosage. During after-treatment my practice is to tell the surgeon to order glucose rectally or in any other way he thinks advisable, just as though the patient had not diabetes. I then give insulin before each administration of glucose in the proportion of one unit of insulin for each gram of glucose ordered. If it is found that the blood sugar is high I add extra insulin; but as the case progresses I am careful to watch that the blood sugar does not fall below normal. It is carbohydrate that the post-operative case of diabetes needs; I give insulin so that the carbohydrate may be utilized, checking the intake of carbohydrate and the blood sugar in order to ensure that the patient is profiting by the carbohydrate. This, I believe, is the secret of making surgery safe for diabetics.

If there is time for deliberate preparation before operation, the blood sugar should be determined and the patient placed on an adequate diet *plus* insulin. There must be no attempt to prepare a diabetic for operation by starvation or undernutrition. This is inviting disaster. If on an adequate diet the patient's blood sugar is not at a safe level insulin sufficient for an adequate diet must be given forthwith. Further, a patient about to undergo an operation demands something above a barely adequate diet, particularly in its carbohydrate content. There are at least three reasons for raising the diet beyond the minimal

requirements: first, the condition which is making the operation necessary; secondly, the effect of the operation as regards shock; and thirdly, the anaesthetic.

ANAESTHESIA.

Anaesthetics by themselves constitute a grave peril to diabetics. For some reason at present not fully explained anaesthesia produces a rise in blood sugar, and it is an old experience that anaesthetics predispose to diabetic coma. Chloroform is the worst in this direction, and next comes ether. Gas and oxygen seems the least dangerous, but it is by no means invariably safe. Local anaesthesia is not devoid of risks. In dental practice, as in ordinary surgery, infiltration anaesthesia may lead to destruction of tissues with extensive necrosis and sloughing. Spinal anaesthesia may be followed by coma just as anaesthesia by inhalation. Dr. A. L. Flemming, my colleague and anaesthetist to the Bristol Royal Infirmary, long ago insisted on the fact that starvation before an operation could produce acetonæmia in non-diabetic patients; *a fortiori* starvation must be forbidden in preparing a diabetic for an anaesthetic. There is, in fact, no anaesthetic which is safe for a diabetic until he has been enabled to take an adequate amount of carbohydrate in his diet. For it must be always borne in mind that it is sugar that protects the diabetic, and insulin only renders the blood sugar utilizable.

PREGNANCY.

The subject of pregnancy and diabetes demands a few words. Whilst glycosuria without high blood sugar is common in pregnancy true diabetes is uncommon. Therefore a diagnosis of diabetes should not be made in pregnancy without blood sugar estimation. In the rare instances where a diabetic woman becomes pregnant or diabetes supervenes during pregnancy the prognosis is usually more serious for the foetus than for the mother. Premature labour takes place in nearly half the cases. Hydramnios is of common occurrence; the foetus may be enormous—overnourished apparently by the rich content of sugar in the maternal blood. It seems¹¹ that the foetal pancreas is practically never deficient, and some observers go so far as to declare that the foetal pancreas helps the mother, so that occasionally the diabetes improves during pregnancy. But it is very rare for pregnancy to exert a permanently favourable influence on a diabetic mother. It rather tends to aggravate the disease. Now, since the introduction of insulin diabetic women are becoming more fertile, and with adequate diet and insulin the pregnancy and confinement may be passed through uneventfully by both mother and foetus. It is imperative to keep a close watch on the mother's blood sugar, nutrition, and, more than all, to be on the look-out for acidosis or acetonæmia. Hepatic insufficiency is a danger even for the non-diabetic mother; it is still more to be feared in diabetes. The coma of eclampsia and diabetes may be difficult to distinguish. The same kind of precautions will guard against each. During pregnancy a diabetic woman may require an increased dosage of insulin; during the puerperium it may be even more essential. Puerperal infections, however slight, will certainly diminish carbohydrate tolerance, and the general principles which apply to surgery must be even more clearly observed. Lactation calls for exceptional nourishment of the mother; her diet will need to be increased, and with it the dose of insulin.

