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THE EXPERIMENTAL PRODUCTION OF ARTHRITIS

A REVIEW

BY

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The cause of rheumatoid arthritis remains unknown. For some years it has seemed that the pathogenesis of the disease might be more easily understood if a convenient animal replica were available for laboratory study. To this end much work on animal arthritis and the resultant considerable literature bear tribute. Nevertheless, it must reluctantly be admitted that not one of these forms of animal arthritis is strictly analogous to the human disease in which there is conclusive evidence neither of infection, of chronic physical or chemical irritation, of endocrine disturbance nor, in spite of suggestive serological changes, of causal immunological disorder.

The reasons determining this apparent inability to reproduce the disease in animals should be examined. That rheumatoid arthritis is a disease peculiar to the primates or to man is a possibility that has not been excluded. The value of further attempts to produce varieties of arthritis in small rodents must be seriously questioned. Consideration of this problem, and the need for promising lines of future inquiry have led the reviewer to gather together those methods which have previously been adopted for the laboratory study of arthritis. Previous surveys of the subject are listed in Table I.

No attempt has been made to divide the methods according to the purpose of the investigator, but for convenience the methods have been classified as infective, chemical, endocrine, immunological, and physical.

It is clear that the popularity of these experimental methods is determined by the particular era in which the work is performed, while the expressed purpose of the studies reflects contemporary interest in individual diseases. In the same way the animals chosen for investigation are usually those most easily available, cheapest, and most readily maintained, rather than those which would on theoretical grounds be expected to provide the most satisfactory analogy with the subjects of human disease. In many ways, therefore, the experimental study of arthritis has been handicapped by considerations irrelevant to the basic biological problems, and it is perhaps not surprising that the overall impression gained from a review such as this is of conflict, confusion, and stagnation. There is little doubt that future progress will depend upon more rational, more extensive and, almost certainly, less economical experimental design.

TABLE I

REVIEWS IN CHRONOLOGICAL ORDER

Author	Date	Subject
Redfern	1850	Experimental lesions of cartilage
Garrod	1859	Early nomenclature
Garrod	1876	Early nomenclature
Bannatyne	1896	Pathology of rheumatoid arthritis
Meyer	1901	Infective arthritis
Menzer	1902	Infective arthritis
Pommer	1929	Degenerative joint disease
Key	1930	Degenerative joint disease
Vannotti	1934	Allergic arthritis
Westcott	1941	General review
Findlay	1946	Pleuropneumonia-like organisms (P.P.L.O.)
Collins	1949	General review
Chevillard	1952	General review; measurement of responses
Dresner	1955	Aetiology of rheumatoid arthritis
Wilson and Miles	1955	Infective arthritis
American Rheumatism Reviews 1-12	1935-1959	*Ann. intern. med.*, 8-50. (13th review in preparation.)

I. EXPERIMENTAL PRODUCTION OF ARTHRITIS BY INFECTIVE AGENTS

The experimental study of infective arthritis began with the bacteriological era and historically has tended to follow the emphasis placed on organisms of diminishing size.

In the present account the infective agents used to induce arthritis are discussed in sequence according to their relative significance in contemporary research. The authors referred to in the following section are listed chronologically in Table II.

TABLE II

EXPERIMENTAL PRODUCTION OF ARTHRITIS BY INFECTIVE AGENTS

(1) *Pleuropneumonia-like Organisms*

Reviewed by Klieneberger (1940), Sabin (1941), Wallerstein and others (1946), Findlay (1946), and Dienes and Weinberger (1952).

Collier	(1938; 1939a to f)
Collier and Essefeld	(1938)
Findlay and others	(1939)
Collier and Staverman	(1939)
Rhodes and van Rooyen	(1939)
Sabin	(1938; 1939a, b; 1940)
Bonne	(1940)
Sabin and Warren	(1940)
Sabin and Johnson	(1940)
Preston	(1942)
Beeuwkes and Collier	(1942)
Powell and others	(1946)
Tripi and Kuzell	(1947)
Tripi and others	(1949)
Gardner and others	(1949)
Kuzell and Gardner	(1950)
Kuzell and Mankle	(1950)
Kuzell and others	(1951; 1952)
Parkes and Wrigley	(1951a)
Cordy and others	(1955; 1958)
Moulton and Adler	(1957)

Murphy Rat-lymphosarcoma Exudate Arthritis

Jasmin	(1956; 1957a, b)
Richer and Jasmin	(1957)
Hershberger	(1958)

(2) *Streptococci*

Early work reviewed by Meyer (1901) and by Menzer (1902), the more recent literature by Wilson and Miles (1955).

Bannatyne and others	(1896)
Shaw	(1904)
Cole	(1904)
Coombs and others	(1912)
Davis	(1912)
Jackson	(1913)
Schloss and Foster	(1913)
Rothschild and Thalhimer	(1914)
Thalhimer and Rothschild	(1914)
Nathan	(1917)
Cecil	(1931)
Hadjopoulos and Burbank	(1932)
Rinehart and others	(1934)
Rinehart	(1935)
Rawls and Chapman	(1935)
Schultz	(1936)
Brinch	(1936)
Cecil and others	(1939)
Rothbard	(1940)
Angevine and others	(1942)
Friedlander	(1951)
Friedlander and others	(1951b)
Benko and others	(1953)
Smirnov and Beletskaia	(1955)

(3) *Erysipelothrix rhusiopathiae*

Goret and Jean	(1934)
Collins and Goldie	(1940)
Goldie and Collins	(1951; 1956)
Hughes	(1955)
Sikes and others	(1955a, b; 1956; 1957)

(4) *Other Pyogenic Organisms*

Lion	(1890)
Buday	(1890)
Saint-Germain	(1893)
Lanz	(1893)
Bannatyne and others	(1896)
Michaelis	(1897)
Triboulet	(1898)
Apert	(1898)
Poynton	(1898; 1899)
Westphal and others	(1899)
Poynton and Payne	(1900a, b, c, d, *et seq.*)
Beaton and Walker	(1903)
Beattie	(1904)
Nathan	(1917)
Brunschwig and Jung	(1931)
Svartz	(1938)
Cecil and others	(1939)
Rigdon	(1942)
Friedlander	(1951)
Friedlander and others	(1951b)

(5) *Streptobacillus moniliformis*

Levaditi and Selbie	(1930)
Levaditi and others	(1930)
Buddingh	(1944)
Levey and Levey	(1948)
Freundt	(1956a, b)

(6) *Tubercle bacillus*

Schüller	(1880)
Krause	(1899)
Griffith	(1925)
Blacklock	(1957)

(7) *Mycotic Arthritis*

Pepere	(1913)
Bolognesi	(1923)
Gammel and Moritz	(1933)
Lorizio	(1939)
Jasmin	(1957b)

(8) *Typhoid bacillus*

Molinari and Dusso	(1933)

(9) *Corynebacteria*

Levaditi and others	(1931)
Fischl and others	(1931)
Friedlander and others	(1951a)

(10) *Viruses*

Sokoloff and Beegel	(1953)

(1) Pleuropneumonia-like Organisms (Nocard and Roux, 1898).—An extensive literature deals with the relationship of the pleuropneumonia-like organisms (P.P.L.O.) to spontaneous and experimental arthritis. Comprehensive accounts of the nature of the P.P.L.O., of their distribution, and of their relationship to arthritis in man and animals have been given by Klieneberger (1940), Sabin (1941), Wallerstein, Vallee, and Turner (1946), Findlay (1946), and Dienes and Weinberger (1952).

Interest in the association of the P.P.L.O. with arthritis began in 1938-1939. Findlay, Mackenzie, MacCallum, and Klieneberger (1939) referred to the papers of Collier (1938, 1939a) describing an outbreak of spontaneous rat polyarthritis in the Dutch East Indies. Organisms grown in the laboratory and resembling the L.5 group of Klieneberger reproduced the disease after inoculation. Collier's observations were dealt with most fully in a series of reports (Collier, 1938; Collier and Esseveld, 1938; Collier, 1939a-f; Collier and Staverman, 1939); they were outlined in English (Collier, 1939a) and the whole problem was revived in the post-war period (Collier, 1948) in relation to a mouse epizootic. The histological changes found in the rat joints were detailed by Bonne (1940), who regarded them as an osteosynovitis rather than

as an arthritis and described the resulting exuberant osteophytosis.

