ANNALS OF THE RHEUMATIC DISEASES

A REVIEW OF RECENT ITALIAN WORK ON RHEUMATISM*

II.—CHRONIC RHEUMATISM

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THE first Italian Institute devoted exclusively to the study of rheumatic diseases was founded in Acqui (Piedmont), a town famous for its hot springs and muds, in 1929, by the Directors of the Medical and Surgical Clinics of the University of Turin (Professors F. Micheli and M. Donati). It was enlarged and transformed into the Rheumatologic Clinic in 1932. Its clinical material includes several thousands of patients a year. Many other spas have laboratories where researches on rheumatism are carried out (Montecatini, Chianciano, Fiuggi, Abano, Salsomaggiore, etc.). Furthermore, a ward or, more frequently, an out-patient department has been devoted to rheumatic cases in the most important University Medical Clinics (Turin, Milan, etc.). There is also a vast voluntary hospital in Turin, known as the Little Home of Divine Providence, holding about ten thousand cripples, among which are numerous cases of arthritis.

CLASSIFICATION.—The following classification of chronic arthritis and polyarthritis was suggested by Micheli in 1929, and the most important Italian studies have been founded upon it.

1. Chronic rheumatism of known ætiology (gonococcal, syphilitic, tuberculous, pyogenic, etc.).
2. Chronic rheumatism following rheumatic fever.
3. Rheumatoid arthritis:
 - (a) Rheumatoid arthritis of an infective character.
 - (b) Still's disease.
 - (c) Rheumatoid arthritis with no definite infective character.
4. Osteo-arthritis (osteo-arthritis of English authors).
5. Aseptic osteo-necrosis (Perthe's, Köhler's diseases, etc.).
6. Metabolic arthritis (gout, alcaptonuria).

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7. Neurogenic arthritis.
8. Traumatic arthritis.
9. Intermittent hydrarthrosis.
10. Hæmophilic arthritis.
11. Joint tumours.
12. Other, as yet unclassified, joint diseases.

This classification is, of course, only provisional. It is very similar to the one accepted by the Committee of the British Medical Association some years later (1933). It differs a great deal from the American classification, which includes only two classes of chronic rheumatic diseases: rheumatoid arthritis and osteo-arthritis. A distinction between diseases which appear to be different in their clinical course and in their radiological and pathological pictures seems preferable because it facilitates ætiological research work, the best ground for which is a well selected and typical morbid picture. Conversely, a too-advanced unification can be dangerous both for ætiological research and for treatment.

CLINICAL COURSE.—A detailed description of the clinical course of rheumatic diseases can be found in two important publications by Ceconi,^{27, 28} and in a report by Robecchi on rheumatoid arthritis.^{105, 100}

Rheumatic diseases caused by a known agent may be very similar to rheumatoid arthritis, but the different ætiology is a sufficient argument to keep them separate (Micheli⁸²). This group is the only one in which our knowledge is advancing on firm ground (M. Ascoli). Most frequently cases of this group are due to pyogenic streptococci. Among the rare forms may be quoted a rheumatism from malaria (Terzani and Torelli¹⁰⁹).

A few words must be said on tuberculous rheumatism. Since the days of Grocco and Poncet the existence of a tuberculous rheumatism of a toxic nature, without the direct participation of Koch's bacilli, has been maintained. In more recent years these cases have been interpreted as evidence of an allergic articular reaction towards tuberculous virus or toxin (Frugoni, Ferranini⁴⁵). But this tendency has been steadily opposed by others, who consider such cases to be manifestations of a more or less attenuated tubercular infection of the joints. This can only be proved by finding Koch's bacilli in the affected joints and by the pathological picture which shows the common signs of any tuberculous infection (Micheli⁸⁵). This point of view has found further support in a large number of observations by Logroscino.⁶⁵

Syphilitic rheumatism has been studied by Casazza and Cottini,²⁴ G. Truffi,¹¹¹ Liuzzo,⁶³ Lenti.⁵⁸

The second class of Micheli's classification considers chronic rheumatism following rheumatic fever. Chronic rheumatism due to the same causative agent as rheumatic fever is, however, according to Italian authors, an eventuality which, if at all possible, must be extremely rare (Ceconi,²⁸ Micheli,⁸² Rensulli⁹⁶). This class is based exclusively on the clinical evidence of cases of chronic rheumatism setting in closely after an attack, or after recurrent attacks, of rheumatic fever, in which an ætiological diagnosis is not possible. Only this could decide whether we are dealing here with the more or less casual coincidence of two diseases, rheumatic fever and rheumatoid arthritis, or whether rheumatic fever by itself can give rise to a chronic disease.