INSULIN ADMINISTRATION.

This subject can only be briefly touched upon. When a case of true diabetes develops a serious complication or intercurrent disease, or when a surgical operation becomes necessary, the last thing that must be thought of is treatment by fasting or the slightest degree of undernutrition. The patient must receive a diet which contains an adequate amount of protein and calories. A useful rule for calculating these requirements is to allow 1 gram of protein and 35 calories per kilogram of body weight. Several ways of determining these requirements have been suggested, but nearly all of them are based either on the body surface or weight of the patient as he is. In my opinion there is a risk of underestimating the real requirements by

weighing or measuring an unduly wasted body. I prefer to reckon how much the patient ought to weigh if in good health; for this purpose age, height, sex, and the general tendency of the patient's family should be taken into consideration. Having decided on this basis approximately how much the patient should weigh, I prescribe a diet which shall contain 1 gram of protein and 35 calories per kilogram of the assumed weight.

I use Woodyatt's formula for the proportions of protein, fat, and carbohydrate—namely, that the fat in the diet shall be equal to twice the carbohydrate plus half the protein. On this formula the minimal diet for a weight of 50 kilos (or 8 st.) is: fat 139 grams, carbohydrate 57 grams, and protein 50 grams. It is advisable to start immediately with the full adequate diet; there is no time when infection is present or an operation is about to be performed to commence with diets of the "ladder" type. The patient must be well fed from the start, and sufficient insulin must be given to keep the blood sugar at a safe level. It is not a bare subsistence the patient requires, but an allowance (of carbohydrate at any rate) which would nourish him if in good health and give a reasonable margin for combating the infection or facing the shock of an operation. I have already described how, in the after-treatment of operation cases, the surgeon is permitted to give the patient as much glucose, and in such a manner, as he would do if the patient were non-diabetic. Subsequently, as the surgeon modifies the diet, the insulin is adjusted to keep pace with it. But there must be no diminution of carbohydrate because the patient is diabetic. The insulin must be pushed in surgical emergencies as fearlessly as in the dreaded emergency of coma. For the treatment of coma the method recommended by Campbell¹² should be followed.

"Patients in diabetic coma who have not received treatment require larger doses of insulin. As speed is essential and the rate of action of insulin is only doubled by taking ten times the dose, we commonly use 100 units of insulin intravenously as the initial dose. Most of the coma patients are dehydrated and fluid must be supplied liberally. Some of this may be given intravenously as 10 per cent. glucose solution, at a rate not greater than 10 c.cm. per minute. If the pulse rises ten beats per minute, discontinue the injection. Normal saline or 5 per cent. glucose may be injected interstitially and given per rectum by the Murphy drip method after a cleansing enema has been given. Many patients difficult to rouse will respond by automatic swallowing movements when a teaspoonful of fluid is poured into the mouth. Except by direct injection into the circulation it is doubtful if too much fluid can ever be administered to a diabetic in coma. Warmth must, of course, be provided. The room should be warm and warm blankets and hot-water bottles used. Circulatory stimulants should be begun early, digitalis and coffee by mouth or per rectum being the most satisfactory stimulants, pituitrin and ether being used for more acute emergencies. In my opinion alkalis in moderate doses, 15 to 30 grams NaHCO₃, are of value when administered by mouth or per rectum in 5 per cent. solution. The intravenous injection of sodium bicarbonate solution is to be employed with caution as it may induce cardiac dilatation and failure. Hypoglycaemia must be avoided and carbohydrate must be available to replace the defective fat metabolism as well as to burn up the ketones already produced. This is provided by giving the patient approximately 1 gram of sugar for each unit of insulin. The use of a retention catheter and testing the urine for sugar each hour will give ample warning of a deficiency of available carbohydrate."

THE TRANSMISSION OF BLOOD SAMPLES.