A similar outbreak of arthritis in the rat was reported by Rhodes and van Rooyen (1939). Arthritis progressed to healing or to spontaneous amputation. The disease was thought to be similar to that caused by *Streptobacillus moniliformis*, and to that caused by *Ectromelia* in mice, but neither of these organisms was identified. The disease could be transmitted to rats, but not to mice. Sabin (1939a, b) described a form of progressive, proliferative arthritis produced in mice by a P.P.L.O. and likened the disease to rheumatoid arthritis. In another paper (Sabin, 1938), he reported a strain which multiplied in brain as well as on serous surfaces. The treatment of mouse P.P.L.O. arthritis was first investigated by Sabin and Warren (1940) using aurothioglycolate compounds. Paradoxically, these chemicals did not inhibit the growth of P.P.L.O. *in vitro*, but might produce cure of the arthritis. Sabin and Johnson (1940) searched for the organism in cases of Reiter's disease and in rheumatoid arthritis, after Sabin (1940) had described a progressive arthritis in the experimentally infected mouse. Their work emphasized the similarity of the disease to rheumatoid arthritis. Preston (1942), however, found that the inflammatory lesions were principally periarticular and that with increasing virulence the incidence of arthritis diminished. Beeuwkes and Collier (1942) cautiously compared two strains of P.P.L.O. isolated from spontaneous rat polyarthritis and from rats inoculated with material from a case of rheumatic arthritis, but the concensus of opinion (Tripi, Gardner, and Kuzell, 1949) preferred to accept animal P.P.L.O. infections as useful experimental models rather than as exact replicas of any particular human disease. Thereafter the majority of workers used experimental P.P.L.O. arthritis in this way to evaluate therapeutic agents. However, Cordy, Adler, and Berg (1958) (see also Cordy, Adler, and Yamamoto, 1955) passaged goat P.P.L.O. through lambs and found that injection into pigs caused arthritis, serositis, and meningitis, while Moulton and Adler (1957) demonstrated the production of arthritis in chick-embryos inoculated with P.P.L.O. Streptomycin and myocrisin were shown to be effective means of treating experimental P.P.L.O. arthritis (Powell, Jamieson, and Rice, 1946) following the earlier work of Findlay and others (1939), and of Sabin (1940), on the value of gold and of sulphonamides, and that of Snow and Hines (1941) on the influence of obstructive jaundice (Engerman and Meyer, 1959). Tripi and Kuzell (1947) confirmed the value of gold, but Gardner, Fairley, and Kuzell (1949) adopted the reciprocal approach and showed that animals treated with B.A.L. (dimercaprol) had a higher incidence of severe arthritis than controls. Exposure to cold (70° F.) and to ultraviolet light curiously reduced the incidence and severity of arthritis. Similar observations were made with salazopyrin (Kuzell and Gardner, 1950), terramycin, aureomycin, cortisone, and ACTH (Kuzell and Mankle, 1950; Kuzell, Schaffarzick, Mankle, and Gardner, 1951), and organic copper salts. This work was later reviewed (Kuzell, Gardner, Fairley, and Tripi, 1952). It formed the background for studies of a similar nature (Parkes and Wrigley, 1951a) in which the candid conclusion was reached that the histological changes were not sufficiently similar to those of rheumatoid arthritis to provide a valid model.

Jasmin (1956) described a polyarthritis in the rat resulting from injecting the exudate from a pouch bearing the Murphy rat lymphosarcoma. Whether the resulting arthritis was anaphylactic (Jasmin, 1957a, b) or infective (Richer and Jasmin, 1957) was not clear, but there was a good response to cortisol (Hershberger, 1958).

(2) Streptococci.—The early work on the experimental production of infective arthritis, confused by differences of nomenclature, was reviewed by Meyer (1901), and by Menzer (1902). Bannatyne, Wohlmann, and Blaxall (1896) used organisms isolated from a patient with "rheumatism"; streptococci were employed in a similar manner by Shaw (1904) and Harris (1905). Cole (1904) described related experiments but disagreed with the concept of a *Diplococcus rheumaticus* specific to acute rheumatism. Coombs, Miller, and Kettle (1912) and Davis (1912) reported the production in rabbits of lesions resembling those of rheumatic fever. Jackson (1913) injected rabbits with streptococci recovered from a human outbreak; she found evidence of arthritis when the animals were examined at intervals up to 4 months after the injections. Single or repeated intravenous injection of streptococci led Schloss and Foster (1913) to the production of both acute and chronic polyarthritis in monkeys. The chronic articular lesions were nonspecific. Rothschild and Thalhimer (1914) and Thalhimer and Rothschild (1914) confirmed the observations of Cole (1904) and of Davis (1912) and claimed that half the rabbits they injected with *Streptococcus imitis* developed an arthritis similar to that found in human infections with the same organism. They agreed that it was unjustifiable to postulate a special variety of organism on the basis of a capacity to pro-

duce arthritis. Nathan (1917) made experiments of a generally similar nature, but used other pyogenic organisms in addition to streptococci. Hadjopoulos and Burbank (1932) gave convincing evidence that a subacute arthritis could be produced in rabbits by inoculating streptococci of low virulence isolated from cases of chronic febrile arthritis. They concluded that the changes were the direct result of local infection and not of allergy. Rinehart, Connor, and Mettier (1934) considered the relationship between infection and scurvy.

Previous attempts to reproduce acute rheumatism had been unsuccessful, but the influence of subclinical ascorbic acid deficiency was believed to predispose to the development of lesions resembling those of rheumatoid arthritis (Rinehart, 1935). Their suggestion that the arthritis of rheumatoid arthritis is simply the result of subclinical scurvy modified by streptococcal infection has not been substantiated. Pirani, Bly, and Sutherland (1950) extended the study of scorbutic arthropathy to the guinea-pig. Rawls and Chapman (1935), quoting the work of Cecil, Nicholls, and Stainsby (1931), divided a series of streptococci into those which were agglutinable and those which were inagglutinable and resistant to the bactericidal action of fresh blood. Intravenous injections into rabbits showed that more than 90 per cent. of the inagglutinable strains produced arthritis. It seems likely that the reactions observed were simply a measure of virulence. Schultz (1936) made similar studies with Group C streptococci. Using scorbutic guinea-pigs, he found only slight arthritic changes and could not relate them to the presence of infection. A simple account of the histological changes in experimental streptococcal arthritis was given by Brinch (1936), who emphasized the resemblance to degenerative joint disease rather than to rheumatoid arthritis. Dawson (1937) reviewed the evidence implicating streptococci in the pathogenesis of rheumatoid arthritis; he emphasized that no final conclusion could be reached. The work of Cecil, Angevine, and Rothbard (1939), in which haemolytic streptococci were used to cause arthritis in rabbits, led these authors to conclude that the lesions found, although resembling those of rheumatoid arthritis, were not specific. Their work was continued by Rothbard (1940) using the albino rat, and by Angevine, Cecil, and Rothbard (1942) using the rabbit. Rothbard (1940) found that most rats injected with virulent human streptococci developed a purulent arthritis. Blakemore, Elliott, and Hart-Mercer (1941) reported the changes found in joint-ill in lambs, a suppurative arthritis which develops during the first month of life following the infection of wounds with a variety of organisms, of which streptococci are the most frequent. This work has not, so far as I am aware, been made the basis of an experimental study. Friedlander (1951) and Friedlander, Habermann, and Parr (1951b) included haemolytic streptococci among the pyogenic organisms they studied, and a discussion of the effect of Weld's streptotoxin on experimental arthritis was given by Benko, Boszormenyi, Olah, Csati, and Szeitz (1953). Smirnov and Beletskaia (1955) found that deoxycortone (cortexone) exacerbated the arthritis caused in rats by β-haemolytic streptococci.

(3) ***Erysipelothrix rhusiopathiae.***—The paper by Goret and Jean (1934) on the *Bacillus du rouget* or *Erysipelothrix rhusiopathiae* in naturally-occurring swine arthritis at first attracted little attention among those investigating the pathology of rheumatic disease. Joint disease in the rabbit followed intra-articular, subcutaneous, intradermal, or intravenous inoculation. Optimal results were obtained by injecting sublethal inocula subcutaneously. Collins and Goldie (1940) made a detailed study of the infection in swine and of the polyarthritis. They were able to reproduce the disease by the repeated intravenous injection of *Erysipelothrix rhusiopathiae* into each of eight animals. Hypersensitivity was not a prerequisite for the appearance of the chronic proliferative arthritis. Bacteriaemia followed injection; the organism could be isolated from the joints for up to 8 months afterwards. Goldie and Collins (1951) reported similar studies with rabbits. Intravenous inocula much smaller than those which effectively produced pathological changes resulted in arthritis in fourteen of fifteen rabbits. As is commonly the case in the experimental study of arthritis, the clinical recognition of the arthritis was difficult: the need for histological confirmation was emphasized. Ten of the 26 knee joints so studied were found to be diseased. Subsequently (Hughes, 1955; Sikes, Neher, and Doyle, 1956) interest in this disorder increased. Sikes, Neher, and Doyle (1955a) recovered the organism from hogs with the naturally-occurring infection; intra-articular injection was an effective means of infecting unexposed shoats.* Cortisone but not ACTH caused remission (Sikes, Neher, and Doyle, 1955b), while cortexone augmented the disease (Sikes, Neher, and Doyle, 1957). Contrary to this work, Goldie and Collins (1956) showed that in rabbits cortisone favoured the development of arthritis following small repeated inocula.

* shoats: young hogs.

The experimental inoculation of *Erysipelothrix rhusiopathiae* into young hogs or into rabbits offers a method of reproducing a disease in which the joints show many of the histological changes found in rheumatoid arthritis in the human. However, many of these characteristics of rheumatoid arthritis are, in themselves, non-specific; since no organisms have been identified in the human disease, the pursuit of this experimental replica can be regarded only as principally of theoretical interest.