According to the above-quoted classification, there are three varieties of rheumatoid arthritis. Cases in which the disease begins with an acute episode or which in their course present acute stages, with impairment of the general condition, are included in the first group (rheumatoid arthritis of an infective character). The second group comprises cases with high fever, splenomegaly and lymph-gland enlargement of the type of Still's disease. The third group (rheumatoid arthritis of no definite infective character) includes the cases in which endogenous factors, sometimes of familial or hereditary origin, appear to be of most importance, and in which the clinical course does not show the signs of a general infectious disease. Whether these groups correspond to three ætiologically different diseases is, of course, still undecided, and is very doubtful, because their clinical courses often show variable characters according to which many cases ought to be classified first in one group, then in another. Neither radiological nor pathological findings show definite differences between them.

Spondylitis ankylopoietica is considered by Micheli and Ceconi to be a special form of rheumatoid arthritis. But its sexual incidence (more frequent in men) and its radiological signs have aroused doubts upon the correctness of this view.

Still's disease has been the object of detailed studies since the publication of a paper by Micheli and Gamna.⁸¹ Many cases have been described: by Giordano,^{52, 53, 55, 58} Gallerani,⁴⁹ Galdi, Michelazzi,^{79, 80} Cassano,²⁵ S. Levi,^{61, 62} Scardino,¹⁰⁷ Veritti,¹¹⁵ De Filippi,⁴² and others. It may be asserted that the cases

described in Italy form the most numerous group in the medical literature. It is now generally believed that Still's disease is not limited to children, as cases with the same characters have been described by the above-mentioned authors in adults. These cases presented all the features of Still's disease, with the only exception of the symptoms due to alternate growth of bone (Gralka's symptoms, etc.), which are confined to young patients.

Two cases of Felty's leucopenic splenomegaly with polyarthritis have been described by Alessandrini.¹ But most Italian authors do not recognise the autonomy of this syndrome, which has the same characteristics as Still's disease. The leucopenia, in fact, is not a deciding factor, because it is a common feature of many splenic enlargements whatever their cause. Also the cases described by Castellani²⁶ as febrile hepatosplenomegaly with polyarthritis have been ascribed to Still's disease (Robecchi¹⁰⁵).

Spondylitis osteo-arthritis is classified as a common osteo-arthritis. All its pathological and radiological signs concurrently show a substantial identity with osteo-arthritis of other bones.

A climacteric arthritis does not appear in Italian classifications, because an ætiological relation between arthritis and the ovaries has not yet been proved and appears to be very unlikely. Arthritis in menopause is due to climacteric changes in weight and in blood circulation, and does not directly depend on ovarian insufficiency (Pende, Micheli,⁸² Ceconi,^{27, 28} Robecchi,¹⁰⁵ Carlini²³).

Also the clinical entity of a psoriatic arthritis has been denied, as no ætiological relationship can be established between psoriasis and arthritis (Ceconi,²⁹ Robecchi,¹⁰⁵ Micheli⁸²).

DYNAMIC PATHOLOGY.—In Still's disease hæmatological observations have been made by Micheli and Gamna,⁸¹ Giordano,⁵³ Cipriani, Robecchi and Angeleri, Pancrazio,^{85, 86} De Matteis and Verdolini,⁴⁴ Mazzoni.⁷⁷ There is a frequent, but rarely very marked, leucocytosis, with absolute, and sometimes also relative, increase of neutrophils; with absolute and relative increase of lymphocytes and, at times, of monocytes. In acute stages there is a decrease or a disappearance of eosinophils. Lymphocytosis and eosinophilia are also frequent in other types of rheumatoid arthritis (Cipriani, Robecchi and Angeleri). The Arneth count is normal in latent periods; whereas it is clearly shifted to the left in active Still's disease. In osteo-

arthrosis the number of white cells is usually normal, but a relative increase of lymphocytes and eosinophils is frequent. Rieder's and Türk's cells have never been found in chronic rheumatism.

