that the degenerative changes in the thyroid following hypophysectomy are repaired following implantation of anterior lobe substance.

Uhlenhuth would seem to be justified, therefore, in ascribing the metamorphic effect of anterior lobe extracts to the presence of an activator of the thyroid therein. Be that as it may, our own experiments show that not only is the metamorphic factor not identical with the growth hormone—as has been concluded by Spaul—but that it also differs from the gonadotropic hormones. It may be assumed, therefore, that a fourth anterior pituitary hormone (theta) exists. Further experiments will have to show whether it is thyrotropic, as it seems to be.

INTRAVENOUS PYELOGRAPHY.

BY

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EVER since Ehrlich in 1906 produced salvarsan, scientific workers all over the world have been looking for an anti-septic which, when injected intravenously, shall be harmless to the body tissues and yet be able to kill micro-organisms. Their ideal has never yet been realized, but many useful synthetic products have resulted from their search. Uroselectan (sodium 2 oxy-5-iod pyridine-N-acetic acid) is one of these.

For some years prior to 1928 Professor Binz and Dr. Raeth had been experimenting with an organic compound of iodine selectan-neutral, which, it was hoped, would be of use in coccal injections of the biliary and urinary tracts. Erbach, moreover, had shown that this compound, with a high molecular weight, was excreted in part by the kidneys, and naturally these facts suggested that it might throw a shadow of the urinary tract on radiographic examination.

Experiments to this end were carried out by Swick¹ in Lichtwitz's clinic, with only more or less satisfactory results. The clarity of the shadows was variable; they were not sufficiently dense for reproduction, and it was found that, whether the compound was administered by the mouth or intravenously, there was a good deal of individual variation in tolerance. Furthermore, a large number of reactions, such as headache, sickness, and vomiting, were recorded. For these reasons it was later on suggested by Swick and von Lichtenberg that sodium glycin should be substituted for a methyl group, and the solubility of the compound increased by a slight reduction of the iodine content. This work was carried out by Binz and Raeth,² and the compound called uroselectan was the result. The formula of the preparation is shown below.

Chemical and Physical Properties.

It is neutral, soluble in water to more than 50 per cent., and contains 42 per cent. of iodine. Its opacity to x rays is shown in Figure 1. It is an extremely stable chemical compound, which can be introduced into the blood stream in relatively large amounts. If deductions from animal experiments³ are reliable, it is possible to give an intravenous dose of 180 grams to a man weighing 50 kilos, but for clinical purposes 40 grams is all that is necessary to

produce perfectly clear-cut shadows. This amount is dissolved in 80 c.cm. of redistilled water, filtered twice, and autoclaved for twenty minutes. The result is a heavy brown solution, which, however, contains no free iodine. Experiments have been made with a view to sterilizing it by boiling, and a solution boiled for three hours has been used with no ill effects. For children the dose is proportionately smaller. Up to the age of 6 we inject 10 to 12 c.cm. of the 40 per cent. solution; from 6 to 10 years, 20 to 40 c.cm.; and from 10 to 15 years, 50 c.cm.

Technique.

The patient is prepared for the x rays in the usual way, and a preliminary radiogram is taken. The solution at body heat is then injected slowly into a vein, preferably in two equal doses, at an interval of from two to three minutes. For routine purposes radiograms are then taken, a quarter of an hour, three-quarters, and one and a quarter hours after injection.

Generally speaking, the rate of excretion bears a direct relationship to the renal function, as determined by the ordinary tests, and after a quarter of an hour in cases with a good renal function, not only is the whole urinary tract clearly visible, but there is a definite increase in the normal renal shadow. This latter is naturally more easily appreciated in the film than in a reproduction. The standard of radiographic technique demanded is high. The

FIG. 1.—1. Uroselectan. 2. Half uroselectan and half 2 per cent. urea. 3. Half uroselectan and half 4 per cent. urea. 4. 2 per cent. urea. 5. Water. 6. 20 per cent. sodium iodide.

shadow thrown by the drug as it is excreted by the kidney is not quite as dense as that ordinarily obtained by the introduction of media through ureteric catheters, and it is therefore of paramount importance that the maximum contrast should be obtained upon the radiogram. For this reason we use a low penetrating ray such as is emitted from a tube excited by a maximum potential of 65 kilovolts peak.