(4) Other Pyogenic Organisms.—The earlier literature contains many undocumented references to studies of suppurative arthritis (Lion, 1890; Buday, 1890; Saint-Germain, 1893; Lanz, 1893; Michaelis, 1897; Triboulet, 1898; Apert, 1898; Westphal, Wassermann, and Malkoff, 1899). Bannatyne, Wohlmann, and Blaxall (1896) were among the first to describe the experimental production of a suppurative arthritis by the intravenous inoculation of rabbits with organisms, probably bacilli, recovered from the synovial fluid of a patient with "rheumatism" (probably rheumatic fever). A similar approach was adopted by Poynton (1898, 1899), Poynton and Payne (1900a, b, c, d, *et seq.*), Beaton and Walker (1903), and Beattie (1904). The work of Poynton and Payne (1900) gained considerable notoriety. They concluded, on the basis of experiments conducted with rabbits, that human rheumatic fever was the result of infection with a "*Diplococcus rheumaticus*", an organism isolated from human cases of this disease which would cause a purulent arthritis in rabbits. A similar form of suppurative bacillary polyarthritis had been produced by Lanz (1893). Nathan (1917) repeated this work, using a variety of organisms including streptococci, staphylococci, and pneumococci. The work of Brunschwig and Jung (1931) suggested for the first time that certain of these pyogenic infections might not be due directly to bacterial invasiveness. Microscopical lesions in rabbit joints identical with those seen after intravenous or intra-articular administration followed the injection of a 7-day culture after filtration through a Chamberland L3 filter. The authors suggested the action of a staphylococcal toxin. In discursive and poorly illustrated papers, Svartz (1938) reported the production of polyarthritis by the repetitive inoculation of an emulsion of the polymorphic diplococci isolated from patients with polyarthritis; she concluded that the changes resembled those of human rheumatism. Cecil, Angevine, and Rothbard (1939) found lesions in rabbits after the repeated intravenous injection of *Streptococcus viridans*, staphylococci, pneumococci, and *Salmonella paratyphi A*, histologically similar to the non-specific changes they associated with rheumatoid arthritis. Rigdon (1942) contrasted the response of actively and passively immunized rabbits to the intravenous inoculation of a broth culture of *Staphylococcus aureus*, and Friedlander (1951) and Friedlander, Habermann, and Parr (1951b) used the albino rat and mouse in a survey of the effects of haemolytic streptococci. A statistically significant increase in the incidence of arthritis was produced by previous treatment with cortisone acetate.

Neither staphylococci, nor any of the organisms studied in these papers, can be held responsible for rheumatoid arthritis, although they may be secondary invaders. Work on experimental pyogenic arthritis can be accepted as relevant only to the now unimportant problem of human suppurative arthritis (Kellgren, Ball, Fairbrother, and Barnes, 1958).

(5) *Streptobacillus moniliformis.*—Among the lesions described by Levaditi and Selbie (1930), and by Levaditi, Selbie, and Schoen (1930), in mice spontaneously or experimentally infected with *Streptobacillus moniliformis*, were polyarthritis of the vertebral column and subcutaneous nodules. The microscopical appearances were considered to be similar to those of acute or of chronic human arthritis but knowledge of the possible role of P.P.L.O. in mouse arthritis came only later. Survival, which was rare, was accompanied by a deforming arthritis. Buddingh (1944) made an important contribution in his study of the infected chick-embryo, using a strain derived from a human case of rat-bite fever. In the chick, blood stream invasion was followed by almost exclusive localization of the organisms in the synovial membranes of joints, in the lining cells of which the organism behaved as a facultative intracellular parasite. Infected mice were effectively treated with streptomycin (Levey and Levey, 1948). Freundt (1956a, b) described a mouse epizootic due to the same organism. The disease was quickly fatal; arthritis was uncommon. Spontaneous amputation of infected limbs characterized the natural but not the experimental infection.

Because of its tendency to localize in joints with synovial cavities, and because of the resemblance of some of the resulting histological changes to those of rheumatoid arthritis, *Streptobacillus moniliformis* may be thought to provide as satisfactory a replica of the human disease as any other known organism. It is clear again, however, that information derived

from such infections can be applied to the problem of rheumatoid arthritis only with the greatest caution.

(6) Tubercle Bacillus.—Following the work of Schüller (1880), Krause (1899) showed that infection in rabbit and guinea-pig bones rarely occurred at the sites of fractures but was common in joints which had been distorted. The whole problem of trauma in relation to experimental infective tuberculous arthritis was reviewed by Blacklock (1957). Griffith (1925) made the interesting discovery that avian tubercle bacilli injected into rabbits were localized within the joints in each instance. The relevance of this work to the common problems of human polyarthritis is uncertain.

(7) Mycotic Arthritis.—The fungus of mycetoma, *Monosporium apospermium*, was used by Pepere (1913) to produce a purulent arthritis in rabbits, and Bolognesi (1923) made a study of seven fungi and caused a mycotic arthritis in albino rats which occasionally resolved spontaneously. Gammel and Moritz (1933) demonstrated the destruction of articular cartilage in rabbits following the intra-articular injection of *Actinomyces asteroides* and of *Monosporium apospermium*. Granuloma formation was accompanied by bone absorption and necrosis.

In the course of a series of experiments on the properties of *Nocardia sanfelice*, Lorizio (1939) injected the knee joints of rabbits with a culture of the streptothrix. Although the lesions found were those of a subacute inflammation, becoming chronic, a possible similarity to chronic forms of human arthritis was not remarked. More recently *Nocardia asteroides* has been invoked as an explanation for the arthritis caused by the Murphy rat-lympho-sarcoma exudate (Jasmin, 1957b).

The incidence of human mycotic arthritis has risen in recent years, but in the reviewer's experience the infection is more likely to be an associated complication of rheumatoid arthritis than to bear any causal relationship.

(8) Typhoid Bacillus.—In an original approach, Molinari and Dusso (1933) attempted to produce an arthropathic strain of typhoid bacilli by growing virulent bacilli in a medium containing articular extracts. 1 ml. broth culture was injected into the knee joints of rabbits. The claim was made that such organisms, after passage, were organotropic. However, the arthritis was suppurative and mono-articular. This work apparently has not been repeated, but recalls the later experiments of Glynn and Holborow (1952) and of Boake and Muir (1955).

(9) *Corynebacteria.*—Although the claim of Levaditi (1931) that the causative agent of mouse arthritis was a coccobacillus and that of Fischl, Koech, and Kussat (1931) that the infection was due to *Corynebacteria* were both suspect because of the subsequent discovery in arthritic mice of P.P.L.O., further studies of a *Corynebacteria*-like organism isolated by Friedlander, Habermann, and Parr (1951a) showed that this organism could be used to induce a previously undescribed form of polyarthritis in white rats.

(10) Viruses.—Sokoloff and Beegel (1953), in a survey of viruses of rabbit vaccinia, infectious myxomatosis, and virus III, demonstrated that the local injection of these organisms caused an arthritis in rabbits. Trauma to the joints before systemic viral infection, and the local injection of the growth products of Group A streptococci did not cause the virus infection to localize.

Comment

Many forms of infective arthritis have been studied experimentally, principally in mice, rats, and rabbits. These infections provide easily reproducible models of arthritis for laboratory study, and for the testing of analgesic, anti-inflammatory, and chemotherapeutic agents. It remains to be demonstrated that any of these infections is in any way relevant to the problem of rheumatoid arthritis in the human.

II. Experimental Production of Arthritis by Chemical Agents (Table III)

Arthritis produced by the direct application of chemical irritants alone or in combination with physical stimuli has been studied experimentally for at least 100 years. The method is simple and reproducible, but the changes caused have never gained easy acceptance as true replicas of the common forms of chronic human arthritis. This limitation has not deterred first, the student of degenerative joint disease, and secondly, and more recently, the student of rheumatoid arthritis. The diversity of agents employed covers an extraordinary range. In this review the classification of agents as physical or chemical has been adopted for convenience, although, owing to the preconceptions of investigators, it often reflects specific

attempts to reproduce degenerative joint disease or rheumatoid arthritis respectively.

TABLE III

PRODUCTION OF EXPERIMENTAL ARTHRITIS BY CHEMICAL AGENTS

(1) *Distilled water; sodium chloride solution*
- Key (1933)

(2) *Acids; Alkalis*
- Riedel (1896)
- Burckhardt (1924)
- Seeliger (1926)
- Häbler (1928)
- Key (1933)

(3) *Other Protein-Denaturing Agents*

(*a*) *Xylene, turpentine*
- Jordan (1938)
- Ramsey and Key (1955)

(*b*) *Formaldehyde*
- Selye (1949)
- Brownlee (1950)
- Frenk and others (1950)
- Fachini and others (1950)
- Uebel and Korting (1950)
- Amante and Bidone (1950)
- Dugal (1951)
- Parkes and Wrigley (1951b)
- Anttonen and others (1951)
- Bourne (1951)
- Gallini and Grego (1951)
- Madonia (1952)
- Gubner and others (1952)
- Bacchus (1952)
- Gaglio and others (1953)
- Zorn and others (1953)
- Blech and Emrich (1954)
- Bonomo and Chirico (1954)
- Gaglio and Leonardi (1954)
- Saric and others (1954)
- Radino and Bagolan (1954)
- Zorn and Mankel (1954)
- Conti (1954)
- Gerocarni and Calderera (1956)
- Farneti and Miccoli (1956)
- Vykydal and others (1956)
- Gujral and Saxena (1956)
- Maschio and Boschi (1956)
- Zorn and Schmidt (1957)
- Zorn (1958)
- Gujral and others (1959)

(*c*) *Iodine*
- Riedel (1896)
- Burckhardt (1924)
- Key (1930)

(4) *Other Organic Chemicals*

(*a*) Indole, skatole; Indole propionic acid; Tryptamine — Forbes and Neale (1937)

(*b*) Streptococcal toxin; Diphtheria, tetanus, staphylococcal toxoids; Tyramine and other substances; Cortisone, testosterone; Trypsin, gastric mucin; Bacterial mucopolysaccharides; Hyaluronic acid; Friedlander's bacillus, streptococcal vaccines — Jones and Carter (1954)

