in such a case blood can occasionally be seen in the orifice of the Eustachian tube if the nasopharynx is examined with a mirror. These patients completely recovered their hearing in three weeks, when the blood in the middle ear had disappeared and the drum was normal. More commonly the upper half of the drum is ruptured and blood freely escapes into the auditory meatus and down the Eustachian tube to the nose and pharynx. If it is accompanied by the leaking of cerebro-spinal fluid, the fracture is a severe and dangerous one, opening up the subarachnoid space, and all such cases in my experience have been fatal. It is also significant that in the few recorded cases where the internal ear has been fractured the escape of cerebro-spinal fluid has been present. A detailed and thorough investigation of the injuries to the middle and internal ear arising from fractures of the skull has been made by J. S. Fraser, and he gave at the Otological Section of the Royal Society of Medicine in 1916 a full description of the lesions found in a series of cases.

When haemorrhage from the ear is profuse and prolonged it is an indication that the middle meningeal artery or lateral sinus has been ruptured and urgent operative treatment is called for. The auditory meatus is sometimes a vent for this extradural haemorrhage, and should never be firmly plugged. Fortunately the lateral sinus is not often ruptured, and the pressure of the brain and the increased intracranial tension are sufficient to arrest venous bleeding. Haemorrhage from both ears is always an unfavourable sign, and the mortality is 66 per cent.²; whereas in cases of haemorrhage from one ear the mortality is 39 per cent. The average mortality of all cases of fracture of the base of the skull is about 40 per cent.

In those cases where a middle-ear suppuration has existed before the injury, the probability of a meningeal infection is very great and the prognosis is correspondingly unfavourable. In some cases the injury to the ear is followed by a local suppuration which materially adds to the damage, and spicules of bone from a comminuted fracture of the roof of the middle ear and meatus may be found. Mastoid suppuration has also been known to follow a fracture, and such a complication is liable to lead to a meningeal infection.³ Fraser reports a case of otitis media and meningitis which followed twelve months after the fracture of the skull. The injury undoubtedly facilitated the spread of the infection to the meninges. Some of these cases of local suppuration when seen late cannot be distinguished from the ordinary chronic middle-ear suppuration occurring without injury, hence the necessity for examining these patients as soon after the accident as convenient. The history of the absence of deafness and ear disease previous to the injury must be verified when the question of compensation arises.

A peripheral paralysis of the facial nerve has been recorded in about 46 per cent. of fractures of the middle fossa of the skull. It arises in the more severe type of injury, and in a few cases the eighth nerve is involved as well; but in the small number of cases of facial paralysis seen by me the eighth nerve escaped injury. The facial nerve is involved by the fracture as it passes through the facial canal, particularly near the geniculate ganglion. The onset of the paralysis is almost immediate, but if it is delayed this is probably due to haemorrhage into the facial canal, when recovery of the paralysis is more rapid. All the patients seen with paralysis recovered even after long intervals.

The degree of deafness arising from fractures of the skull shows considerable variation. In a number of cases no deafness was reported, and twenty-five cases seen by me on account of deafness were all of the middle-ear type. The four patients in whom effusion of blood into the middle ear was the only detected lesion all showed marked middle-ear deafness when first seen; they completely recovered their hearing with the disappearance of the blood at the end of three weeks, and it was then impossible to detect any lesion. Another case seen twelve months after a severe fracture of the skull, in which the sixth, seventh, and part of the third cranial nerves were paralysed, revealed only a slight degree of middle-ear deafness. The patients in whom fracture was followed by local suppura-

tion and inflammation suffered most loss of hearing; the deafness also became permanent. Any improvement in hearing usually occurs within about eight weeks from the date of the injury, and any deafness remaining after that period is permanent. I have not seen a case of genuine internal-ear deafness arising from concussion alone or from a head injury with such signs of fracture described previously. It is probable that the subjects of injury to the internal ear all die.