A Potter-Bucky diaphragm fitted with a pressure band in conjunction with double intensifying screens is used, the focal plate distance being thirty inches. With a milli-ampere of 60, the exposure will vary with the bulk and build of the patient, and will ordinarily be from one to five seconds. The radiograms are developed for five minutes in a standard developer heated to 65° F. precisely. The radiograms when completed are examined in lanterns of equal illuminant power. No variation from the normal procedure is permissible.

It must be pointed out that important information is obtained by comparing radiograms of a series, and any variation in the relative density of the drug-laden urine must be independent of variations in radiological technique. Several of our patients were radiographed at three-minute intervals, and in one patient radiograms were obtained at intervals of five seconds. Should such procedures become general, and the results of more than academic interest, it may be necessary to devise serial changing cassette holders working in conjunction with a Potter-Bucky diaphragm. The cinematograph may in the future give the perfect serial visualization of kidney function.

CASE I.

This case indicates clearly the results which can be uniformly obtained in a patient with a relatively normal renal function. The radiogram (Fig. 2) shows a stone clearly outlined in the slightly dilated pelvis of the right kidney. The left kidney is normal. There was in this case no need for cystoscopy, although it was carried out as a check on a new method. Fig. 3 shows the slightly dilated pelvis of a movable kidney. The outline of the upper ureter and the increased density of the renal shadow are also clearly seen.

CASE II.

The radiogram (Fig. 4), taken after operation, shows clearly a filling defect in the lower calyx of the right kidney of a youth aged 19, who was the victim of a "buffer accident." His kidney was split in front and behind to a depth of 1 cm.

visualized. Normal shadows sometimes show more dilatation than is usually visible with ordinary pyelography, probably because spasm due to the presence of a catheter is eliminated. In order to show up the lower ureter it is necessary to empty the bladder before making each routine exposure. We have not succeeded, as others have done, in visualizing on screen examination the pelvic shadow accurately enough for pyeloscopy.

Interpretation of Results.

In our series of about sixty radiograms we have noticed that the shadow of the left kidney appears slightly less dense than that of the right. This is apparently not dependent on a diminution of renal function.

FIG. 2.

FIG. 3.

FIG. 4.

Reactions of Patients to Injection.

In our experience, and in that of others, the injections have been followed by no ill effects. Within a few minutes the pulse rate is increased by 10 to 15 beats to the minute and the blood pressure is raised 10 to 12 mm. of mercury. These both return to normal within fifteen minutes, and remain so. During this short period of raised blood pressure some patients complain of slight giddiness. Occasionally there is a transient cramp in the anterior shoulder muscles, but this is in no way distressing. A patient who was very nervous and complained of giddiness was easily able, immediately after injection, to stand up for screen examination. In one case a small quantity was injected outside the vein. From this accident no ill effects were observed. After injection no free iodine is found in the blood and urine, and in cases with a normal renal function no iodine can be found in the blood within a quarter of an hour of injection.

Experience has shown that the injection can be given perfectly safely even in cases with such a marked decrease of renal function that the dye has been retained in the circulation from twenty-four to thirty hours. The only known contraindications to its use are anuria, uraemia, and cases in which the liver as well as the kidney are grossly diseased. One death in such circumstances has been reported.⁴

General Consideration of Results.