(*c*) *Histamine*
- Uebel and Korting (1950)
- Jones and Carter (1954)
- Bensley (1955)

(*d*) *Scorbutic Arthropathy*
- Rinehart (1935)
- Schultz (1936)
- Pirani and others (1950)

(*e*) *Proprionitriles*
- Wawzonek and others (1955) and many subsequent papers

(*f*) *Papain*
- Thomas (1956)

(*g*) *Caragheenin*
- Williams (1957)
- Gardner (1957a; 1960)

(*h*) *Hydralazine*
- Comens (1956)
- Gardner (1957b)
- Dubois and others (1957)

(*i*) *Mustard*
- Coutu and Selye (1950)
- Teodoru and others (1952)
- Ducommun and Coutu (1952)
- Ducommun and others (1952)
- Coutu and others (1953)
- Radino (1957)

(1) Injection of Distilled Water or of Sodium Chloride Solution.—As part of an extensive series of investigations into the factors determining degenerative joint disease, Key (1933) injected distilled water, and normal or 10 per cent. sodium chloride into the knee joints of rabbits. Distilled water produced thickening of synovial tissues and an excessive amount of fluid, but, strangely, the changes found with normal sodium chloride were more severe. The conclusion that such lesions resembled those of osteo-arthritis should probably be interpreted as an indication only of their non-specificity.

(2) Injection of Acids or of Alkalis.—Burckhardt (1924) attempted to define the conditions necessary for the production of arthritis deformans in various species. He injected carbolic acid into the limb joints of guinea-pigs, rats, rabbits, and dogs. The work was essentially a repetition of that of Axhausen (1913), who supported the theory that for degenerative joint disease to develop a nidus of dead articular cartilage was necessary. Burckhardt explored the role of immobilization of the joint on the evolution of arthritis by suturing limbs beneath the skin, by cutting the motor nerves (see Nozoe, 1938), and by placing a metal ring round the flexed limb. Seeliger (1926) attributed degenerative joint disease to acidity of the synovial fluid and attempted to reproduce the disease in rabbit knee joints by injecting N/50 hydrochloric acid. Villous hyperplasia and replacement fibrosis of articular cartilage led him to judge his theory to be supported by these results. The work was repeated by Häbler (1928), who noted that distilled water caused more rapid and more severe damage than acid, suggesting the importance of a disturbed colloid state and altered cartilaginous elasticity rather than of a simple change in acidity. Key (1933) used caustic soda, and lactic, acetic, or hydrochloric acids for a similar purpose, experiments deriving from the bizarre combination of caustics and heat said by Mannheim (1929) to have been studied by Kremjanski (1868).

Riedel (1896) reported work with caustic ammonia or tincture of iodine. The appearances of the

degenerating articular cartilage resembled the non-specific lesions produced by electrolysis (Axhausen, 1913, 1914).

Fischer and Timbrell (1927) are reported by Mannheim (1929) as authors of work on experimental arthritis with radium bromide. As far as the reviewer is aware this is the only instance in which local irradiation has been used for this purpose.

(3) Other Protein-Denaturing Agents.—Although Jordan (1938) had used xylene and turpentine (*a*) in his studies, it was the adoption by Selye (1949) of formaldehyde (*b*), as a means of inducing what he termed a self-perpetuating arthritis in the rat, which popularized protein-denaturing agents as tools for causing experimental chemical arthritis.

Selye showed, not surprisingly, that formaldehyde injected around the limb joints of rats caused acute inflammation. Large doses induced a more chronic lesion with oedema, hyperaemia, connective tissue proliferation, and stiffness. Relating this work to his earlier studies on hormone-induced arthritis (Selye, Sylvester, Hall, and Leblond, 1944), Selye claimed that the formaldehyde arthritis was aggravated by deoxycortone acetate (cortexone) or by crude anterior pituitary preparations, but was almost completely inhibited by cortisone or by ACTH, suggesting an antagonism between the two groups of hormones.

A spate of papers followed. A few workers showed that some of the essential conclusions on which Selye based his theories could not be substantiated. Many others greeted Selye's work with less discretion and elaborated his hypotheses. Brownlee (1950) confirmed that formalin injected beneath the plantar aponeurosis of the rat caused arthritis. In adrenalectomized animals he compared the influence of deoxycortone and of ascorbic acid, concluding that deoxycortone exacerbates the arthritis in normal rats but less severely in adrenalectomized animals. Frenk, Wolfe, and Paschkis (1950) could not relieve the arthritis with deoxycortone and ascorbic acid. Fachini, Ceresa, Rubino, and Morpurgo (1950), Amante and Bidone (1950), Uebel and Korting (1950), Gallini and Grego (1951), Anttonen, Rinne, and Rinne (1951), Gaglio, Mazzone, and Leonardi (1953), Bonomo and Chirico (1954) extended Selye's work. By contrast, Parkes and Wrigley (1951b) failed to show that ACTH or cortisone alleviated the arthritis, but confirmed that deoxycortone exaggerated local swelling. Bourne (1951) was unable to define the self-perpetuating chronic arthritis likened by Selye to rheumatoid arthritis, and confirmed in fact that the arthritis was usually more accurately described as a periarthritis. Frequently the joints were not directly involved and neither cartilaginous erosion nor granulation tissue could be found. Dugal (1951), however, showed the aggravating effect of cold on the formalin-induced swelling, and the ameliorating effect, in adult rats, of ascorbic acid. Madonia (1952) suggested that methyl thiouracil acted *via* the pituitary/adrenal axis in suppressing the development of formalin arthritis. Gubner, Cote, Hughes, Oleson, Ruegsegger, and Williams (1952) confirmed the benefits of cortisone and of ACTH. Bacchus (1952) found that ascorbic acid did not influence the formalin changes in adrenalectomized rats, suggesting that ascorbic acid acted on the intact adult animal by influencing the adrenal cortical hormones. Formalin arthritis was studied by Zorn, Plagwitz, Wolf, Kraul, and Schirmeyer (1953) and by Saric, Tessier, Rivière, and Bertharion (1954), principally from the aspect of treatment with drugs like isonicotinic acid hydrazide. Not unexpectedly, Radino and Bagolan (1954) showed that ultrasonic vibration caused exacerbations of both formalin and serum arthritis. Zorn and Mankel (1954), Zorn and Schmidt (1957), and Zorn (1958) continued their therapeutic studies with quinoline derivatives, with female sex hormones, and with harpagophytum root, but made no real contribution to our knowledge of the pathogenesis or therapy of the human disease. Adenosine triphosphoric acid was used by Conti (1954), and phenylbutazone by Gaglio and Leonardi (1954) in similar observations, while Blech and Emmrich (1954) showed that partial hepatectomy 1 or 2 days before the injection of formalin reduced the resistance of animals to the inflammatory agent. More recently, a variety of additional therapeutic agents, including cortisone and vitamin B_6 (Gerocarni and Calderera, 1956), heavy metals (Vykydal, Klabusay, and Trnavsky, 1956; Farneti and Miccoli, 1956), cortisone, phenylbutazone, myocrisin, and salicylates (Gujral and Saxena, 1956), and extracts of *Glycyrrhiza glabra Linn.* (Gujral, Sareen, Tangri, Roy, Gupta, and Amma, 1959), have been used in similar experiments. Maschio and Boschi (1956) compared a formalin arthritis of rabbits with the arthritis caused in dogs by the local resection of cartilage (see Kroh, 1909).

Like the majority of chemical agents employed to cause experimental arthritis, formalin has been used in experiments made in most instances to fit preconceived theories, and not simply to test unsubstantiated hypotheses; this has led to a considerable volume of work on the pathogenesis of arthritis in the rat but little of this can be accepted as immediately relevant to the problem of rheumatoid arthritis in man. The use of formalin invites

comparison with earlier work designed to produce osteo-arthritis (Axhausen, 1913; Pommer, 1915), and its local influence is open to critical assessment because of the demonstration that its action is often to produce periarticular rather than articular inflammation, doubtless because of the difficulty of making true intra-articular injections into small rodents.

(4) Other Organic Chemicals

(*a*) The demonstration of excessive amounts of indole in the urine of patients with rheumatoid arthritis led Forbes and Neale (1937) to inject indole, skatole, and indole propionic acid into the joints of rabbits, producing a chronic arthritis. No far-reaching conclusions were drawn; neither the design nor the prosecution of this experiment stand close scrutiny.

(*b*) Very many other organic chemicals and extracts, the majority ineffective (Table III, 4*b*), were used by Jones and Carter (1954) in an attempt to find a reproducible form of arthritis in the guinea-pig. Mucopolysaccharides from various sources were effective in causing occasional synovial lesions, but the changes were not specific, were not associated with anaphylaxis, and often developed before antibody formation was demonstrable. Work with the polysaccharide extracts of Friedlander's bacillus (Jones, Carter, and Rankin, 1954) led to a series of important observations (Jones and Carter, 1957a, b; Jones and Mayne, 1958), in which the evolution of the arthritic lesions in the guinea-pig was studied with ^{14}C-labelled polysaccharide, and in which the modifying influences of cortisone and of ACTH on the mucopolysaccharides of the involved tissues were investigated.

(*c*) Bensley (1955) discussed the factors involved in the production of arthritis by histamine, a drug which had also been studied by Uebel and Korting (1950) and by Jones and Carter (1954). Local inflammatory and generalized endocrine changes were caused by single or repeated injections of sterile isotonic histamine acid phosphate; the chronic changes resembled those of human arthritis.

