function of the thyroid; in a case of severe myxoedema in a girl of 11 years the transplant was taken from a patient whose goitre had to be removed. A few weeks later the girl developed between the peritoneum and fascia lata, where an apparently healthy piece of gland from the goitre patient had been transplanted, a hypertrophic goitre of the size of an apple, and at that time all her symptoms of myxoedema had disappeared; she was quite well for five years, when she had typhoid fever; the abdominal goitre became infected and an abscess formed which had to be opened; within a few weeks all her symptoms of myxoedema came back. Von Eiselsberg of Vienna a year ago published a similar case; the patient had been cured of myxoedema by transplanting a piece of gland of a goitre patient in the peritoneum below the liver. The patient died several years after the transplantation from pneumonia. At the *post-mortem* examination a hypertrophic goitre of the size of a hen's egg was found under the liver.

We have succeeded in demonstrating experimentally that the transplant is active. As a rule such experiments have been conducted in a way that could not give a result. The transplantation has usually been made into an animal with a normal thyroid gland; the organism had no want of thyroid and the graft did not live. We proceeded in a different way. We first removed the animal's thyroid almost totally, avoiding the parathyroids, and then waited until the animal developed characteristic symptoms of hypothyroidism. Then a piece of normal thyroid gland of a healthy animal of the same species was transplanted into the upper end of both tibial bones. We then waited until the symptoms of myxoedema in the transplanted animal had disappeared, and a few months later removed the two pieces of gland from the bones, and within a few weeks the symptoms of myxoedema reappeared. I believe that by these observations and experiments we have proved that the transplant can live and, in view of our clinical results, recommend this as the method of choice in cases of hypothyroidism. We believe that it should be tried also in cases of total absence of the thyroid gland.

Selection of Transplant.

The method of performing transplantation in our cases was that described by my father Theodor Kocher in 1909. There are three types of transplantation that can be employed: we may take (1) a normal gland of an animal; (2) pieces of a goitre from a case of Graves's disease; (3) the hypertrophic thyroid tissue around a nodular goitre. We have used all three methods. As early as 1908 we used some heterotransplants from sheep and goats. The best glands to transplant are those from pregnant animals. This method has given a good result in some cases. One of the cases of congenital total absence of thyroid gland mentioned above was entirely cured by transplantation of two pieces the size of a cherry of a normal thyroid gland of a pregnant sheep into the two tibial bones. As a rule, however, homotransplants are much better. They are best taken from the hypertrophic gland of a severe but recent case of Graves's disease, which is in a condition of exquisite cellular hypertrophy and active new formation of vesicles. The best part of the gland to be taken is the upper pole or posterior part of the gland near the superior thyroid artery. It is essential that the pieces of gland (we take usually two to four pieces of the size of a small cherry) shall be put into the receiver's body immediately after being cut out of the donor. The receiver must be ready on a table next to the donor, and the bed for the transplant must be carefully prepared beforehand and in particular all haemorrhage carefully stopped. Besides the glands of patients with Graves's disease, we have very often taken pieces of the hypertrophic thyroid tissue around goitre nodules in young healthy goitre patients. Of course, in every case the donor is examined very carefully beforehand; tests for syphilis and tuberculosis must more especially be done.

The Operation.

As mentioned above, we transplant mostly into the upper end of the tibial bone, where, with Doyen's trephine, the corticalis is opened and a bed in the bone marrow made, exactly of the size of the transplanted piece. We have chosen this bone, first, because it is very vascular and has a

special affinity to thyroid tissue, as shown by the frequent bone metastasis in malignant goitre, and secondly, because the gland is very well protected from injury in the bone. However, we also transplant into the sheath between the fascia transversa and peritoneum, or into the peritoneal cavity. But in the latter it is better to stitch the parietal peritoneum over the transplanted piece of gland and not to put the gland free into the peritoneal cavity. If the graft is to be successful, the healing of the wound must take place without any rise of temperature or other post-operative reaction. The most important of all is the pre-operative and post-operative treatment. The patient must take thyroid some time before and several weeks after the transplantation, in order to decrease his actual want of thyroid, because if this is very strong the transplanted gland tissue is simply eaten up by the organism. The non-observation of this is the most common cause of failure of transplantation, especially in cases of total congenital absence of the gland.