In rheumatoid arthritis the albumin-globulin ratio is close to the lowest normal figures and plasma fibrinogen is slightly increased. In uratic arthritis fibrinogen increases during attacks and is normal in latent periods. In osteo-arthritis the ratio is normal and fibrinogen is also normal or slightly increased (Cipriani and Robecchi).

The sedimentation rate is almost constantly increased in rheumatoid arthritis. In uratic arthritis, during latent periods, its figures are generally normal even when blood uric acid is very high. The sedimentation rate increases during attacks, especially when they are accompanied by fever and marked swelling (Cipriani and Robecchi). The same authors have emphasised the importance of the sedimentation rate for the indication of stimulant physical therapy: this treatment must be delayed as long as the sedimentation rate is greatly increased.

Normal sedimentation rate has been found in 44 per cent. only of patients suffering from osteo-arthritis. This fact is due to secondary inflammatory phenomena which very often appear when osteo-arthritis has lasted a long time, as was the case in the patients investigated for this inquiry (Robecchi¹⁰⁵).

The blood tryptophane shows the same behaviour as the sedimentation rate (Pescarmona⁹⁰).

In some thousands of rheumatic patients the fasting blood sugar was frequently higher than normal. In sixty cases the glucose tolerance test was performed and showed delay in the rate of removal of glucose from the blood-stream. These data, which confirm those established by Pemberton, have been interpreted as being due to changes in the peripheral circulation and not to modified insular activity (Robecchi and Battistini¹⁰³).

The increased oxalic acid level in the blood and the changes in the oxalic acid tolerance test have been considered to be consequences of the altered carbohydrate metabolism (Marcolongo and Barone,⁷⁵ Robecchi, Battistini and Quaglia,^{15, 103} Di Marco⁷⁴).

Blood calcium is not rarely increased in rheumatoid arthritis. This may depend on the rarefaction of bone, which is very pronounced in this disease. Blood calcium in osteo-arthritis and in uratic arthritis remains within normal limits (Robecchi and Battistini¹⁰³).

Blood phosphorus and the calcium-phosphorus ratio have normal values, according to the same authors and to Angeleri and Pescarmona.⁶

Slight changes have been noted in blood potassium, but the potassium calcium ratio is not changed (Coggi³⁸).

Inquiries on sulphur metabolism have shown that the glutathione concentration in the blood is normal. The rate of oxidation of sulphur is frequently decreased, and this change is related to the gravity of the clinical condition, as it is more evident in the most advanced cases. This finding is common to rheumatoid arthritis and to osteo-arthritis. Uratic arthritis, however, shows normal values (Battistini, Robecchi and Quaglia^{11, 13, 14}).

Serum complement is frequently decreased in rheumatic fever, but it is mostly normal in rheumatoid arthritis (Robecchi, Battistini and Silvani^{9, 12}).

The behaviour of the iso-agglutinating power of blood serum has been studied in various patients and in healthy individuals under different conditions (Ravenna⁹⁴). In rheumatoid arthritis it is more or less increased, while it shows normal figures in osteo-arthritis, uratic arthritis and fibrositis (Angeleri, Battistini and Robecchi¹⁰³).