(*d*) It is probably desirable to refer at this point to the view of Rinehart (1935) that the lesions of rheumatoid arthritis were mimicked by those of experimental scurvy (Schultz, 1936; Pirani, Bly, and Sutherland, 1950); this opinion did not take sufficient account of the non-specificity of many of the lesions in the human disease, and the published illustrations were not sufficiently clear to confirm or refute this theory.

(*e*) The recent interest in experimental lathyrism (Wawzonek, Ponseti, Shepard, and Wiedenmann, 1955) drew attention to a means of causing experimental maldevelopment of joints and ligaments. The effective proprionitriles have not apparently been used in conjunction with agents specifically damaging joint tissues such as anti-synovial antisera.

(*f*) It is not clear whether the necrosis of rabbits' ear cartilage caused by papain (Thomas, 1956) offers an approach to this problem.

(*g*) The reviewer has found it convenient to employ the highly sulphated mucopolysaccharide carragheenin (Jackson, 1956a, b; Williams, 1957) as an agent to produce arthritis in rabbits and guinea-pigs (Gardner, 1957a, 1960). Repetitive periarticular injections lead to sustained synovial inflammation; in selected microscopic fields it is found possible to locate changes indistinguishable from those commonly seen in rheumatoid arthritis in the human (Gardner, 1960). Such changes, however, are individually not specific.

(*h*) Considerable interest was aroused by the description of the hydralazine syndrome (Dustan, Taylor, Corcoran, and Page, 1954), but the enthusiastic description of an experimental form of systemic lupus erythematosus (Comens, 1956) has not been confirmed (Gardner, 1957b; Dubois, Katz, Freeman, and Garbak, 1957), and joint changes analogous with those of the human disease (Cruickshank, 1959) have not been found.

(*i*) The use of mustard in causing an experimental arthritis was popularized by Coutu and Selye (1950), who injected 0·1 ml. of a 10 per cent. mustard suspension into eighteen intact rats and eighteen adrenalectomized rats. The authors were unable to confirm the claim of Brownlee (1950) that deoxycortone and ascorbic acid were beneficial. Teodoru, Feyal-Cabanes, and Jequier (1952), studying mustard arthritis, showed that chloramphenicol did not influence the anti-inflammatory effect of cortisone in spite of its stimulating effect on the reticulo-endothelial system. Ducommun and Coutu (1952) observed the effect of fasting on mustard arthritis, and Ducommun, Jacot, Coutu, Koch, and Selye (1952) compared the anti-inflammatory effects of irgapyrine and phenergan on the same condition; these anti-inflammatory effects could be produced in adrenalectomized rats. Coutu, Gareau, and Ducommun (1953) claimed that deoxycortone exaggerated the arthritic response which was minimized by cortisone. It is clear from the illustrations in this and in earlier papers that the mustard arthritis induced in rats was a poor replica of

rheumatoid arthritis in man. Coutu, however, emphasized that the differences were quantitative and not qualitative, a point which requires objective confirmation or refutation. Later, Radino (1957) extended her study of the effects of ultrasonics to mustard arthritis, including work on the histochemistry of the connective tissues.

Comment

Several organic and inorganic chemicals may be used to induce convenient forms of experimental arthritis in small laboratory animals. These forms of arthritis provide acceptable models for the study of the pathological physiology of joint disease, but none can be regarded as reduplicating in detail the evolution and behaviour of rheumatoid arthritis.

III. Experimental Production of Arthritis by Altered Endocrine Mechanisms (Table IV)

(1) Action of Deoxycortone Acetate in Normal Rats.—The possibility that arthritic changes resembling those of rheumatic fever and of rheumatoid arthritis might be produced experimentally by altered endocrine function was suggested by Selye (Selye and Hall, 1943; Selye and Pentz, 1943; Selye, Sylvester, Hall, and Leblond, 1944). The production of joint lesions in rats by giving very large amounts of deoxycortone acetate (cortexone) was described. In the original report three animals out of eight given deoxycortone developed arthritic changes; these changes appeared within 10 days of starting treatment, and subsided and reappeared in different joints without obvious reason. Many animals in the colony died from intercurrent infection and the possible role of infection in causing arthritis was not given sufficient consideration. From this work, which included studies of adrenalectomized and of thyroidectomized animals, the conclusion was drawn that the adrenal cortex plays an important part in the pathogenesis of rheumatic fever and of rheumatoid arthritis in man.

Not all workers were able to verify these results. Harrison (1946) and Pemberton, Eiman, Patterson, and Stackhous (1947) encountered arthritis in a group of rats on standard laboratory rations, in a group on grossly unbalanced diets, and in a group receiving large amounts of deoxycortone by injection. Pemberton and his associates were unable to show that thyroidectomy, adrenalectomy, or gonadectomy influenced the incidence or severity of the arthritis which took the form of focal areas of articular cartilaginous degeneration and ulceration. Many rats, they admitted, were heavily parasitized and controls were poorly defined. The published illustrations are unconvincing. Pirozynski and Akert (1949) repeated Selye's work. Among seventeen rats no spontaneous deaths occurred during the experiment; after 2 to 3 weeks fifteen showed a subacute non-suppurative focal polyarthritis. Controls were not used. Haour (1949) considered that the arthritic changes attributed to deoxycortone were not specific. The whole problem of the hormonal production of arthritis was discussed by Justin-Besançon, Rubens-Duval, Villiaumey, and Kahn (1953) in one of the few reviews of methods for the experimental study of arthritis. In their own work fifty rats were treated in accord-

Table IV

Experimental Production of Arthritis by Altered Endocrine Mechanisms

(1) *Action of Deoxycortone Acetate in Normal Rats*
- Selye and others (1944)
- Harrison (1946)
- Pemberton and others (1947)
- Haour (1949)
- Pirozynski and Akert (1949)
- Justin-Besançon and others (1953)
- Siebenmann and Uehlinger (1953)
- Salgado (1955)
- Smirnov and Beletskaia (1955)

(2) *Effect of Adrenal Damage in Deoxycortone Arthritis*
- Harrison (1951)

(3) *Action of Deoxycortone in Adrenalectomized Rats*
- Selye and others (1944)
- Tarnopolsky and others (1951)

(4) *Action of Deoxycortone in Thyroidectomized Rats*
- Selye and others (1944)
- Pirozynski and Akert (1949)

(5) *Action of Deoxycortone in Thyroparathyroidectomized Rats*
- Harrison and Barnett (1953)

(6) *Arthritis and the Influence of Cold in Adrenalectomized Rats*
- Chamorro (1945)

(7) *Action of Pregneninolone in Adrenalectomized Rats*
- Chamorro (1945)

(8) *Action of Adrenal Cortical and Anterior Pituitary Extracts in Castrated Thyroidectomized Rats*
- Soto and Nava (1950)

(9) *Action of Stilboestrol Alone or with Cortisone*
- Coutu (1950; 1953)
- Jones and Carter (1954)

(10) *Hormonal Response to Parabiosis*
- Hall and Hall (1951)

(11) *Action of Anterior Pituitary Hormones*
- Bassi and Bassi (1946)
- Soto and Nava (1950)
- Selye (1950a, b)
- Reinhardt and Li (1953)
- Franz (1957)
- Jasmin and Bois (1959)

(12) *Action of Somatotropic and Thyrotropic Hormones in Thyroidectomized Rats*
- Salgado (1955)

(13) *Effects of Radiothyroidectomy in Mice*
- Silberberg and Silberberg (1954a, b)

ance with Selye's descriptions and they claimed to have produced a comparable arthritis. Their experiments remain open to criticism, but their review, with 107 references, is valuable. Siebenmann and Uehlinger (1953) agreed with Selye and others (1944) in attributing to deoxycortone and salt an inflammatory reaction, but they could not accept the implied analogy with human disease. Salgado (1955) referred to earlier work in which only two of 250 rats given deoxycortone developed arthritis detectable clinically, while of 100 rats given somatotrophin none developed arthritis. Smirnov and Beletskaia (1955) also found that deoxycortone alone was ineffective.

(2) Effect of Adrenal Damage in Deoxycortone Arthritis.—Harrison (1951) studied the production of arthritis in uninephrectomized rats given deoxycortone and salt. He showed that inadvertent damage to the arterial supply to the left adrenal could cause zonal necrosis, and suggested that this might account for the sensitizing influence of uninephrectomy in Selye's experiments through diminished secretion of glucocorticoids.

(3) Action of Deoxycortone in Adrenalectomized Rats.—The removal of the adrenals was considered by Selye and others (1944) and by Tarnopolsky, Schajowicz, Lustig, and Montuori (1951) to predispose to joint involvement in animals given deoxycortone, particularly during exposure to cold. However, adrenalectomy in the rat may be an uncertain procedure (Harrison, 1951).

(4) Action of Deoxycortone in Thyroidectomized Rats.—Selye and others (1944) and Pirozynski and Akert (1949) considered the influence of thyroidectomy on the evolution of the arthritis caused by deoxycortone. They agreed that thyroidectomy predisposed to arthritis but there was no indication whether this was a specific endocrine effect.

(5) Action of Deoxycortone in Thyroparathyroidectomized Rats.—Harrison and Barnett (1953) treated rats by thyroparathyroidectomy, with or without uninephrectomy. Five of the first group and three of the second developed arthritis within 33 days. There was, however, a high incidence of endemic infection in the colony and only thirteen animals survived to the end of the experiment. It is not possible to be certain that the lesions reported were similar to those of rheumatoid arthritis.