The treatment of these injuries to the ear is not always one of masterly inactivity, and a careful watch should be maintained for the onset of suppuration. Absolute rest in bed for a long period is essential, and the less that is done to the ear the better. The head is raised and a number of pillows are allowed. The auditory meatus is gently cleaned with spirit; a piece of sterile wool is lightly placed in the orifice and changed frequently. If there is any discharge of cerebro-spinal fluid the skin should be dried and smeared with an antiseptic ointment such as the dilute yellow oxide of mercury. Packing of the meatus with gauze, and, of course, syringing and drops, are to be firmly deprecated. If suppuration arises the whole aspect of the case is changed and vigorous methods should be adopted to establish free drainage. The drum should be incised if necessary, and there should be no hesitation in performing a simple mastoid operation at the slightest indication. The mastoid operation must be conducted gently, preferably by a motor burr or drill to avoid the jarring of the mallet and chisel.

The early recognition and treatment of suppuration is essential to the prevention of the dangerous meningeal or intracranial infection.

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UNCOMMON ILL EFFECTS OF SALVARSAN TREATMENT.*

BY

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FATALITIES from salvarsan therapy do not stand in the front of the minds of the present generation of venereal specialists as they did amongst those who first used this drug with trepidation, and hope, in 1911. For when the arsenobenzols were originally introduced their use became associated with a formidable list of ill effects.

Experience has not demonstrated any certain method by which the type of patient unsuitable for salvarsan therapy can be picked out and treated in other ways;¹ neither old age, aneurysm, phthisis, chronic Bright's disease, high blood pressure, nor severe valvular disease of the heart can, in themselves, be considered as contraindications to its use. Ill effects may follow the administration of small doses²; they may occur at the beginning, at the middle, or at the completion of a full course of salvarsan treatment. No brand of manufacture seems to be exempt, though at times a run of toxic effects from the use of any one make compels the physician for expediency to omit this temporarily from his armamentarium. It would be wrong to say that these remedies are safe remedies, though I would be the last to express anything but gratitude for their invention and the highest appreciation of the way in which this country has been saved from an epidemic of syphilis by the energetic establishment of venereal clinics after the war by the Ministry of Health. The rarity of congenital syphilis must be most gratifying to the officials of the Ministry of Health, when they reflect upon this matter.

Dr. E. T. Burke has recently published a treatment of venereal disease (1927), in which four and a half pages are given on untoward effects of salvarsan therapy. The ill effects there referred to are:

"headache, shivering, vomiting, dyspnoea, palpitation, fainting, and so on. During the actual injection there may be nausea,

* A paper read in the Section of Dermatology at the Annual Meeting of the British Medical Association, Cardiff, 1928.

and vomiting, a feeling of fullness in the throat, a huskiness in the voice; the face may become flushed and the conjunctivae injected. At times there are severe cramps in the limbs and abdomen, diarrhoea and cardiac distress, and in many of such cases there is undoubtedly a psychological factor at work."

After these immediate reactions Dr. Burke records an intermediate type of general or local urticaria or an oedema of the face and hands. Haemorrhagic encephalitis is included in this group, which may be rapidly fatal. He states that it seems to occur most frequently among alcoholics. I have seen but one case, and it occurred in an abstemious primipara.

Under the title "delayed reactions" he refers to "exfoliative dermatitis most prone to occur in neurotic patients." Jaundice is the other and last-mentioned untoward effect. This record might, I think, be fairly considered as a minimizing report when contrasted with the following two accounts. The list collated and published by the Salvarsan Committee of the Medical Research Council³ in 1922 recorded cases of urticaria, discrete erythema, papular erythema, exfoliative dermatitis, pemphigoid eruption, Raynaud's syndrome with gangrene, and purpura as toxic effects following the employment of arsenobenzol preparations. Mouradian⁴ published an appalling list of "accidents." These included cases of intestinal paralysis, serious uterine haemorrhage, choleric diarrhoea, cephalalgia with migraine, epileptiform convulsions with sensorimotor troubles, febrile icterus, epistaxis, and haematuria followed by anuria.

The cases recorded below are outside this list and are of interest because of their gravity and apparent rarity. I feel certain that many cases are lost sight of through the dissociation of clinics from general hospitals or because such ill effects are delayed and the practitioner in attendance is not in touch with the salvarsan administrator.