DIFFERENTIAL DIAGNOSIS OF RHEUMATOID ARTHRITIS AS A CLINICAL ENTITY.

BY

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AND

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ALL authorities are now agreed that an important factor in the etiology of the arthritides is some form of infective process, and a certain degree of progress has been made in the classification of this amorphous group of clinical material by the recognition of special types as being due to specific infective agencies such as the tubercle bacillus, the pneumococcus, gonococcus, etc. But there remains a large number of cases of non-specific origin which in the past have been aggregated under the term "rheumatoid arthritis." Those with experience in this class of case are not satisfied, however, with this and have preferred the more vague terms of "multiple non-specific infective arthritis," "focal arthritis," or "indeterminate arthritis." Several attempts have been made to differentiate so-called true rheumatoid arthritis from this group, and it is our purpose to report our preliminary investigations for the furtherance of this object.

We would define rheumatoid arthritis as a disease of insidious origin, affecting young adults in particular, usually running a prolonged subacute or chronic course with periodic exacerbations, but occasionally acute in its onset and manifestations, leading to serious deformity of structures in intimate relationship to joints, and associated with digestive disturbance, upset of general metabolism, alteration of the normal blood picture, and with glandular enlargement.

ETIOLOGY.

Patients suffering from rheumatoid arthritis frequently give a history of previous debilitating disease or some prolonged physical strain. A history of rheumatic fever seems to occur more frequently than can be accounted for by the incidence of this disease in the general population. But this condition does not produce chronic intra-articular disease, though repeated inflammatory reactions do occur and may cause such laxity of ligaments and impairment of joint circulation that the synovial membrane is liable to be attacked by other infective agencies. Influenza is another predisposing cause, probably acting simply by the general lowering of resistance, though serous membranes in all parts of the body are liable to inflammatory changes after this disease. Pregnancy and childbirth with their general upset of digestive and metabolic processes are recorded in many instances as the starting point of the attack.

Certain observers¹ have cited cervical and uterine infections, pyelitis, otitis media, furunculosis, etc., as the factories of infection, but we are very doubtful whether these extra-digestive foci are of any real importance in this particular group of cases except in so far as they lower the general resistance. Pyorrhoea and dental caries are frequently, if not always, present, but these conditions are so wellnigh universal that they cannot be held to be solely

responsible. The same applies to tonsillar infection, which, though not so obvious as pyorrhoea and therefore less frequently recognized, is one of the maladies to which most men are heir, and therefore again this cannot be held to be the only factor in the etiology of rheumatoid arthritis.

In almost all cases of the group under discussion there is a history of dyspepsia, which takes the form of anorexia, flatulence, and constipation, the last being a constant feature; but it is unusual to discover any local focus in connexion with the intestinal tract, such as an obviously inflamed gall bladder or appendix. The exact etiology of rheumatoid arthritis, therefore, must remain obscure until such time as the nature of the "soil" has been more fully investigated, when recognition of the type or types of "seed" concerned in the production of the disease should present less difficulty.

CLINICAL FEATURES.

The predominant feature of rheumatoid arthritis and the one for which the patient seeks advice is the swelling and pain of the joints. The first to be affected are usually the small distal joints, especially of the upper limb. It is characteristic of the early cases to show swelling of the second or second and third metacarpo-phalangeal joints, with pain and slight swelling of the wrist, which precedes ulnar deviation; one or more of the mid-phalangeal joints are often involved and show the characteristic spindle shape. In the later stages the larger joints may be affected, the disease sometimes spreading from joint to joint throughout the body. A symmetrical distribution characterizes the progress of the disease.