(6) Arthritis and the Influence of Cold in Adrenalectomized Rats.—Considered by Chamorro (1945).

(7) Action of Pregneninolone in Adrenalectomized Rats.—During work on pregneninolone, Chamorro (1945) observed the spontaneous development of arthritis in both treated and control groups among a series subjected to adrenalectomy. Because of the need for adrenalectomy he could not reconcile his findings with those of Selye. The number of animals studied was small.

(8) Action of Adrenal Cortical and Anterior Pituitary Extracts in Castrated Thyroidectomized Rats.—Soto and Nava (1950) were able to find articular swellings in eighteen of nineteen animals to which anterior pituitary and adrenal cortical extracts had been given following castration and thyroidectomy.

(9) Action of Stilboestrol Alone or with Cortisone.—Coutu (1950, 1953) studied four groups of adrenalectomized rats. To one group stilboestrol, to another cortisone, and to another both hormones were given. The extent of the arthritis was assessed by measuring limb diameters with calipers. Diethyl-stilboestrol was found, on this reckoning, to potentiate the effect of cortisone in inhibiting such a form of arthritis.

(10) Hormonal Response to Parabiosis.—In the course of a study of the "hypertensive hyalinosis syndrome", Hall and Hall (1951) noticed that many of the rats given salt to drink developed swollen joints. The swellings flitted unpredictably from joint to joint; small nodular lesions were found. In long-standing cases, cartilaginous erosion was added to synovial oedema and hydrarthrosis. To account for this response the currently acceptable theory of mineralocorticoid hyperfunction was advanced. This theory has not been substantiated. Incidental infection was not considered as a possible cause.

(11) Action of Anterior Pituitary Hormones.—Selye (1950a, b) produced an experimental arthritis resembling rheumatoid arthritis by the injection of freeze-dried material from anterior pituitaries. Reinhardt and Li (1953) compared twenty control animals with eighteen others from which the ovaries and adrenals had been removed and to which

freeze-dried pituitary extract had been given. Radiographs made after 6 months' treatment revealed joint erosions, localized osteoporosis, marginal lipping, and calcification. No histological evidence was adduced in this otherwise important paper; the authors conceded that sensitization to growth hormone had not been excluded as a cause of the arthritis. Nor was endemic infection considered. Franz (1957) quoted the work of Bassi and Bassi (1946a, b, c) in a study of acromegalic arthropathy, and Jasmin and Bois (1959) made similar claims for prolactin. Their illustrations show normal rat tissues.

(12) Action of Somatotropic and Thyrotropic Hormones in Thyroidectomized Rats.—Salgado (1955) showed that two of a group of animals given somatotropic hormone after thyroidectomy developed arthritis. By contrast no animals in a similar group given thyrotropic hormone developed such changes.

(13) Effects of Radiothyroidectomy in Mice.—Silberberg and Silberberg (1954a, b) showed that mice subjected to thyroid irradiation by ^{131}I developed articular lesions distinct from the degenerative joint disease found in ageing mice. In males, more susceptible than females, there was a strong positive correlation between the incidence of articular changes and that of hypophyseal tumours consequent on the thyroidectomy.

COMMENT

Few people now believe that the forms of arthritis induced by endocrine disturbances in small laboratory animals are strictly analogous with the arthritis of rheumatoid disease. It is possible that the extension of such studies to animal species more closely resembling man may prove more rewarding.

IV. IMMUNOLOGICAL METHODS FOR THE EXPERIMENTAL PRODUCTION OF ARTHRITIS (Table V)

(1) Local Injection of Sensitized Animals with Serum.—A form of joint inflammation was produced by Friedberger (1913) after the aseptic injection of sterile homologous serum into the knee joints of sensitized rabbits. Unsensitized animals and those given heterologous serum showed no such response. To this early work an important stimulus was given by the reports of Klinge (1929, 1930, 1931, 1933), who demonstrated that the local injection of foreign serum into the limb joints of sensitized rabbits caused an acute inflammatory reaction in which fibrinoid change was prominent and which was followed by a proliferative arthritis resembling rheumatoid arthritis and by degenerative and deforming sequelae. Murasawa (1934), in somewhat different circumstances, found that horse serum given intravenously to rabbits caused no joint lesions, but Sonnenburg (1934) confirmed that an hyperergic serum arthritis developed in rabbits, particularly when injected joints were rested. Immobilization alone caused only local osteoporosis, but prolonged immobilization of the injected joint resulted in ankylosis. More and McLean (1949) sensitized rabbits with horse serum; repeated injections were given 17 to 18 days later. Only six of the 53 pairs of knee joints examined showed lesions more severe than those of control animals. By contrast, Ungar, Damgaard, and Weinstein (1951) injected guinea-pigs intravenously with anti-egg albumen serum, and followed this one hour later by a smaller local injection into the ankle joints. The degree of swelling, measured with a micrometer screw gauge, was proportional to the amount of antibody nitrogen injected. De Marchin (1952) was able to demonstrate an inhibitory influence of ACTH on the evolution of arthritis in guinea-pigs provided the hormone was given before the joints were injected. Similar studies were made by Cereser (1953). Again, Fassbender and Pippert (1954) sensitized rabbits with horse serum and showed that hyaluronidase exaggerated the resulting joint swelling, while intravenous rutin reduced it. Coburn and Haninger (1954) provided what they concluded was an experimental replica of rheumatic fever by the production, with rabbit anti-egg albumen serum, of the passive Arthus phenomenon in guinea-pigs. In a further paper (Coburn, Graham, and Haninger, 1954), it was demonstrated that egg white incorporated in the diet of young guinea-pigs afforded protection against the anaphylactic arthritis produced by the local Arthus phenomenon. Bocking and Brien (1955) compared immediate (anaphylactic) and delayed (bacterial) sensitivity in rabbits, contrasting the responses with those obtained with local injections of formalin or with blood. The lesions of rheumatoid arthritis, it was thought, were most closely simulated by delayed hypersensitivity responses. Strogonow (1956) also used the Arthus phenomenon to induce allergic arthritis in the rabbit. He considered that the central nervous system played an important role in this reaction, a view not generally accepted in laboratories where Pavlovian theory is not dominant.

TABLE V

IMMUNOLOGICAL METHODS FOR THE EXPERIMENTAL PRODUCTION OF ARTHRITIS

(1) *Local Injection of Sensitized Animals with Serum*	
Friedberger	(1913)
Klinge	(1929; 1930a, b, c; 1931; 1933)
Murasawa	(1934)
Sonnenburg	(1934)
More and McLean	(1949)
Ungar and others	(1951)
de Marchin	(1952)
Cereser	(1953)
Fassbender and Pippert	(1954)
Coburn and Haninger	(1954)
Coburn and others	(1954)
Bocking and Brien	(1955)
Strogonow	(1956)
(2) *Local Injection of Foreign Proteins Other than Serum*	
Gudzent	(1933)
Brunschwig and Henry	(1933)
Goldie	(1938)
Soeur	(1949)
Gardner	(1957a)
(3) *Injection of Homologous Tissues or of Adjuvants Alone*	
Cavelti	(1947)
Humphrey	(1948)
Peck and Thomas	(1948)
McKee and Swineford	(1951)
Glynn and Holborow	(1952)
Stoerk and others	(1954)
Boake and Muir	(1955)
Pearson	(1956)
Odell and Key	(1957)
Pearson and Wood	(1959)
(4) *Injection of Anti-Homologous Tissue Antisera*	
Favour and others	(1955)
(5) *Local followed by Systemic Injection of Antigenic Material*	
Faber	(1915)
Kinsella and Hagebush	(1929)
Moritz and Morley	(1931)
Brunschwig and Henry	(1933)
Angevine and others	(1942)
Morgan and Bennett	(1947)
(6) *Other Observations on Sensitization to Foreign Material*	
Angevine and others	(1942)
Jones and others	(1954)
(7) *Influence of Immunity on Infective Arthritis*	
Freundt	(1956a, b)

(2) Local Injection of Foreign Proteins Other than Serum.—Gudzent (1933) injected rabbits subcutaneously with food extracts of high protein content, and repeated the injections 8 to 10 days later. After 3 to 4 weeks, smaller amounts of the same extract were injected into the joints, and an inflammatory reaction appeared within 24 hours. Further injections caused a recurrence, but this was also sometimes spontaneous. Similar reactions were elicited with peptones prepared from animal proteins, novoprotein (of plant origin), and pyrifer (an extract of dead coliform bacilli). Gudzent concluded that this form of experimental arthritis was similar to certain forms of human rheumatism, which were likely therefore to have an origin in allergy to unknown proteins. Brunschwig and Henry (1933) injected rabbits intra-articularly with filtrates of *B. subtilis*, *Strept. viridans*, and diphtheria bacilli. When the animals were killed 24 hours later, the joint swellings were sterile. After 21 days there was synovial thickening with plasma-cell infiltration but no gross cartilaginous destruction. Egg white and human serum reacted similarly. Goldie (1938) confirmed Klinge's observations and caused a non-suppurative arthritis in rabbits by giving subcutaneous followed by intra-articular injections, using as antigen a suspension of ground-up haemolytic streptococci. Soeur (1949) made similar studies. Their conclusion, generally similar to that of Gardner (1957a) who used sterile human synovial fluid to inject guinea-pigs, was that a sustained arthritis could be produced by repeated injections of foreign protein, but that there was no satisfactory evidence of an allergic mechanism.