Very often, owing to the rapidity with which the urine runs down into the bladder, the whole line of the ureter is not seen unless serial radiograms are taken. If, however, there is any blockage of the ureter from stricture within, or from pressure without, the ureter is easily

As a rule, uroselectan is very rapidly excreted unchanged. We have serial radiograms taken at three-minute intervals after injection in several cases. Generally speaking, there is a satisfactory shadow after six minutes, and in fifteen minutes there is a perfectly clear outline of the whole of the urinary tract. In one case where radiograms were taken at five-second intervals all the major calyces were faintly but definitely outlined five minutes after injection. Within six hours 80 to 90 per cent. of the iodine is eliminated.

Dr. Obermer, to whom we are greatly indebted, has been unable to find any trace of free iodine in the urine of patients after injection. Fig. 5 shows the relative opacity of the urine secreted at varying intervals.

Uroselectan is easily recovered from the urine. On the addition of hydrochloric acid it forms a heavy white precipitate when the pH reaches 2.8 to 3. It can therefore be used as a good test of renal function. Chemical estimation, however, is not always necessary, because, as Fig. 5 shows, the specific gravity is a very reliable guide to the amount of the drug present. It should reach

FIG. 5.—1. Urine passed a quarter of an hour after injection; sp. gr. 1030. 2. Half an hour after injection; sp. gr. 1037. 3. Three hours after injection; sp. gr. 1050. 4. Five hours after injection; sp. gr. 1045. 5. Ten hours after injection; sp. gr. 1030. 6. Sixteen hours after injection; sp. gr. 1027. 7. Twenty-one hours after injection; sp. gr. 1015.

between 1045 and 1050 within an hour, during which period the bulk of the drug is excreted. Whether, as a test of renal function, it is as reliable as the indigo-carmin or the urea concentration tests, remains to be seen. There exist facts which suggest that infection is much more potent in retarding its excretion than that of indigo-carmin.

Von Lichtenberg states, and our experience confirms his view, that while an advanced non-infected hydronephrosis will give an excellent though perhaps delayed shadow, a pyonephrotic and infected or a congested kidney may give no shadow at all.⁵

CASE III.

The radiograms in this case (see Fig. 6) illustrate excellently how an infected kidney may fail to yield a shadow. The right kidney pelvis, which filled within a quarter of an hour, is dilated, and shows cupping of the calyces, possibly due to an infection. There is no uroselectan shadow of the left kidney, but the faint outline of multiple calculi can easily be seen. At biopsy, after operation, multiple chronic staphylococcal abscesses were found scattered throughout the renal cortex.

FIG. 6.

From the patient's point of view this in itself is the greatest possible advantage.

In cases where cystoscopy and catheterization of the ureters is difficult or impossible its routine use will be a necessity—for example, in children, and patients with ureteral strictures or pelvic tumours which compress the ureters from without. In cases of movable kidney it is easy to estimate the degree of mobility because the patient can stand up, or, in fact, assume any position that circumstances may require.

The disadvantages are two—namely, its expense, which is considerable, and the fact that no shadow is obtained when the renal function is greatly diminished.

It is probable that in the future intravenous pyelography will invariably be carried out before the decision is arrived at that the patient must be submitted to the ordeal of ureteric catheterization.

REFERENCES.

- ¹Swick: *Klin. Woch.*, 1929, No. 45, p. 2087. ²Ibid. ³Ibid. ⁴Ibid.
⁵Von Lichtenberg and Swick: *Klin. Woch.*, 1929, No. 45, p. 2089. ⁶Ibid.

SWELLING OF THE FEET AND ANKLES NOT ASSOCIATED WITH ALBUMINURIA OR GROSS ORGANIC DISEASE.