The morbid process chiefly affects the synovial membrane and ligamentous structures round the joint, and although this is swollen it is rare that fluid can be extracted in any quantity. That the pathological involvement is not confined to these parts is shown, however, by the changes in bone structure as disclosed by x-ray photographs. These changes consist chiefly of rarefaction in the neighbourhood of joint surfaces. It is, indeed, remarkable in late cases with most marked deformities how slight are the osseous changes. As the disease advances the ligaments become much relaxed, with resulting ulnar deviation of fingers and wrist and valgus deformities of the toes and complete flat-foot. In the same way the larger joints, though showing less deformity in the absence of muscular contractures, become markedly unstable, and lateral mobility of the knees is very noticeable.

That the joints are not the only manifestation of the disease is apparent. There would seem to be a general metabolic upset involving the endocrine glands. Clinically there are many signs suggestive of hyperthyroidism. Excessive sweating, fibrillary twitchings, a tendency to disordered action of the heart, and overbrisk tendon reflexes are met with, and there is often that nervous instability and apprehensiveness which is associated with disordered endocrine function. The vasomotor system is markedly upset, with flushing and even dermatographia; or a condition of the extremities approaching Raynaud's disease may be found. The skin shows trophic changes, comprising loss of subcutaneous fat and a glazed appearance with loss of hair. The muscular wasting is early and pronounced and more than can be accounted for by the disuse of a limb consequent on the joint condition. It is this wasting, especially of the intrinsic muscles and subcutaneous fat of the hands, that emphasizes the characteristic spindle appearance of the joints.

If careful examination is made in the region of the joint, enlargement of the lymphatic glands can be detected. Inasmuch as the hands are earliest and most severely affected the glands most definitely involved are the epitrochlear, but axillary, femoral, and inguinal are also found enlarged. In 20 cases showing a clinical joint picture as described above all showed enlargement of glands.

The blood picture presents characteristic changes in the majority of cases. Secondary anaemia is common, but by no means universally severe, and a slight or moderate leucocytosis is often met with. The importance of the total white count, which may vary in the course of the disease, is overshadowed by that of the differential, which shows a

definite increase in the small mononuclear cells relative to the polymorphonuclears. This feature, however, is only important in conjunction with the other clinical signs, as it is met with in many other forms of arthritis. In 19 cases examined out of the 20 cases mentioned above, all showed a relative increase in small mononuclears. In certain cases the spleen is found to be palpable, but this is never excessive and by no means constant.

Examination of the gastric contents shows absence or diminution of free hydrochloric acid in the majority of cases, and this, in our opinion, is frequently the crucial factor in the whole clinical picture. Thus, in the 20 cases examined, 14 had complete achlorhydria, one a trace of free hydrochloric acid only, 2 marked diminution, while 3 were normal. The test used was Ewald's test meal.

COURSE OF THE DISEASE.

The onset is usually between the ages of 20 and 30, though cases commencing in the adjacent decades are by no means uncommon. It should be noted that this excludes cases of Still's disease, which is presumably rheumatoid arthritis in children. The course is prolonged, extending over years.

Initially there is often a period of pyrexia, the temperature swinging up to 101° or 102°, but not usually higher. This may recur during the succeeding years for a few weeks at a time for no very obvious reason after long periods of remission. The active inflammatory condition may spread from joint to joint, dying out of some and affecting others, and eventually there is a tendency for the condition to die out altogether, often leaving behind it severely deformed joints and (if care is not taken in the management of the case) serious contractures and ankyloses in bad positions.

THEORETICAL CONCLUSIONS.