The functions of the superficial blood capillaries are seriously impaired in rheumatoid arthritis (Lunedei and Corradini); this fact also has been established by means of specialised techniques—*e.g.*, with the test of capillary reactions after exposure to cold—by Angeleri, Battistini and Robecchi.⁵

PATHOLOGY.—Numerous contributions to the pathology of rheumatoid arthritis have been made by Micheli and Gamna,⁸¹ Ceconi,²⁸ Costa, Cassano,²⁵ Fieschi,⁴⁶ Galdi, Gentili,⁵⁰ Parenti,⁸⁷ Scardino,¹⁰⁷ Simonetti, S. Levi,⁶⁰ Tripputi, Oggioni and Toldo, Bini,¹⁷ Magrassi.⁷¹ Their data have been collected and completed with numerous personal observations by C. Giordano in an extensive paper published in 1937⁵² and in a very recent report.⁵⁵

Pathological material is relatively abundant for Still's disease. But it is very scarce, especially in early stages, in the other two types of rheumatoid arthritis, on account of their very long clinical courses. Generally, lesions found at post-mortem examinations do not show the active morbid picture, but its late consequences. Pathological examination of early lesions must be confined to some tissue fragments, obtained by biopsy, or to the post-mortem examination of patients deceased from intercurrent diseases.

The descriptions of joint lesions, either in early or in late stages, are essentially the same as can be found in all modern textbooks. The fact is to be noted that the changes found in all types of rheumatoid arthritis, including Still's disease, appear to be similar and indistinguishable.

Sometimes chronic pyogenic rheumatism presents a similar pathology; but the diffuse or nodular infiltrations of synovia and periarticular tissues often contain many neutrophil leucocytes, whereas in rheumatoid arthritis the infiltration is mostly formed by lymphoid and plasmatic cells and by monocytes.

Lymph-gland lesions are very rare in rheumatoid arthritis, except in Still's disease, in which they form one of the characteristic features. Their histologic picture has been described as that of a common subacute or chronic inflammation without peculiar characters (Giordano,⁵³ Michelazzi,^{79, 80} S. Levi⁶²).

Chronic tubercular polyarthritis may show a clinical picture very similar to that of Still's disease, not only because of the aspect of the joints, but also because of the presence of a well-marked adenopathy (Giordano, Reitano). In these cases histological examination of a gland, showing the presence of typical tuberculous changes, often decides the diagnosis.

Enlarged spleen in Still's disease presents a chronic lymphatic hyperplasia, with regressive changes in the wall of the follicular vessels. When the splenic enlargement is very conspicuous there are signs of congestion and those phenomena of meso-arteritis and peri-arteritis which, according to what I maintained in a paper on the pathogenesis of congestive splenomegalies,⁹³ are probably the principal change responsible for all congestive splenic enlargements.

Subcutaneous nodules have the same characters in acute rheumatic fever and in chronic rheumatism. They have no diagnostic value in the differential diagnosis of these diseases, and cannot serve to ascribe both diseases to a single ætiological factor, for similar changes may be found in many specific diseases due to other causes, either infectious (frambœsia, syphilis) or not (traumatic nodules) (Ravenna,⁹⁵ Pozzo,⁹¹ Giordano,⁵⁵ Scardino¹⁰⁷).

Fibrinous or exudative pericarditis has frequently been found in Still's disease. Other cardiac changes are extremely rare.

Valvular disease, occasionally found in rheumatoid arthritis patients, can be referred to previous rheumatic fever, the clinical

course of which might have been overlooked on account of the absence of articular symptoms. Myocardial changes have rarely been found in post-mortem examinations of rheumatoid patients. Their characters differ a great deal from those of rheumatic myocarditis, because of their slight intensity and because their diffuse lymphocytic and polynuclear cell infiltrations never look like typical Aschoff's nodules (Micheli and Gamma,⁸¹ Gior-dano,^{52, 53, 55} Robecchi¹⁰⁵).

Articular effusions show the chemical characters of exudates in rheumatoid arthritis, in osteo-arthritis, in uratic and in traumatic arthritis. In a series of more than 1,500 arthritics, the joint effusions were shown to be frequent in Still's disease and in chronic arthritis related to trauma, while they were relatively rare in the other types of rheumatoid arthritis and in osteo-arthritis (Cionini and Robecchi^{37, 38}).

RADIOLOGY.—Lupo's important study on the radiology of chronic joint diseases, read at the 23rd Congress of the Italian Society for Hydroclimatology (Acqui—S. Remo, June 1934),⁷⁰ has been extended and published in a recent detailed article.^{70a, 71} This work is worthy of note because it is based on the study of several thousands of patients (from the wards and out-patients departments of the Medical Clinic of Turin and the Rheumatologic Clinic at Acqui), as well as because of the scarcity of our knowledge on this matter.