(3) Injection of Homologous Tissues or of Adjuvants Alone.—Among the most controversial aspects of the whole unsettled subject of experimental arthritis, are the reports dealing with the production of arthritis by the injection of homologous tissue, often with adjuvants designed to stimulate homologous tissue antibody formation (Freund, Casals, and Hosmer, 1937). The concept of sensitization to a homologous or autologous body tissue component, perhaps initiated by some incidental damaging factor, is a widely discussed, commonly quoted, and largely unsubstantiated hypothesis, which has been advanced to account for the pathogenesis of connective tissue disorders such as rheumatoid arthritis and systemic lupus erythematosus. The adoption of this hypothesis as a basis for the study of experimental arthritis may be traced to the work of Friedberger (1913), Masugi (1933), Klinge and Knapper (1935), Cavelti (1945, 1947, 1948), and Cavelti and Cavelti (1945a, b, c). Cavelti and Cavelti (1945a) put forward evidence to show that Group A β-haemolytic streptococci could render antigenic material obtained from the kidneys of an homologous organism. They described the production by this means of homologous tissue glomerulonephritis in the rat (Cavelti and Cavelti, 1945b, c), and of antibodies to heart, skeletal muscle, and connective tissue (Cavelti, 1947). This work, extensive and detailed, has not been confirmed. Indeed, Humphrey (1948) concluded that evidence for the production of such an anti-homologous kidney antibody was lacking. Peck and Thomas (1948), in equally thorough but negative work, injected 350 rabbits with homologous heart and kidney together with adjuvants from Group A and Group C β-haemolytic streptococci grown on protein-free media. In further unsuccessful work,

McKee and Swineford (1951) injected aseptic suspensions of joint and kidney tissue with washed, heat-killed streptococci. No anti-synovia antibodies or joint lesions were found. Glynn and Holborow (1952) were more successful in a limited experiment with heterologous chondroitin derived from human cartilage, but repetition of the almost identical experiment by Boake and Muir (1955) yielded no evidence of arthritis when rabbits were injected with homologous chondroitin and killed streptococci. The results of Glynn and Holborow were attributed to the presence in the antigen of traces of heterologous protein.

Renewed interest in the problem of producing an homologous tissue arthritis was aroused by the report of Stoerk, Bielinski, and Budzilovich (1954). These authors claimed to have produced a chronic polyarthritis in rats by injecting homologous spleen and adjuvants. Antibiotics did not influence the persistence of the lesions and repeated cultures grew no P.P.L.O. This work has not been confirmed. Somewhat similar experiments, repeated unsuccessfully by the reviewer, were described by Pearson (1956), who claimed to have produced joint and other lesions with injections of homologous muscle and adjuvants. This careful work was followed by an admission that similar joint lesions could be elicited by injecting Freund's adjuvants without muscle. Although P.P.L.O. had been recovered from several of the original animals, these organisms were not believed to be responsible for the arthritis (Pearson and Wood, 1959). Odell and Key (1957) used egg albumen as antigen with Freund's adjuvants in similar work in the rabbit; they confirmed that adjuvants alone caused a more severe arthritic reaction than when mixed with antigen.

(4) Injection of Anti-homologous Tissue Antisera.—Favour, Goldthwait, and Bayles (1955) reported the injection of cell-free saline extracts of guinea-pig synovia into rabbits. They subsequently injected into guinea-pigs the rabbit anti-guinea-pig synovia serum obtained in this way, after labelling with ^{131}I. No antibody localization in the joints was detected nor was there histological evidence of synovial lesions.

(5) Local Injection followed by Systemic Injection of Antigenic Material.—Faber (1915) described the injection of rabbit knee joints with killed streptococci; 14 to 65 days later a further, intravenous injection was made. Gross lesions developed only when additional intravenous injections were given. Kinsella and Hagebush (1929), using a freeze-dried preparation of streptococci in the same manner, produced an allergic arthritis. Moritz and Morley (1931) injected bacterial filtrates from *B. coli* and *B. typhosus* into rabbit knee joints, and cutaneous injections were given synchronously; 20 to 30 hours later intravenous injections of the same antigen were made. Six of eleven animals showed a synovial reaction, with endovascular damage, thrombosis, and vascular necrosis. Similar studies were made by Brunschwig and Henry (1933). Angevine, Cecil, and Rothbard (1942) considered that a previous intra-articular injection of killed streptococci or streptococcal nucleoprotein sensitized joints to a subsequent intravenous injection of homologous organisms, resulting in a more chronic reaction than occurred when the preliminary injection was intravenous or intradermal. Morgan and Bennett (1947) produced a chronic rabbit arthritis by repeatedly injecting extracts of the somatic antigen of the typhoid bacillus. As with the classical Schwartzman reaction, there was extensive local vascular damage with thrombosis and necrosis followed by repair.

(6) Other Observations on Sensitization to Foreign Material.—Jones, Carter, and Rankin (1954) emphasized that the capacity of a series of injections of the polysaccharides extracted from Friedlander's bacillus to cause joint changes was a measure neither of the anaphylactogenic nature of the extract, nor of its nitrogen or protein content. In the guinea-pig there was no correlation between the occurrence of cardiac or of joint lesions; the changes produced by mucopolysaccharides from various sources were non-specific.

(7) Influence of Immunity on Infective Arthritis.—In a series of experiments with *Streptobacillus moniliformis*, Freundt (1956a, b) showed that, while death occurred too quickly in non-immune groups for arthritis to develop, the joint inflammation appeared in a relatively high proportion of surviving immunized animals.

Comment

Disturbed immunological mechanisms in rheumatoid arthritis are suggested by several of the common characteristics of the disease. The location of gamma globulin and rheumatoid factor on synovial margins, for example, has been confirmed. Nevertheless, there is no direct evidence that rheumatoid arthritis is caused by a disorder of the immune mechanism, and it remains likely

that the serological criteria diagnostic of the disease are associated and not causal features.

In view of these points, it is doubtful whether any of the forms of experimental arthritis produced by the stimulation of immunological mechanisms bear any true relationship to the spontaneous disease. Like the varieties of arthritis induced by chemical and physical agencies, they retain some value in the testing of analgesic drugs, but it cannot be accepted that they have as yet thrown light on the pathogenesis of rheumatoid arthritis.

V. Physical Methods for the Experimental Production of Arthritis (Table VI)

The lack of clear distinction between the pathological changes in rheumatoid arthritis and those of degenerative joint disease, which prevailed until 1896 (Bannatyne, 1896, 1904) in spite of the considerably earlier definition of rheumatoid arthritis (Garrod, 1859), renders difficult the interpretation of many experiments employing physical agents. Many early workers attempted to reproduce degenerative joint disease (Pommer, 1915, 1929; Axhausen, 1913); more recently the use of physical agents has become common in experiments which have as their aim the reproduction of rheumatoid arthritis.

(1) Local Injection of Irritants.—Key (1929) injected adult rabbit joints with citrated blood or with India ink. The acute inflammatory reaction subsided within 12 days. He later claimed (Key, 1930) to have confirmed the experiments of Axhausen (1913), which suggested that degenerative joint disease followed cartilaginous necrosis, and those of Burckhardt (1924), in which immobilization of the damaged joint led to atrophic rather than to hypertrophic changes. Key concluded, after injecting the knee joints of guinea-pigs with carbolic acid, iodine, or alcohol, that the nature of the injected substance was not important provided damage was caused, and that this damage, if continued, would result in a deforming arthritis.

Coulon, Charlier, and Vandersmissen (1954) produced an experimental rat arthritis by the local injection of a 10 per cent. kaolin suspension. Cysteinamine was ineffective in treatment.

Comparable work by Ramsey and Key (1955), injecting 10 per cent. turpentine oil or talc in water, into the knee joints of 22 rabbits (using India ink as a guide to the sites of injection) showed that hydrocortisone accelerated the return of the damaged tissue to normal.

Table VI

PHYSICAL METHODS FOR THE EXPERIMENTAL PRODUCTION OF ARTHRITIS

(1) *Local Injection of Irritants*	
Blood, India ink, carbolic acid, iodine, alcohol	Key (1929)
Kaolin	Coulon and others (1954)
Turpentine, talc	Ramsey and Key (1955)
Surgical sutures	Mannheim (1929)
(2) *Local Cauterization*	
Heitzmann	(1874)
Mannheim	(1929)
(3) *Local Trauma*	
Redfern	(1850)
Sury	(1918)
Wehner	(1923)
Müller	(1924)
Mannheim	(1929)
Barthels	(1932)
Bich	(1932)
Bernstein	(1933)
Nozoe	(1938)
Magnuson	(1941)
(4) *Resection of Bone, Cartilage, or Synovia*	
Kroh	(1909)
Wehner	(1923)
Key	(1931)
Barthels	(1942)
Arnulf and others	(1954)
(5) *Local Electrolysis*	
Axhausen	(1913; 1914)
Mannheim	(1929)
(6) *Deprivation of Nerve Supply*	
Nozoe	(1938)
(7) *Local Cooling*	
Manteuffel	(1913)
Schiavetti and others	(1952)
(8) *Reduction in Blood Supply*	
Wollenberg	(1909)
Axhausen and Pels	(1911)
Walkhoff and others	(1911)
Goldhaft and others	(1930; 1933)
Bennett and Bauer	(1937)

According to Mannheim (1929), Billroth made comparable studies on the response of articular cartilage to the insertion of surgical sutures. A non-suppurative inflammation was induced.

