their medical advisers, I have made myself acquainted with their after-histories, which have been on the whole extremely satisfactory. There have been three definite failures—one an acute case, where an insufficient quantity of serum was perhaps responsible, and two which relapsed after a period of some months' good health, and where there was every possibility of reinfection. Further operation had to be undertaken in all three cases, otherwise the results have been good. In spite of their dislike of subcutaneous injections many of the women have said they were glad to have them, as they felt the benefit. In nearly every case relief of pain was a marked feature. Seen after varying intervals of months the patients described themselves as feeling splendid, being fit for anything, and able to do their own washing—in fact, they form a marked contrast to many other cases of gonorrhoeal infection where no serum had been given at operation, and where the presence of peritoneal adhesions causes so much pain and disability. In one case pregnancy was apparently proceeding normally. Discharges had stopped, and it was difficult to collect enough for bacteriological examinations, all of which were negative.

SPECIAL CASES.

Case 1.

A good result was obtained by the intraperitoneal use of serum in the case of Mrs. B., the mother of two children, one a girl suffering from gonorrhoeal vaginitis, while the baby had ophthalmia neonatorum. There was a left-sided pyosalpinx and an abscess in the pouch of Douglas. One tube and ovary were removed, and 20 c.cm. of serum were left in the pelvis, the abdomen being closed without drainage. There was a very slight febrile reaction the night of operation; temperature 100°, pulse 90. The patient made a good recovery. When seen eight months later she looked fit and well, and declared that she had never been in better health.

Case 2.

Mrs. V. was a case of acute salpingitis, associated with metrorrhagia. The abdomen was opened, sero-pus mopped out of the pelvis, and the tubes washed with saline solution, but not removed. Serum was administered subcutaneously in saline. There was no febrile reaction. The result was excellent, and her doctor reports that her pelvic condition ten months after operation is most satisfactory.

Case 3.

Mrs. P. was a case of arthritis of the wrist occurring about the seventh month of pregnancy (primipara). There was a profuse cervical discharge. The patient was taken into hospital and 20 c.cm. of serum were given every few days subcutaneously in saline until 150 c.cm. had been given. One injection was made into the tissues round the wrist-joint and caused a marked local reaction, with redness and swelling of the limb. This passed off, and both discharge and pain ceased. The baby was born in the maternity hospital and was quite healthy. Both mother and baby were seen some months later in the out-patient department in excellent condition; wrist movements were normal and leucorrhoea had ceased. In this case the patient had left her husband.

Case 4.

Another favourable result was in the case of Mrs. J., where there was a history of leucorrhoea extending over two years. After the birth of a child arthritis of the left hip developed and the patient was confined to bed. She was taken into the maternity rest home for treatment, with her baby, aged 9 weeks. No gonococci were present, but her husband was also suffering from joint pains. Two subcutaneous injections of serum were given at an interval of eight days, each producing a very marked febrile reaction the same evening. The breast-fed baby also developed a serum rash. In this case the result was excellent. Pain ceased and the patient was able to leave the home in about three weeks. When seen in the out-patient department three months later she could walk well, had no pain, and was very pleased with herself.

Case 5.

In a chronic case of hydrosalpinx (Mrs. N., married six years, husband a sailor, no children) both tubes were opened up. Three doses of serum were given subcutaneously at intervals of forty-eight hours. There was a marked febrile reaction each evening, the pulse being 116 and temperature 104.6° on one occasion. This patient was seen nine months later—fornices clear, no discharge. She said she was in excellent health.

Case 6.

Another case, Mrs. T., is interesting for the light it throws on obscure causes of puerperal infection. This patient had been under treatment during pregnancy for both gonorrhoea and syphilis in the venereal disease department.

Before admission to the maternity home discharge had ceased for some weeks, and the Wassermann test was negative. The confinement was normal and was conducted under the strictest

aseptic conditions, which include the shaving of the vulva and the wearing of gloves by all associated with the conduct of the labour. On the fifth day a rigor occurred, and the temperature rose to 102.8°, pulse 120. The patient was anaesthetized and thoroughly examined, the uterus being curetted and douched. It seemed so probable that the case was one of latent gonococcal infection lighting up in the puerperium that at the same time I gave 10 c.cm. antigonococcal serum with 10 c.cm. antistreptococcal serum. The latter was given not because the case was believed to be one of streptococcal infection, but as a prophylactic against a secondary infection. Temperature and pulse dropped to normal, and the patient made a good recovery.