The most important conclusions of Lupo deal with the radiologic picture of rheumatoid arthritis and its comparison with those of rheumatic fever, pyogenic rheumatism and gonococcal arthritis. According to this author the radiological changes of rheumatoid arthritis are the following:

1. Conspicuous and early increased bone transparency, which differs from disuse atrophy, because it is more homogeneous, is confined to spongy tissue and is accompanied by loss of density balance, due to a relatively increased density of the cortex (appearance "en demi-deuil" of French authors).
2. Progressive narrowing of the joint spaces, characterised by its uniform extension along the whole line of the joint.
3. Plastic, wax-like deformation of the epiphyses, caused by the shrinking of the joint capsule.
4. Lastly, destruction of the articular extremity and disappearance of the joint line and bony ankylosis.

To these changes may be added the acceleration in the ossi-

fication of carpal osseous nuclei (Gralka's symptom), which is frequently evident in infants suffering from Still's disease, but which is not characteristic of this, because it depends on the circulatory changes induced by an inflammatory process in the wrists of children.

These changes have been found in cases of rheumatoid arthritis of an infective character, of rheumatoid arthritis with no definite infective character, and of Still's disease. No differences could be found for a distinction between these diseases, except for spondylitis ankylopoietica, which is the only one that presents a different radiological picture. I have already pointed out that this is an important argument against the inclusion of spondylitis ankylopoietica in this class.

The first change to be found in spondylitis ankylopoietica is ossification in the ligaments of the vertebræ and of some large joints. This lesion precedes atrophy by a long time. Changes of true rheumatoid arthritis of the vertebræ show a quite different character—*i.e.*, marked increase of bone transparency, with accentuation of the borders of the vertebræ, which appear like reels, and lipping in their edges. This lipping may be easily distinguished from osteophytic formations.

The findings in cases of rheumatic fever are very different and, substantially, negative. The only features are: (1) Slight increase of articular spaces, probably due to effusion; (2) barely appreciable bone atrophy, which is present only in cases of very long duration and is due to inactivity; (3) inflammatory thickening in the peri-articular tissues.

Radiological changes in pyogenic rheumatism are characterised by the appearance of small, more or less circular zones of atrophy, sometimes confluent in polycyclical areas of decreased opacity. These areas are situated in an epiphysis or in the spongy bone and sometimes are surrounded by a thin halo of diminished transparency. By the confluence of the above-mentioned areas a large breakdown of bone tissue may result and then the picture becomes similar to that of other forms of chronic arthritis.

The first radiological finding in acute septic arthritis is bone destruction in the articular border, surrounded by a blended halo of demineralisation. Disuse atrophy appears secondarily.

In gonococcal arthritis Lupo has shown a characteristic change that has diagnostic value for its evidence in early stages, when the diagnosis may fluctuate between rheumatic fever and septic

arthritis. Closely beneath the thin line of increased opacity that limits the bone towards the joint cavity, a thin line of increased transparency appears; it looks as if it had been skilfully drawn. Its length is variable and sometimes it extends along the whole joint border. This peculiar aspect corresponds to the laminar sequestration which is characteristic in the pathology of gonococcal arthritis. In advanced cases this sign is less evident and the finding is similar to that of other septic arthritides.

A study of the Roentgen aspect of arthritis in undulant fever has been made by Benassi.¹⁸

ÆTIOLOGY.—The predisposing or determining causes of rheumatoid arthritis have been sought in familial factors. Their importance is shown by the high familial incidence (about 30 per cent., Robecchi¹⁰⁵). Rheumatoid arthritis has been observed in four young members of one family (two boys and two girls) by Robecchi and Pescarmona,⁹⁸ and a very rare instance of Still's disease in two brothers has been recently described by Giordano.⁵⁶

Surroundings and occupational factors ought not to be of a marked importance in rheumatoid arthritis, because this disease is very frequent also in well-to-do patients. The often-observed rheumatism of laundry workers and rice-field labourers is due to recurrent rheumatic fever and not to rheumatoid arthritis (Robecchi¹⁰⁵).