PATHOGENESIS AND TREATMENT OF A COMMON SYMPTOM.*

BY

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OEDEMA without albuminuria occurs in a variety of well-known conditions, such as several of the anaemias, chlorosis, war oedema, starvation oedema, beri-beri, and varicose veins in the legs. It also not infrequently precedes the appearance of albuminuria in the early stages of some cases of nephritis and pregnancy kidney. The type of oedema which is described here, however, is one which is quite commonly met with, especially among patients of the so-called hospital class, though it is by no means confined to them. It cannot be ascribed to any of the conditions already enumerated, and is seen chiefly in adult women, in the form of "puffiness," or swelling of the feet and ankles. It is, however, occasionally met with in debilitated adult males, and even in children. In women,

not always of the poorer classes, it is the cause of much misery and distress, partly for cosmetic reasons, and also because in bad cases walking is difficult or impossible, and so leads to loss of employment. Tennis and dancing also have frequently to be given up because of this symptom. The milder cases do not seek advice for this, but for associated symptoms of that state of subnormal health commonly called "debility," such as headaches, constipation, lassitude, amenorrhoea, etc. Other patients complain chiefly of swelling of the feet, and are diagnosed as cases of anaemia, and iron, tonics, and various glandular extracts are prescribed. Some of the wealthier resort to beauty parlours, where they are given massage and local hypertonic salt compresses. As a rule none of these measures appears to be very effective in affording relief for this exceedingly common symptom.

The Pathogenesis of "Swollen Feet."

There are, of course, several varieties of "puffy," swollen, or "thickened" feet and ankles which are not associated with cardiac, renal, or other gross organic disease. In some cases the swelling is due entirely to an increase in the water content of the tissues of the part, in others to excess of fat, and again in others to a combination of excess of both water and fat. There is also the variety associated with blueness of the extremities, referred to by Parkes Weber¹ under the descriptive title of "erythrocyanosis crurum puellarum." No hard-and-fast line can be drawn between these conditions in many cases, but this paper is concerned only with the enlargement of the extremities, generally the feet and legs, due to true oedema, or excess of water in the tissues.

As will be seen later, there is reason to believe that the relative frequency with which the oedema is complained of in the feet and ankles is probably due entirely to the effects of gravity, as in reality the excess of water, or oedema, is present in all the tissues of the body, though often not in sufficient amount to attract attention. During the course of the day the oedema tends to drain down to the feet, and by the evening has there collected in sufficient amount to be noticed by the patient.

The following case is typical of the disorder which is being considered here.

A lady, aged 36 years, was sent to the out-patient department complaining of pains and swelling in the feet and legs, most marked in the right ankle, which she had noticed for several months. The swelling was most prominent in the evening, and had usually almost disappeared on rising in the morning. The periods were regular, but rather scanty. The swelling was always much worse at the time of the menstrual periods. She had frequent severe headaches and a tendency to constipation. Six months ago she had lumbago, the only definite illness she remembered having had in her life. She was pale, and the complexion was "greasy" and spotty. The hands were not swollen or blue, but were clammy and sweaty. Examination of the heart revealed nothing abnormal, and there was no albuminuria. There was no obvious focus of sepsis. She was unmarried. The blood pressure, blood urea, and urea concentration were all normal. A blood examination, for which I am indebted to Dr. L. Hewlett, showed: red blood cells 5,936,000 per c.mm., haemoglobin 90 per cent., colour index 0.8. The plasma bicarbonate was 0.0278 M. (normal=0.0300 M.). The urine contained no albumin. It is clear, then, that in this case neither heart disease, kidney disease, nor anaemia provides an adequate explanation of the oedema. The latter was not sufficient to prevent walking, but it was of that degree which would have attracted the attention of lay persons.

Elsewhere² it has been shown that "debility," whether occurring in children or adults, is a state which is generally associated with some degree of "acidosis," which, in turn, is frequently accompanied by an increase in the water content of the body as a whole. The term acidosis was defined as a reduction of the concentration of bicarbonate in the plasma, and therefore does not necessarily imply any change in reaction (pH) of the blood.

It is suggested here that it is this underlying "acidosis," the exact cause of which is not known, which leads to excess of water in the tissues, and that in minor degrees of the disorder the accumulation of fluid is only sufficiently great to attract attention under the influence of gravity, and hence the frequency with which it apparently occurs in the feet and ankles alone. Taking the group as a whole, there is a considerable diminution in the plasma bicarbonate values in these waterlogged subjects, compared

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