The diagnosis was confirmed by the presence of gonococci in the uterine discharge. There were no streptococci.

From such a limited number of cases I do not presume to draw any definite conclusions, but I think these favourable after-histories warrant further experiment and study. I am hoping also to receive some assistance from bacteriological and immunity experts respecting the best method of administration of the serum, with regard to the site of the injections, their incidence, and the amount to be given. On theoretical grounds it is surprising that subcutaneous injections have been so successful, bearing in mind the nature of the microbe. Can one expect to reach an organism secreting an endotoxin by the blood stream, or must some other method be found by which it can be attacked locally?

Also, what is the explanation of the vigorous febrile reaction in chronic cases where subcutaneous injections have been used, while in the acute infections, where the tubes are pouring out pus, there is practically no febrile reaction either with the subcutaneous or intraperitoneal method?

In conclusion, I should like to take this opportunity of thanking Professor Nicolle of the Pasteur Institute for his kindness in placing so much valuable serum at my disposal; to Professor Beattie and his staff for numerous bacteriological examinations; and to Dr. Ruth Nicholson and my house-surgeons and sisters for their assistance with the notes and observations.

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ALBUMINURIA IN RELATION TO LIFE ASSURANCE.*

BY

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In the following remarks I shall deal only with albuminuria in youth and early adult life. From the point of view of prognosis and examinations for life assurance and appointments for clerkships, etc., I prefer to divide the subject under four main headings.

I.—Albuminuria Connected with Definite Nephritis, Chronic Heart Disease, Acute Febrile Diseases, Amyloid Disease, and other Conditions, such as are met with in Hospital Wards and Ordinary Medical Practice.

These cases are well known, and in the present discussion we are not concerned with them, excepting in regard to so-called "residual albuminuria" following an attack of acute nephritis. As long as there is albuminuria of this "residual" kind a life cannot be regarded as up to the normal standard; there may still be a slumbering inflammatory process in the kidneys (one or both). Mere functional recovery in the general condition of a patient, with persistence of albuminuria, does not mean that the life is a first class one any more than does functional recovery in a case of cardiac valvular disease with the persistence of a valvular murmur and cardiac hypertrophy. The extra amount to be placed on the life should depend on a variety of circumstances—for instance, the presence or absence of tube-casts, the amount of the leakage of albumin, the results of various tests as to efficient

* Read at a discussion on the subject at the Assurance Medical Society, January 5th, 1921.

functional activity of the kidneys, the length of time that the albuminuria has lasted, the blood pressure, and the condition of the candidate in other respects.

II.—Transient Albuminuria Due to Various Causes.

Under this heading I would include cases of albuminuria due to slight temporary nephritis and renal irritation, cases connected with dietetic errors, food idiosyncrasies, or the action of drugs, and cases of transient albuminuria caused by excessive muscular work. In many cases that I would place under this heading the precise cause of the albuminuria must remain uncertain, but the important point is that the albumin disappears rapidly and completely and that the general health is and remains good. In such cases several examinations are naturally often required before the life can be regarded as a first-class one.

III.—Postural or Orthostatic Albuminuria.

Under this heading I group the cases characterized by the occasional, but not invariable, presence of albumin (sometimes little, sometimes much) in the urine passed when the patient is up (that is to say, has been up for some time) but not in that passed when he is in bed or immediately after he has been lying for some time—for instance, in that passed immediately after the night's rest on getting out of bed in the morning. The albuminous urine in these cases frequently contains an excess of "nucleo-albumin" or mucin,* and not rarely calcium oxalate crystals are found on microscopic examination, and sometimes a few red blood corpuscles. "Cylindroids" in fair numbers are frequently observed, but the presence of true tube casts, excepting a few occasional hyaline casts (found with the aid of the centrifugal machine), should be regarded as suggesting some superadded renal irritation or slight actual nephritis.† I believe that the only practical way to distinguish these cases in ordinary practice is to obtain samples of the candidate's urine passed immediately after getting out of bed in the morning. In genuine cases these samples of urine should be found to be quite free from albumin. It is an unfortunate mistake occasionally made to speak of the "morning urine" in cases of orthostatic albuminuria being free from albumin, for it is precisely the urine passed at about 10 o'clock in the morning which may be especially albuminous. For practical purposes I think that what is called "lordotic albuminuria" (L. Jehle and others) should be regarded as a variety of orthostatic albuminuria in which a decidedly lordotic position of the body acts as an essential and determining (though not the only essential) cause of the albuminuria.‡