Females are more frequently affected by rheumatoid arthritis: the proportion observed by Robecchi is 35 males to 100 females.

The relationship between rheumatic fever and rheumatoid arthritis must be mentioned here, not only because of the possibility of chronic rheumatism following rheumatic fever, but also because some authors believe that true rheumatoid arthritis is always due to the same ætiological agent as rheumatic fever. This opinion has been opposed in Italy, because of the differences between the clinical pictures, the cardiac complications, the response to salicylates, the pathological pictures and numerous other reasons that have been discussed by Micheli,⁸² Ceconi,^{27, 28} Robecchi,¹⁰⁵ Andrei and Ravenna^{2, 3, 95} and Giordano.⁵⁵ All these characteristics, which are not decisive when considered separately, cumulatively give very sharply defined individualities to the clinical and pathological pictures of rheumatic fever and rheumatoid arthritis. Some common histologic notes, the fibrinoid swelling and the lympho-monocytic nodules, are by no means characteristic evidence of an identical

ætiology. The importance of subcutaneous nodules has been emphasised too often (Ravenna,⁹⁵ Giordano⁵⁵).

Endocrine glands have no direct importance in the ætiology of rheumatism (Pende, Ceconi,²⁸ Micheli⁸²). The pathology of the parathyroid glands and the results of their removal or of more or less superficial operations in the neck has been frequently studied (Francaviglia, Bendandi,¹⁹ Conti,³⁹ etc.); they have been inconsistent, and the prevalent opinion is that the clue to the right understanding of chronic rheumatism is not to be found there (Micheli,⁸² Robecchi,¹⁰⁵ Usseglio¹¹⁴).

Excluding some well-known metabolic forms of arthritis (gout, alcaptonuria), no definite importance has been given to abnormalities of nutrition. The importance of malnutrition in the pathogenesis of osteo-arthritis has decreased, while the value of hereditary, traumatic and local circulatory factors has increased (Robecchi¹⁰⁵).

Nervous factors undoubtedly have a determining importance in some arthritides. These are considered in a special class, which includes tabetic arthritis and other joint deformations accompanying nervous diseases. Among these are the joint changes of encephalitic parkinsonism, which have been studied by Pennacchiotti.⁸⁹ But the coincidence of nervous changes with rheumatoid arthritis is too rare for the admission of any relationship between these diseases (Robecchi¹⁰⁵). Neither can osteo-arthritis micro-atrophicans (Blum) be referred to nervous changes (Usseglio and Ceresa,¹¹³ Ceconi^{27, 28}).

Bacteriology has decided the ætiology of all the rheumatic diseases which are included in the class of rheumatism due to a known ætiological agent. The causative agents (streptococci, staphylococci, gonococci, Koch's bacillus) have been found in affected joints. This fact not only explains the ætiology, but also shows the inconsistency of any theory that tries to explain these joint lesions as a toxic or allergic mechanism.

In rheumatoid arthritis, including Still's disease, bacteriological examinations have been very numerous; but results have been negative, with few exceptions (Gallerani,⁴⁹ Corelli^{40, 41}). These researches have been carried out on joint fluid, or synovial and peri-articular tissues, surgically removed during acute phases, and on regional glands and subcutaneous nodules (Giordano^{51, 52, 54}). The prevalent opinion is that rheumatoid arthritis is a true infectious disease: the fact that the causative agent has not yet been found does not mean that it does not exist, but that

it is still undiscovered (Micheli⁸²). The negative bacteriological findings in Still's disease are one of the strongest arguments against the acceptance of a causative agent common to this disease and sepsis lenta such as the *Streptococcus viridans*. A marked difference between these diseases has been established also from the clinical view-point (Micheli^{81, 82}).