CASE I.—Post-salvarsan Melanodermia.

A dark, well-built man of 50 was infected with syphilis when 17, and was treated then with caustic to the sore and six months' medicine. In 1923 his Wassermann reaction was positive, and he received eleven doses of neosalvarsan between the end of December, 1923, and the middle of January, 1924, from a competent private doctor. After the eleventh injection his skin became so uncomfortable that he changed his doctor. He was sent into the London Hospital on July 1st, 1924, with general erythrodermia and free generalized exfoliation. A differential blood count showed: stained blood leucocytes 14,300 per c.mm., polynuclear neutrophils 80.5 per cent., polynuclear eosinophils 2 per cent., small lymphocytes 5 per cent., large lymphocytes 5 per cent., large hyaline cells 8.5 per cent.

By September 18th the exfoliation and redness had disappeared: the patient's skin was smooth but deeply pigmented, as dark as an Indian's, most uniform in the large flexures, but elsewhere on the trunk and limbs were numerous small circular areas of sharply defined white skin.⁵ A photograph of this startling condition was published in the *British Journal of Dermatology*, 1925 (p. 87).

This condition has been vaguely recorded by two French writers, Goulay⁶ and Bouteillier; Goulay says that arsenobenzol erythrodermia leaves some kind of melanodermia, and Bouteillier contrasts the great frequency of exfoliative erythrodermia with the rarity of melanodermia and keratodermia. (See Case II.)

CASE II.—Post-salvarsan Maculo-melanodermia with Follicular Hyperkeratosis.

An unmarried French-polisher, aged 26, came to the London Hospital in June, 1927, with a primary syphilitic sore of six weeks' duration, together with inguinal adenitis and a faint macular eruption on the thorax. The Wassermann reaction was positive. He was treated with seven weekly injections of neokharsivan, one of 0.6 and six of 0.9 gram. Two weeks after the last injection both legs were red and swollen. He stayed at home until December 19th, giving a history that he had become red, had skinned all over, and had lost a good deal of his hair. There was now a startling dappled appearance of the skin of his trunk, neck, and upper limbs, due to a macular, non-infiltrated deposit of brownish-black small ovals of pigment. There was no generalized adenitis, no relapse of the primary sore, but over the trunk, thighs, and arms, both in front and behind, was a most profuse development of projecting small uncoloured horny spines protruding from uninfamed pilo-sebaceous orifices. He was admitted to the London Hospital on January 2nd, 1928; since then a very few spines have become reddened, many have developed blackened tips and can be expressed like hardened comedones; in addition, he has developed a moist eczematous plaque on his right wrist, and a small, infiltrated, pink, slightly itching eruption of the right anterior axillary fold.

There are now no condylomata, no buccal lesions, or pigmentation. The patient feels thoroughly well and has a negative Wassermann reaction. There is no arsenic in the urine and no albumin; the total and differential blood counts show no abnormality.

I showed this case at the Royal Society of Medicine⁷ on January 19th, 1928, and an excellent photograph will be found in the *London Hospital Gazette* of March, 1928.

CASE III.—Multiple Subcutaneous Abscesses Associated with Arsenical Exfoliative Dermatitis.

A woman, aged 32, attended my clinic at the London Hospital in February, 1927, with a primary sore and several secondary skin lesions. The Wassermann reaction was positive. She was given an intravenous injection of 0.6 gram of neosalvarsan on February 27th, and this was repeated on March 6th, 13th, and 27th.

On April 4th the patient developed an irritating generalized morbilliform rash, and was given sodium thiosulphate intravenously. She was admitted into hospital. The whole skin gradually became uniformly more thickened, moist, and weeping in the flexures, cracked and scaling elsewhere. There was an abnormal enlargement of glands. There was profuse diarrhoea with occasional blood in the stools, the temperature ranging between 99° and 102° F. The output of urine at times fell below 20 oz. per diem and showed albumin. The patient lay supine in bed in a typhoid state.