(2) Local Cauterization.—Mannheim (1929) reported that Kremjanski (1868) cauterized the joints of the sternum and the ensiform cartilage of rabbits with a red-hot iron followed by the systemic administration of mercuric sulphide; 4 to 7 days later, fatty degeneration of the cartilage and cell destruction were found with mercuric salts in the perichondrium. From the same source we learn that Henzmer (1875) transfixed the capsules of rabbit hip joints with red-hot needles and cauterized the joints with zinc chloride. Neither pus formation nor cartilage cell proliferation followed. Heitzmann (1874) cauterized with red-hot irons the femoral condyles of rabbits, cats, and dogs. In the damaged areas he found cartilaginous calcification, cell degeneration, and an increased amount of interstitial ground substance.

(3) Local Trauma.—Redfern (1850) detailed the behaviour of cartilage cells in damaged joints. Much relevant work was quoted by Mannheim (1929), but often without the exact source. Sury (1918) compressed and distorted the knee joints of guinea-pigs several times weekly for 4 to 5 months. The joints of a further group he hit repeatedly with a hammer. Subsequent vascularization and ossification of the degenerate cartilage were found. Wehner (1923) rubbed and compressed the exposed articular cartilage while Müller (1924) produced epiphyseal displacement and femoral subluxation. By this means, and by arranging the tendons of the biceps to draw constantly across the head of the humerus he induced degenerative joint disease. Mannheim (1929) injected irritant fluids, and used both local bone destruction and prolonged local trauma to cause degenerative changes; he reported that Bonn had dislocated the radius, resected the capitellum or dislocated the radius, and fractured the ulna. In each instance changes resembling osteo-arthritis were found, and Bonn did not accept aseptic necrosis of cartilage as a prerequisite. Mannheim also reported that Schmidt had fractured the femoral epiphyses and then injected blood, concluding that cartilaginous destruction and arthritis were secondary to capillary damage, and that Billroth had made similar observations. Barthels (1932) performed synovectomy in rabbits, using the degenerative changes which appeared to support the contention that cartilage depends upon synovial fluid for normal metabolism. Bich (1932) combined traumatic dislocation and subluxation of the knee joints in rabbits with the subsequent injection of hydrochloric acid and studied the effect of alkalis on non-traumatized joints. Bernstein (1933) produced experimental arthritis in dogs by the exposure and ligation of lumbar veins, and Nozoe (1938) concluded that both local trauma and a metabolic disturbance were necessary factors in causing a neuropathic arthropathy. The work of Magnuson (1941) in dogs also emphasized a multiplicity of factors, including infection or chemical disturbance in addition to repeated trauma.

(4) Resection of Bone, Cartilage, or Synovia.—In a study of the pathogenesis of degenerative joint disease, Kroh (1909) resected part of the articular surface of rabbit femoral condyles and concluded that the disease developed following an incongruity in the joint surface. This view, unsubstantiated by histological evidence, neglects the observation that a fibrillary change in superficial articular cartilage is the earliest detectable histological lesion in this disease. The work of Wehner (1923) referred to above was followed by that of Key (1931), who also resected parts of the articular cartilages in twenty rabbits. His conclusions were similar to those of Kroh (1909). Unlike Axhausen (1913), he did not agree that the presence of a nidus of dead cartilage was necessary for degenerative changes to develop. Dead cartilage (he stated) placed in a joint is destroyed and removed without causing further damage. Barthels (1942) chose to excise the patella, and Arnulf, Benichoux, Desloux, and Morin (1954) used comparable methods in their study of the value of plastics in the treatment of chronic arthritis.

(5) Local Electrolysis.—Axhausen (1913, 1914) was the principal proponent of the value of electrolysis in the study of degenerative joint lesions. A current was applied to the articular surfaces; degenerative changes followed use of the joint. When a current of 2·5 milliamps alone was applied for 20 sec., aseptic cartilage and bone necrosis never occurred. Mannheim (1929) confirmed these observations.

(6) Deprivation of Nerve Supply.—Nozoe (1938) made a series of interesting observations on the relationship between joint integrity and nerve function. He deprived rabbit knee joints of their innervation by cutting lumbar segments 4 to 7 and sacral segments 1 to 2. The local injection of potassium permanganate then caused degenerative changes. Similar changes were induced by feeding 2 g. sucrose per kg. body weight daily. Nozoe concluded that local trauma, neuropathy, and a metabolic factor appeared to be necessary for the evolution of degenerative joint disease.

(7) Local Cooling.—Manteuffel (1913) approached the same problem by repeatedly cooling the lower legs of guinea-pigs by means of an ether spray. Vascular stasis was induced. Cartilaginous degeneration and an overgrowth of connective tissue followed. Schiavetti, Terzani, and Spitz (1952, contrasted the influence of cold and of trauma on the development of joint lesions in the rat and noted the effect of antibiotics.

(8) Reduction in Blood Supply.—It has always seemed likely that an alteration in the blood supply might explain the manner in which a noxious agent could cause arthritic lesions in rheumatoid arthritis as well as being an important accessory factor in the degenerative disease of elderly persons. Obliterative arterial disease near such joints is frequent, and the articular cartilage, dependent for its normal metabolism on the integrity of the synovia, is often the site of replacement fibrosis. Wollenberg (1909) was apparently the first to demonstrate joint changes

following a mechanical reduction in blood supply to the joint. Axhausen and Pels (1911) repeated Wollenburg's experiments, but concluded that the claim that an impaired blood supply was a factor in causing degenerative joint lesions was unjustified; they favoured the view that the presence of a nidus of necrotic cartilage was essential. Again, Goldhaft, Wright, and Pemberton (1930) claimed confirmation of the work of Wollenberg (1909). Degenerative and hypertrophic changes followed the occlusion of the patellar blood supply in dogs. Walkhoff Ewald, and Preiser (1911) repeated the same work in dogs and rabbits but with negative results. Goldhaft, Wright, and Pemberton (1933), in further studies, showed, not surprisingly, that the response of dogs to such procedures was conditioned by their maturity. Finally, Bennett and Bauer (1937) repeated these experiments yet again, this time with convincingly positive results.

Comment

Physical agents damaging to joints have been used experimentally to produce forms of arthritis which most frequently resemble degenerative joint disease in the human. There is no evidence that such methods lead to changes which by their nature or disposition resemble those of rheumatoid arthritis. The future elucidation of the nature and cause of rheumatoid arthritis is unlikely to result from methods of the kind mentioned in this section.

Summary

The cause of rheumatoid arthritis is not known. One of the reasons for this lack of understanding may be the absence of a true experimental replica of the disease. As part of an approach to this problem, a review has been made of the principal methods which have been described for producing arthritis experimentally. The methods, considered chronologically, have been divided for convenience into five groups: infective, chemical, endocrinological, immunological, and physical.

The conclusion is reached that none of the forms of experimental arthritis at present known bears more than a superficial similarity to rheumatoid arthritis in the human. It appears possible that this disease may be confined to man or to the primates. The suggestion is made that our understanding of the aetiology and pathogenesis of rheumatoid arthritis may be better advanced by a concentration of experiment on the organ and tissue responses in man and the anthropoid apes, than by a dissipation of effort on the laboratory study of arthritis induced in small rodents.

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Arthrite expérimentale

RÉSUMÉ

On ne connaît pas la cause de l'arthrite rheumatismale. Il est possible que cette méconnaissance serait due au fait qu'on n'ai jamais pu créer une copie expérimentale exacte de cette maladie. Comme une partie de l'approche à ce problème on passe en revue les principales méthodes décrites pour produire une arthrite expérimentale. Ces méthodes, considérées chronologiquement, ont été divisées, pour des raisons pratiques, en cinq groupes: infectif, chimique, endocrinologique, immunologique et physique.

On conclut que toutes les formes d'arthrite expérimentale connues à l'heure actuelle ne ressemblent à l'arthrite rhumatismale de l'homme que superficiellement. Il est bien possible que cette maladie soit limitée à l'hombre ou aux primates. On suggère que nos connaissances de l'étiologie et de la pathogénie de l'arthrite rhumatismale avancerait mieux si l'on concentrait l'expérimentation sur des réactions des tissus et des organes humains et anthropoïdes plutôt que dissiper des efforts en l'étude de laboratoire de l'arthrite provoquée chez des petits rodents.

Artritis experimental

SUMARIO

La causa de la artritis es desconocida. Una de las razones de este desconocimiento puede ser la falta de una verdadera reproducción experimental de la enfermedad. Como una parte en el estudio de este problema, se pasa revista a los principales métodos descritos para la producción experimental de la artritis. Dichos métodos, considerados cronológicamente, fueron divididos por conveniencia en cinco grupos: infectivos, químicos, endocrinológicos, imunológicos y físicos.

Se concluye que ninguna de las formas de artritis experimental conocidas en el momento presenta con la artritis reumatoide en el hombre más que una similitud superficial. Parece posible que esta enfermedad se limita al hombre o a los primates. Se sugiere que el conocimiento de la etiologia y patogenia de la artritis reumatoide puede avanzar más por una concentración de experimentos sobre la respuesta de organos y tejidos en el hombre y monos antropoides que con una dispersión de esfuerzos en el estudio en el laboratorio de la artritis producida en pequeños rodentes.