I have been asked how blood may be sent by post for purposes of blood sugar estimation. The following plan is one that I have found useful and effectual. With a hypodermic syringe withdraw 1 c.cm. of blood and empty it into a small glass tube (such as is used in laboratories for precipitation tests—Widal, Wassermann, etc.) containing a few crystals of neutral potassium oxalate. Shake the blood thoroughly to mix it with the oxalate and prevent clotting. Wash the hypodermic syringe well with plain water and then absolute alcohol. Draw up into the syringe exactly 0.2 c.cm. (or 5 minims) of oxalated blood, then fill the syringe exactly to the 1 c.cm. mark (or to the 20 minim mark) with absolute alcohol. Shake well and empty the contents of the syringe into a second small glass tube. Cork tightly and dispatch, properly packed, by post. The mixture of oxalated blood and alcohol will contain a 1 in 5

solution if the syringe was graduated in cubic centimetres, and a 1 in 4 solution if graduated in minims. The blood sugar can be estimated accurately from the alcoholic solution.

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NOVASUROL AND OTHER DIURETICS IN CARDIAC OEDEMA.

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THE value of mercury as a diuretic in the treatment of cardiac dropsy has long been recognized, the drug being usually prescribed along with digitalis, as in Guy's pill. The combination of digitalis with mercury was so much the rule that some doubt existed as to whether mercury possessed any diuretic action independent of its association with digitalis. This point may be said to have been settled, as mercury in the form of metallic mercury (pil. hydrarg.), for example, will increase the elimination of urine in cardiac dropsy apart from the administration of digitalis, though the diuresis may not be so marked as when the latter is given as well. The appearance, therefore, of an organic compound containing a large percentage of mercury, capable of being injected intramuscularly or intravenously, and exhibiting powerful diuretic properties, is of interest.

Novasurol has been studied in America and in Germany, but, save for a recent article by Dr. A. R. Gilchrist of Edinburgh, observations upon its clinical use do not seem to have been reported in this country. It contains 33.9 per cent. of mercury, and the dose is 1 c.cm. of a 10 per cent. solution. The amount of mercury, therefore, in one dose is comparatively small—only 0.0339 gram, or about that contained in 1½ grains of pil. hydrarg.; nevertheless, the diuretic action is much more pronounced than in the case of metallic mercury administered in the usual way by the mouth. As the mercury in novasurol is not in an easily ionizable form, it possesses a low toxicity and is non-irritating locally, provided that none escapes into the subcutaneous tissues. Moreover, griping and a tendency to diarrhoea—drawbacks attendant upon the oral administration of mercury—are obviated. The solubility of the drug, permitting of its rapid absorption from the site of injection, probably favours a more intense and rapid action than that exhibited by metallic mercury or calomel.

CASE I.

This case appeared to be peculiarly suitable for the study of various diuretics. The cardiac failure was progressive, little influenced by digitalis and not complicated by any abnormal rhythm. A record of the output of urine over a period of 109 days, during which different diuretics were administered (see graph), shows that novasurol was capable of causing a profuse diuresis when all other diuretics, including metallic mercury, had failed. The patient was a man, aged 68, suffering from syphilitic aortitis, with aortic and mitral incompetence and oedema of the legs, together with some ascites. The urine contained traces of albumin, while the blood urea nitrogen was 22 mg. per cent., and the blood chlorides 450 mg. per cent., showing that there was no evidence of chronic nephritis. He was put on a light dry diet and the intake of water was kept approximately constant. During the first week no drugs were given and the effect of rest in bed was observed. Then tincture of digitalis $\text{m} \times \text{t.i.d.}$ was administered, and no increase in the urine was noted. On the twentieth day caffeine gr. iij t.i.d. was added, but little if any change in the output of urine followed. The digitalis and caffeine were then discontinued and urea in large doses, 15 grams thrice daily, was given over a period of five days, when the volume of urine increased from 600 up to 2,590 c.cm., after which it gradually returned to the previous level. When the output had decreased to about 400 c.cm., digitalis and