In the discussion on the after-history of cases of albuminuria occurring in adolescents, which took place on May 2nd, 1911, at the Medical Section of the Royal Society of Medicine, I made some remarks on the favourable prognosis in such cases,§ and said that I did "not think that albuminuria occurring in apparently healthy adolescents could justly be regarded as belonging to any other class than orthostatic albuminuria, unless it could be definitely ascertained that the urine passed immediately on getting out of bed after the night's rest contained albumin." If anything, I am now still more convinced that in uncomplicated cases of orthostatic albuminuria the life may be regarded as a normal one from the life assurance point of view. Moreover, no young person should be prevented from living an ordinary active life merely because of the presence of orthostatic albuminuria. Indeed, for these cases an active life—as much as possible in the open air, without over-fatigue—is probably the best. True orthostatic albuminuria may occasionally be met with up to 25 to 30 years of age (and possibly even later in life). In some way or other it is often connected with the tall

"lanky" build of body suggestive of visceroptosis; it has been much written about, especially by Continental authors, and, as every doctor now knows, is frequently associated with, and excited by, lordosis (Jehle). There is nothing surprising in the fact that it may occasionally exist in association with true nephritis (for instance, after scarlatina), and that it may be met with in the subjects of tuberculosis, syphilis, etc. The few *post-mortem* examinations that have been recorded tell us nothing more than this. It seems, indeed, quite natural that, occurring, as orthostatic albuminuria not rarely does, in "overgrown" children and in tall, flat-chested and often lordotic adolescents, it should be occasionally associated with early pulmonary tuberculosis. I have observed orthostatic albuminuria in two young men with grave forms of congenital heart disease.¶ Dr. Mackenzie Wallis has kindly informed me that in the albuminuric case to which he referred—a man in whom albuminuria was present for thirteen years without apparently harming him until at last he died at the age of 30 years from uraemia—the albuminuria was not of the orthostatic type, and was almost certainly due to a true chronic nephritis.†

In regard to prognosis (and life assurance) in cases of adolescent albuminuria help can doubtless be obtained from a chemical examination by estimating the relative proportions of serum-albumin and globulin in the urine,‡ but it is of at least as great importance to ascertain whether the albuminuria conforms to the orthostatic type—whether albumin is altogether absent from the urine passed immediately on getting out of bed in the morning—though this latter investigation may give rise to considerable inconvenience if the examinee cannot be trusted.

IV.—The Presence of Albumin (frequently only a trace) accompanying Minute Quantities of Pus, Blood, or Semen in the Urine.

The slight opacity in the urine due to the presence of minute quantities of pus or blood, or pus and blood, in the urine may easily be overlooked, or wrongly neglected as of no importance, in examinations for life assurance or appointments such as clerkships, etc. (Naturally in the case of females a difficulty is more likely to arise owing to admixture of the urine with vaginal or slight leucorrhoeal discharge.) The haze which calls for a microscopic examination may be not more than that due to the presence of bacteria in urine from cases of bacteriuria or in urine which is decomposing. I do not know how it compares with the opalescence which, according to Mackenzie Wallis, may exceptionally be observed in urines containing an excess of eglobulin.§ Whenever it is evident by the ordinary tests that an opacity (however slight) in the urine is not due to phosphates (or, after cooling, to urates), a

* F. P. Weber, Congenital Heart Disease, with Extreme Secondary Polycythaemia and Orthostatic Albuminuria, *Edinburgh Medical Journal*, 1909, New Series, vol. ii, p. 18; F. P. Weber and G. Dorner, Congenital Pulmonary Stenosis, *Proceedings of the Royal Society of Medicine*, Clinical Section, London, 1911, vol. iv, p. 85. In connexion with these two cases I find that F. Eigenberger (*Zentralblatt für innere Medizin*, Leipzig, 1920, vol. xli, p. 354) refers to the case of a young man with polycythaemia rubra (secondary to cardiac disease, if I rightly understand the author) in whom the presence of orthostatic (lordotic) albuminuria was discovered; a lordotic position of his body caused his urine to contain albumin, a little blood, and abundant cylindroids.

† Dr. Mackenzie Wallis tells me that though there was well marked globulinuria in this case, the patient was observed to have puffiness about the eyes in the early mornings; his brachial systolic blood pressure was constantly 160 mm. Hg. and red blood cells (though no tube casts) were found in the urinary deposit. The case has been described in full by Dr. Ivor J. Davies, *Lancet*, 1920, ii, p. 1249.