It is admitted that not nearly enough observations have been carried out to warrant definite conclusions on this clinical group; but this only purports to be a preliminary communication, and it is hoped to carry out further investigations to confirm or modify the views expressed above. Considerable work has already been done on the subject of achlorhydria by Hurst and his collaborators² at Guy's Hospital, especially in connexion with Addison's anaemia and subacute combined degeneration of the spinal cord. First they have shown that achlorhydria may be apparently congenital, for in 4 per cent. of perfectly healthy young men without digestive symptoms this condition was found. Hurst further concludes that the achlorhydria precedes not only the anaemic conditions in which it is so frequently discovered, but also those cases of chronic gastritis which formerly were supposed to be the cause of the achylia. The gastritis is due to the failure of the normal softening and diluting action of the juice, and as the food is not sufficiently digested in the stomach it will irritate the intestine in the same way and cause intestinal dyspepsia. At the same time proteins will reach the small and large intestines unchanged, and with them numerous bacteria which would normally be destroyed by the acid disinfecting properties of the gastric juice. The decomposition of the proteins by these bacteria produces further irritative material which modifies the absorption of toxins. Hurst³ mentions the presence of achylia gastrica in rheumatoid arthritis; Woodwark and Mackenzie Wallis⁴ have described diminution or absence of free HCl in 9 out of 10 cases; and Faber⁵ has described achylia gastrica in 15 out of 65 patients suffering from chronic polyarthritis. In our view, however, it is probable that this polyarthritis included joint conditions other than that group which we are attempting to differentiate, and that if the observations were confined to those cases showing joints of the typical kind and distribution with glandular enlargement and lymphocytosis, then a much higher percentage of achlorhydria would be found.

In discussing the pathogenesis of subacute combined degeneration and Addison's anaemia, Hurst⁶ suggests that the passage of the *Streptococcus longus* from infected teeth and gums through the stomach into the large intestine, owing to the absence of free hydrochloric acid, produces various toxins either from their own activity or from the breaking down of undigested proteins. He suggests that the incidence of anaemia or subacute combined degeneration

depends on the relative production of a haemolysin or a neurotoxin. We would suggest a similar genesis in many instances of rheumatoid arthritis by means of a toxin with a special affinity for synovial membrane.

However, it must always be remembered that the whole metabolism is upset, and further work is required to investigate other possible factors responsible for the production of the clinical changes observed. Many observers have assigned importance to the isolation of various strains of streptococci from the stools, but the results are so far very variable and no reliable conclusions can be drawn. It is possible that the factor of achlorhydria may have some influence in determining this state of affairs, in view of the work of Billings⁷ and his collaborators on the variability of streptococcal strains in different media.

We wish to thank Dr. Munro, pathologist at the Royal Mineral Water Hospital, Bath, who was responsible for the blood counts and gastric analyses mentioned above.

REFERENCES.

- ¹ Lindsay, J.: *Bulletin of Committee for Study of Special Diseases*, vol. ii, p. 106. ² Bennett, T. I., and Ryle, J. A.: *Guy's Hospital Reports*, 1921, 71, 286. ³ Hurst, A. F.: *Lancet*, 1923, i, p. 111. ⁴ Woodwark, A. S., and Mackenzie Wallis, R. L.: *Lancet*, October 5th, 1912. ⁵ Faber, K.: *Berl. klin. Woch.*, 1913, i, 958. ⁶ Hurst, A. F.: *Brain*, xiv, p. 266. ⁷ Billings, F.: *Lane Med. Lectures*, Stanford University, 1916.

A LARGE RENAL CALCULUS.

BY

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LARGE stones of the kidney are not common; in this case the calculus weighed 1 lb. 3½ oz., and it is of interest that the symptoms were very mild and that operative treatment was successful.

The drawings by Mr. Thornton Shiells show well the shape of the calculus (Fig. 1) and the left kidney removed with it (Fig. 2). The main mass of the calculus lay in the dilated renal pelvis; the short branches occupied five of the much damaged calyces. The outlet from the renal pelvis is small, and below that the ureter is seen to be greatly dilated and its wall much thickened. The small calculus partially blocked the left ureter at its lower end close to the bladder.

FIG. 1.—Calculus.

FIG. 2.—Kidney with dilated pelvis.