Numerous investigations have been made to explain the constant failure to discover germs in joints affected by rheumatoid arthritis, while refusing to deny an ætiology by known bacteria. Many experiments are related to the so-called allergic-focal infection. According to this theory a focus of localised infection might induce a bacterial hypersensitivity in the organism and entry into the circulation of bacterial toxins might provoke the morbid picture of rheumatoid arthritis as the result of a general anaphylactic reaction. I have already summarised the results of these experiments, which are in part related to the ætiopathogenesis of rheumatic fever. They have yielded no proof to support the role of allergy, because the experimental lesions have always been found in tissues where the presence of germs could be demonstrated or might have been demonstrated (Andrei and Ravenna,^{2, 3} Magrassi). The pathological comparison between experimentally induced changes and the lesions of human rheumatic fever has made it possible to exclude an identity or even a close similarity. In rheumatic fever this comparison is relatively easy on account of its typical pathology (Ravenna⁹⁵). The pathology of chronic rheumatism is not so sharply defined or so characteristic, and every morphological comparison is, therefore, difficult and undecisive. The question of an eventual allergic origin must be resolved on other bases. Neither have instances of experimental arthritis induced by injection of foreign protein yielded results applicable to the pathogenesis of rheumatoid arthritis (Locatelli, Barbiroli⁷).

Interesting advances have been made in the ætiopathogenesis of gout. The investigations can be divided into two groups; the first deals with the general pathogenesis of gout and the second with the pathogenesis of the arthritic attack. The summary of the work done in the first group would be too lengthy; these researches deal with the renal insufficiency, the hypertension and the gastric anacidity of gouty patients (Battistini, Robecchi, Quaglia and Pescarmona^{10, 16, 101, 105}). The second group has shown suggestive results on joint pathology. Uric acid has a peculiar tropism for joints; it is a very modest phlogogenous

agent, but it can strengthen the inflammatory potency of other substances. Allergic phlogosis is greatly reinforced by uric acid (Rondoni). This fact is probably a consequence of its power to increase the permeability of membranes (Chini). In experimental animals an allergic phlogosis due to intravenous injection of foreign protein in a previously sensitised animal can be localised in a joint by means of a preparatory introduction of uric acid (Chini). Various papers by Chini³¹ and an interesting review by Robecchi¹⁰² deal with the practical value of these findings, which go to show that the attack of gout is due to an allergic reaction towards different allergens, probably of alimentary origin, and that this reaction is localised in joints by the uric acid.

TREATMENT.—The therapy of chronic rheumatism is based upon hygienic treatment and sometimes on diet (Pisani⁹⁰ got satisfactory results with Pewsner's desensitising diet); upon anti-infective agents (general stimuli—proteinotherapy and chemotherapy, and local stimuli—histamin and similar poisons, and also the Chinese acupuncture which has recently been tried by Vinai¹¹⁶); upon topical drugs, physical treatment and orthopaedic procedures. A recent review on the therapy of rheumatism has been published in the *Gazzetta Medica Italiana*, 1938, vol. 97, no. 12 (December).

Surgical removal of foci of chronic infection (teeth, tonsils, appendix, gall-bladder, prostate, etc.) has not aroused the same enthusiasm in Italy as in other countries. This matter, however, has been the object of extensive observations by the Schools of Professors Frugoni (Rome), Micheli (Turin) and Azzi (Turin). Their principal results have been collected in a Report on Focal Infections, read by Lusena and Chini at the 39th Congress of the Italian Society for Internal Medicine, Pavia, October, 1933; in a synthetic report by Frugoni,⁴⁸ in many experimental studies by Andrei and myself,^{2, 3} Mela,⁷⁸ Lucca,⁶⁷ Spina¹⁰⁸ and Chini,^{32, 33, 34, 35, 36} and in a recent detailed review on connections between tonsils and internal diseases by Chini.³⁰ From the therapeutic view-point the prevalent practice is to remove chronically inflamed organs only when they are, by themselves, a direct cause of disease (Micheli,⁸² Ceconi,²⁸ Malan).