‡ Cf. R. L. Mackenzie Wallis, Non-nephritic Albuminuria, *Proceedings of the Royal Society of Medicine*, Section of Medicine, 1920, vol. xiii, pp. 96-104.

§ Mackenzie Wallis (loc. cit., p. 100) writes: "In my opinion eglobulin is really globulin which has associated with it a small quantity of lipids. In this respect eglobulin is identical with the lecithin-globulin isolated from pseudo-chylous effusions, the degree of opalescence depending on the amount of associated lipids. This eglobulin is precipitated by acetic acid in the cold, and is, in my opinion, the protein present in the urine which gives this test. An excess of this eglobulin containing excess of lipids, either in the blood, pleural, pericardial, or peritoneal effusions, or in the urine, gives rise to a marked opalescence, and when this globulin is removed then the opalescence disappears." Mackenzie Wallis quotes a case described by Bramwell and Paton (1892), in which actually the urine spontaneously deposited rhombic crystals of globulin. In regard to pseudo-chylous effusions cf. also Mackenzie Wallis and Schöberg, *Quarterly Journal of Medicine*, Oxford, 1910, vol. iii, p. 301; Mackenzie Wallis, *Proceedings of the Royal Society of Medicine*, Medical Section, 1913, vol. vi, p. 135; and H. A. Lediard, *Ibid.*, p. 123.

* A trace of nucleo-albumin in the urine passed immediately on getting out of bed in the morning must not be mistaken for albumin.

† The brachial systolic blood pressure in these cases is in general, I think, slightly below rather than above the average.

‡ The voluntary assumption of a lordotic position of the body (artificial lordosis) is sufficient in some subjects to induce temporary albuminuria. This favours the view that in cases of "orthostatic albuminuria" it is not the ordinary muscular exercise of walking about, but really the upright position of the body, which induces the leakage of albumin in the urine when the affected individual gets up after a night's rest.

§ Cf. also F. P. Weber, Remarks on Orthostatic Albuminuria, *British Journal of Children's Diseases*, London, 1911, vol. viii, pp. 395-399. In this paper I referred to individual cases I had met with.

microscopical examination (even a hasty one, without waiting for a sediment to form and without the help of the centrifugal machine) may prove of extreme value. At examinations for appointments and life assurance the discovery of minute quantities of blood, not sufficient to produce any reddish coloration of the urine, may lead to the detection of renal tuberculosis, as in the case of a young man whom I recently examined for a clerkship. In such cases the correct diagnosis must of course be confirmed by special examinations, such as by cystoscopy and by catheterizing the ureters, to see if only one kidney is affected. On repeated examinations in cases of this class the urine may sometimes be found apparently free from albumin (by the ordinary boiling and acidifying test), though its slight opacity when freshly passed should lead to a microscopical examination being made. On rare occasions, in such cases, even the slight obvious opacity may temporarily be absent from urine, which by microscopical examination of the centrifuge sediment is found to contain minute quantities of blood or pus.

I understand from Dr. Lister (though I have not observed it myself) that the urine at the commencement of an attack of gonorrhoea (congestive stage) may sometimes contain a little albumin even before the appearance of any purulent discharge.

After the subsidence of an attack of haematuria of uncertain causation the presence of a little pus in the urine by microscopical examination may indicate grave disease, such as a malignant tumour involving the pelvis of one kidney.* This whole subject, however, I need not further discuss here.

ON THE ACTION OF CERTAIN SPECIAL PREPARATIONS ON MALARIAL PARASITES AND THEIR EMPLOYMENT IN THE TREATMENT OF MALARIA.

BY

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THESE investigations were carried out at No. 4 General Hospital, S.A.M.C., Roberts Heights, during 1917-19 on malarial patients invalided from the German East African campaign. The majority of the cases were of a severe type, associated with marked anaemia and debility, numerous relapses occurring in hospital while under quinine treatment (25 to 30 grains daily). Of 8,788 hospital cases 61 per cent. showed benign tertian parasites in their peripheral blood, 23 per cent. malignant subtertian, 16 per cent. both benign tertian and malignant subtertian parasites. The average period in hospital and convalescent camp of these cases was fifty-one days, during which time the blood was examined at weekly intervals and the patients kept on routine daily quinine treatment. Parasitological relapses occurred during this period of observation in 24 per cent. of the benign tertian cases, 11 per cent. of the malignant subtertian cases, and 39 per cent. of the mixed infections. The circumstances under which these cases contracted malaria (a particularly strenuous military campaign in the tropics) suggested a special terminology to meet this resistant clinical condition—namely, "campaign malaria," which apparently owes its intractability to repeated reinfection associated with severe physical strain in unacclimatized individuals only partially protected from a tropical climate and frequently insufficiently supplied with suitable food.