Dr. H. E. Archer has kindly analysed the calculi and reports as follows:

Renal Calculus.—Weight 1 lb. 3½ oz. (555 grams). Samples taken at five points between the external surface and the centre show a composition, almost constant, of ammonium magnesium phosphate and a little calcium phosphate. The superficial layers also contain a little calcium carbonate. The branches consist of ammonium magnesium phosphate.

Ureteric Calculus.—Weight 2.8 grams. The composition is similar.

The patient was a man, aged 58, who was under my care at St. Peter's Hospital. From youth until he was 35 years old he was in the merchant service, then he retired and lived in Plaistow. For the last twenty-three years his urine has always been dark, sometimes as dark as port, and occasionally he had passed clots of blood. For the last five years his urine had smelt foul. For two years he had occasionally had pain in the left groin but never any renal or vesical pain. A fortnight before admission for the first time he suffered from frequency of micturition, with fever and rigors.

There was no family history of stone. His previous health had been excellent, except for malaria when 21 years old, and acute appendicitis requiring operation five years ago, and gout in one toe three years ago.

On examination the left kidney was easily palpable and obviously greatly enlarged and a little tender. It was freely mobile. His urine was very foul, alkaline, and contained albumin and pus with coliform bacilli and cocci. Cystoscopy showed marked cystitis and an enlargement of the prostate, which could also be felt per rectum. The orifice of the left ureter was inflamed; the efflux was unduly frequent and decidedly purulent. The right ureter was healthy and its efflux clear. X rays showed a large shadow in the left renal region.

The left kidney was explored through the usual incision in the loin, and the kidney containing its calculus was excised and also the greater part of the ureter and the small calculus in it.

Healing was slightly delayed by some suppuration in the scar. Two months later the enlarged prostate was enucleated suprapubically, and he has made an excellent recovery from both operations.

TREATMENT OF URTICARIA WITH COLLOSOL MANGANESE.

BY

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In a large skin clinic a considerable percentage of cases of urticaria, which are most intractable to treatment, are encountered. Although the pathology of urticaria is by no means definitely understood, I think we may reasonably assume that it is due to the action of an irritant on the vessels at the point where the cutaneous lesions make their appearance. This irritant, be it a toxin or protein, may reach the vessels from an external source or from the blood stream. As an illustration of the former I may cite the urticarial rash caused by nettles; the rash in this case is produced by an irritant from the plant reaching the blood and lymphatic vessels through the skin. As an example of the latter, the urticaria following the ingestion of certain shellfish may be taken; here the toxin or protein would appear to reach the blood stream through the intestinal canal.

It is the experience of every dermatologist that often cases are met with for which no cause can be assigned. It was owing to this experience that I was induced to try collosol manganese in the treatment of urticaria. Metals given in a colloid state increase oxidation and stimulate the protein colloidal particles in the serum, resulting in the dispersion of these particles so that the surface exposed to the invading particles becomes greater. The increased activity of the protein particles in the tissue and fluid has a destructive action on the invading protein or toxin.

It was with this theory in mind that I decided to try collosol manganese in some obscure cases of urticaria. The following four cases are given to illustrate the effect.

CASE I.

A woman, aged 27, unmarried, had suffered from daily attacks of "nettle rash" for twelve months. When I first saw her the face, arms, legs, chest, and neck were thickly covered with flat wheals varying in size from a coffee bean to a five-shilling piece. There was intense itching and burning. I gave her 0.5 c.cm. collosol manganese by intramuscular injections. On returning at the end of a week she reported that the rash had been much better and the burning and itching sensation decidedly diminished. I gave another 0.5 c.cm., and she again reported an improvement at the end of the second week. I gave her four more injections (1 c.cm., 1.5 c.cm., 1.5 c.cm., and 2 c.cm.) at weekly intervals, and at the end of six weeks of treatment she was quite free of her trouble. Six months afterwards she had a slight recurrence, and