This does not exclude the possibility of cases of pyogenic rheumatism caused by germs entering the blood-stream from a chronic infective focus. But the spread of germs from an acute inflammatory process, where the focus has not yet become circumscribed, is likely to be a more frequent eventuality. Whether

the removal of the primitive focus of infection can cure the rheumatism is an unresolved question; but it is difficult to understand why germs living in joints or in peri-articular tissues should not be able to grow and to multiply after the removal of the so-called foci, and why the joint disease should need a continuous supply of germs from the primitive focus.

Inflammation of the tonsils or of another organ can be followed by a recurrent attack of a latent or healed rheumatism. But this does not imply a common ætiological agent. The massage of inflamed tonsils can induce a new acute articular attack; the same results can, however, be obtained in the same patients with any protein shock, with a milk injection for instance, where all infective mechanisms can be excluded. The positive result of the tonsillar massage (the so-called tonsillar-test) demonstrates no more than the existence of foreign protein in the tonsillar tissue (Robecchi, Olivetti and Malan⁸⁴).

Also the successes that sometimes have been obtained with vaccine therapy are probably due to non-specific stimulo-therapy and do not prove an ætiological connection between the injected germs and the rheumatism (Corelli,^{40.} ⁴¹ Fieschi,⁴⁶ Usseglio,¹¹⁴ Andrei and Ravenna³).

The same conclusion has been drawn from the clinical observation on many patients who have already been deprived of all possible foci of chronic infection and yet do not show a more favourable clinical course than others (Micheli⁸²).

Oily suspensions of gold salts give very good results which it is impossible to obtain with other methods in the treatment of rheumatoid arthritis. The action of gold salts is not strictly bound to the dose and should not be confined to a shock therapy. Notwithstanding its well-known dangers, such a therapy forms the best means at our disposal for the treatment of chronic rheumatism (Angeleri, Battistini, Robecchi,⁴ Usseglio,¹¹⁴ Finazzi,⁴⁷ Galdi).

A new method in the treatment of arthritis was employed by Rinaldi, a physician in a small village near Siena (Tuscany). His method was kept a secret, but was published after his death, following an inquiry by the Department of Health of the Italian Home Office (Marotta, Lazzarini and Calò⁷⁶). Rinaldi's method consisted essentially in injections of strong doses of sodium glycerophosphate, together with small doses of sodium cacodylate and strychnine. It has been tried by Lucherini,^{68.} ⁶⁹ Usseglio,¹¹⁴ Caccuri,²² Del Prete,⁴³ M. Levi,⁶⁰ Sartori¹⁰⁶ and others, who gave intravenous injections of 10 c.c. of a solution containing

2.5 grammes of glycerophosphate in distilled water. This method has been employed in all chronic rheumatic diseases. Daily injections must be given for 20 days. This treatment has an evident and rapid action on pain and swelling; the patients also feel better and their appetites increase manifestly; they become euphoric, feed more abundantly and the movements of affected joints improve. These results can be obtained in a few days, but they are only temporary. Since this treatment appears to be harmless, it can be employed in everyday practice even though it does not produce the miraculous effects that had been claimed. After all, we do not yet know of any other miraculous treatment of arthritis.

Studies on mud-therapy have been made by Peserico and Pisani. A recent review of its results, stating indications and contra-indications in rheumatic patients, has been published by Quaglia.⁹² As mud-therapy acts as a lively stimulus, its use must be carefully delayed during acute periods, both in rheumatism and in gout. The sedimentation rate may be very helpful in indicating the right time for beginning the treatment. The effect of this therapy on uric acid metabolism has been studied by Comel, Barengo⁸ and Jandolo.⁵⁷ The variations of complement in the blood during mud-therapy have been studied by Robecchi, Battistini and Silvani.¹³

Among other therapeutic attempts that have had a limited or unconfirmed success I would mention the injection of cerebrospinal fluid in chronic arthritic patients (Negro) and the intraspinal injection of phenolsulphonaphthalein (Boschi²¹).

In the local treatment of arthritis, histamin has been used with success (Negri,⁸³ Jacchia) and good results have been claimed with intra-arterial injection of gentian violet (Lucarelli⁶⁶) and with novocain infiltration of the peri-articular tissues (Tri-podi,¹¹⁰ Mansione and Bugliari⁷³) in mono-articular arthritides.

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