The frequency with which relapses occurred and the slowness with which these patients recovered a condition of good health emphasized the importance of testing any

remedy which might cut short the period of treatment necessary and reduce the number of relapses. Accordingly these investigations were initiated, with the object of providing if possible a more effective treatment. It is not proposed to deal in this paper with the comparative studies made of the results of treatment of different infections with varying doses of quinine administered by the oral, intramuscular, and intravenous routes. The practical outcome of this work, however, was the adoption of a standard treatment for all average cases of malaria. This treatment consisted of 30 grains of quinine in solution by the mouth daily for three weeks, followed by 20 grains daily for one month and subsequently 10 grains daily for two months.

NEO-SALVARSAN, SALVARSAN, NEO-KHARSIVAN, KHARSIVAN, GALYL.

In view of the debilitated condition of many of the cases selected for treatment it was necessary to exercise the greatest care in the employment of these toxic preparations. Accordingly the patients were specially prepared, and the dose of the "606" preparations employed was invariably about half that dose commonly used for the treatment of syphilis (neo-kharsivan, neo-salvarsan, 0.45 gram; salvarsan, kharsivan 0.3 gram; galyll 0.2 gram).

Until some experience of these preparations had been obtained in malarial patients it was customary at first to give intravenous injections at weekly intervals. Subsequently, however, it was found that intravenous injections could with safety be given on alternate days for three or four injections, and in one of the cases reported in this series fourteen intravenous injections of 0.2 gram galyll were administered during an inclusive period of twenty-two days, as many as five injections being given on successive days without any obvious harmful effects.

During the past three years some thousands of intravenous injections of these preparations have been administered in malarial subjects without a single fatality. It is therefore clear that the employment of intravenous injections of the above preparations in malarial subjects is not attended by any appreciable or special risk, provided the doses and methods recommended are used and the precautions enumerated are fully observed.

Apart from the general contraindications in regard to the employment of these preparations commonly recognized when considering the treatment of syphilis, it is necessary specially to consider the following points in regard to the employment of these preparations in malarial subjects.

(a) *Tachycardia and Dilatation.*—These are symptoms of the disease resulting from anaemia and toxæmia. They improved, however, rapidly as a result of intravenous injections of salvarsan and galyll, and in 154 cases subjected to this treatment, the majority of whom had some cardiac embarrassment, not a moment's anxiety on this score was experienced.

(b) *Pyrexia.*—Some observers have held that following an injection of "606" or galyll the temperature often rises 1 to 1.5 degrees, sometimes accompanied with slight rigor, nausea, and vomiting as part of the general reaction to the drug. In a series of over 790 injections these phenomena were observed only seven times with the above doses.

(c) *Renal Complications.*—As these drugs are toxic, it is necessary for the patients' safety that they should be eliminated fairly rapidly. Where, therefore, there is a history of recent nephritis, or where the symptoms of such a condition are present (albumin, oedema, etc.) an injection should not be given.

(d) *Gastro-intestinal Conditions.*—As vomiting is also a fairly frequent symptom of reaction after injection, severe vomiting, diarrhoea, or obstinate constipation should be corrected before an injection is given.

Preparation of the Patient.

Sufferers from malaria should have complete rest in bed for at least twenty-four hours before an injection. Their diet should be light and easily digested during this period. The bowels should be opened either by a purgative pill (for example, pil. hydrarg. coloc. co. with hyosc.) the previous night, followed by saline (mist. alba) the following morning or by an enema in the morning before injection. A light breakfast—one egg, two slices of toast, and one cup of tea—given at least four hours before injection, may be allowed, but no food should be

* In one such case, a man, aged 35 years, under my observation in 1918, the patient (owing to some mistake) was forced to join the army, but was soon transferred to a military hospital and then set free. He died in March, 1920, and the post-mortem examination showed a malignant tumour and pyonephrosis of the left kidney, with secondary tumours elsewhere in the body. This was Case II in a paper which I published (in regard to another subject) in the *International Clinics*, Philadelphia, 1920, series 30, vol. iii, pp. 43-51.