During this time a great number of subcutaneous abscesses developed, resembling the "cold abscesses" of tuberculous infections in that there was an absence of any surrounding inflammatory reaction. Over forty of these abscesses were opened, one to two eggcupfuls of thick blood-stained pus being evacuated from each. Cultures from this pus showed the presence of *Staphylococcus aureus*. This phase extended over three weeks.

Towards the end of May the patient's condition began steadily to improve, the thickening of the skin diminished, the fissuring and exfoliation abated, and no new abscesses were formed. There was no shedding of hair or nails. On June 12th she was able to walk unaided; there was only slight scaling of the limbs and round the orbits, and the patient's general condition was sufficiently good to allow of her discharge from the ward, she having rapidly and steadily gained weight. Her appetite remained good throughout the illness, in spite of the fact that on more than one occasion recovery seemed a remote possibility.⁸

CASE IV.—Cutaneous and Subcutaneous Necroses, Perforation of the Nasal Septum with Arsenical Exfoliative Dermatitis.

A man, aged 42, a caretaker, had a primary penile sore and generalized rash in 1908, and was treated, when in the navy,

FIG. 1.—Case IV. Salvarsan necrosis of skin and bone.

with thirteen mercurial injections. His Wassermann reaction was negative in 1920.

On August 16th, 1927, he attended the syphilis clinic of the London Hospital with a well-defined ulcer on the right leg. The Wassermann reaction was weakly positive. He had four injections of neokharsivan, 0.9 gram, at weekly intervals. Six days after the last injection the eyes became puffy, and he developed a universal lividity of the skin. He was admitted into the ward on October 3rd, and treated at once with intravenous sodium thio-sulphate. He showed a generalized erythema, puffy face, swollen limbs, and temperature rising daily from 98° to 104° F. in a fortnight. There was no enlargement of the spleen; no bradycardia. The urine showed a trace of albumin; no sugar; deposit—few leucocytes, epithelial cells, and amorphous urates. No tubercle bacilli were found. Culture showed the presence of *B. protus*.

Blood examination on October 13th showed: stained blood leucocytes 30,000 per c.mm., polynuclear neutrophils 48 per cent., polynuclear eosinophils 41.5 per cent., small lymphocytes 7 per cent., large lymphocytes 1 per cent., large hyaline cells 2.5 per cent.

On November 7th the patient developed an acute abscess of the neck. A probe was introduced and passed between the skin and structure of the neck for three inches on the right side. In addition there were gangrenous sloughs on his back and right

FIG. 2.—Case IV. Salvarsan necrosis of bone of heel.

heels. The nasal septum perforated. The previous day the heels and back were in perfect order. A radiogram taken on December 22nd showed necrosis of the bone of the os calcis. At this time both legs were markedly pigmented. The patient was discharged well on January 3rd, 1928.

CASE V.—Pulmonary Embolism.

This man was first seen on January 21st, 1927, with a primary syphilitic sore. He was treated at the London Hospital with seven weekly injections of novarsenobillon; the last six doses were 0.9 gram. Early in March he had some irritation of the neck, which he treated with iodine, and on March 6th he was admitted with exfoliative dermatitis. He became extremely ill with high fever, delirium, and albuminuria; he recovered from this, but his nasal septum perforated. On April 7th he complained of small boils on the left axillae and right groin. I examined him at 2 p.m. on April 12th, when he seemed fairly well, able to sit up in bed unassisted, tongue moist, pulse 80 regular, and exfoliation confined to the scalp, palms, and feet. At 10 o'clock that night he complained of distress in his chest, he became unconscious, cyanotic, and died within five minutes. No *post-mortem* examination was permitted, but the symptoms were sufficiently definite of pulmonary embolism from a clot dislodged from the iliac veins.

I have recorded uncommon but important ill effects following the administration of salvarsan remedies for syphilis. The knowledge of these possibilities makes it important that no practitioner should undertake the intravenous salvarsan therapy of syphilis without having facilities for immediate transference of his patients from an ambulatory clinic to a ward. The knowledge of these possibilities must be brought before the attention of the public if public support is to be sought for the compulsory treatment of venereal disease. Otherwise there will arise a feeling of resentment among the uninstructed should a severe accident or a fatality follow the compulsory administration of these most important but toxic remedies.

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THYROTOXICOSIS AND INDICANURIA.*

BY

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THIS paper embodies the results of an investigation undertaken to discover what relationship existed between the intestinal dissociation of aromatic amino-acids and thyroid hyperactivity. It is known that when tryptophane is decomposed in the intestine indole is eliminated in the urine as indican (potassium indoxyl sulphate), and as it is a simple matter to test for this substance it was thought that some light might be thrown on the question if the degree of indicanuria were estimated in a series of individuals suffering from thyrotoxicosis and compared with similar observations upon a series of non-thyrotoxic individuals.

It is possible, of course, that urinary indican may not be a true index of tryptophane decomposition, as the greater part of the indole may be eliminated in the faeces, but it seems reasonable to suppose that the urinary concentration of this substance will follow roughly the intestinal content. The degree of indicanuria, therefore, was measured in a large number of individuals. The technique adopted was a colorimetric one, the indican being estimated as indigo blue. To 2 c.cm.

of urine an equal amount of hydrochloric acid was added, then 0.5 c.cm. of hydrogen peroxide; the whole was shaken, and finally 1 c.cm. of chloroform was added. The colour

* An investigation of the hypothesis which ascribes thyrotoxicosis to an increased absorption of unchanged aromatic amino-acids from the intestine.

was estimated after standing for four minutes. It was assumed that the acid converted the indican to indoxyl and sulphuric acid, and the peroxide promoted the oxidation of indoxyl to indigotin, the chief constituent of indigo blue.

The individuals whose urine was examined comprised three groups. Daily observations were made and graphs prepared, with the degree of indicanuria as the ordinate and the day of the week as the abscissa. The groups were comprised as follows:

Group I consisted of seven normal healthy persons.

Group II consisted of fifty-seven patients suffering from various conditions, but without evidence of thyrotoxicosis, the series including two cases of non-toxic goitre.

Group III consisted of patients with exophthalmic and other varieties of thyrotoxicosis. Twelve cases were investigated, one, a case of exophthalmic goitre, at some length, to see whether there was any effect on the urinary indican output during the slight attacks of post-operative thyroidism following ligation of the thyroid vessels.

The results were as follows:

Group I.—Five of the seven persons investigated gave varying concentrations (Fig. 1 shows an indican curve from this group), while two males, aged respectively 23 and 16, gave completely negative readings for over a month.

Group II.—Thirty-eight women and nineteen men were investigated; 971 observations were made—580 on women, 391 on men. It is interesting to note that of the observations on women 41 per cent. were negative and only 5 per cent. reached the highest degree of concentration, while of those on men only 23 per cent. were negative and 18 per cent. reached the maximum concentration (Figs. 2 and 3). In this group were two men and five women with urine completely free from indican.

Group III.—Several of the most toxic cases in this group had high concentrations of indican. The curves generally resembled those of healthy subjects, and in the case investigated to see whether the post-operative reaction following ligations had any effect on the urinary indican it was found that there was no constant effect, a slight rise occurring after two ligations, no change after one, and a slight fall after another. Furthermore, careful observations during the clinical course of cases of exophthalmic goitre failed to reveal any constant change in the urinary indican that could be correlated with an increase or decrease in the degree of intoxication (Figs. 4 and 5).

FIG. 1.—Healthy youth, aged 18.

FIG. 2.—Married woman, aged 28, with a tuberculous abscess in the abdominal wall.

FIG. 3.—Boy, aged 17, with large endemic goitre.

FIG. 4.—Man, aged 30, with acute exophthalmic goitre.

FIG. 5.—Married woman, aged 53, with severe exophthalmic goitre. The arrows mark points at which ligations were performed.

Since collecting the cases into groups, many more, particularly toxic and non-toxic goitre cases, have been investigated with similar results.

The findings may be summarized as follows:

(a) In healthy persons there may be little or no urinary indican without any evidence of thyrotoxicosis, and from