

THE BRITISH JOURNAL OF OPHTHALMOLOGY

MAY, 1949

COMMUNICATIONS

PATHOGENESIS OF CONCURRENT EYE AND JOINT DISEASES*

BY

ERIK GODTFREDSSEN

COPENHAGEN

THE reasons for discussing the subject of concurrent eye and joint diseases in this Society are (a) the great interest displayed in it by Swedish clinicians (Sjögren, Stenstam, Stig Holm, Edström and Osterlind); and (b) the recent advances concerning the pathophysiology and serological diagnoses of the joint diseases (blood cultivation and antibody measurements, including the antistreptolysin titre and agglutination test). These advances, together with the intensified research work within the field of allergy, which has led to the discovery of the antihistamine substances, as well as to the unfolding of further possibilities in virus pathology (thanks to the electron microscope and better methods of cultivation) have thrown new light on various joint diseases. As the aetiology and

* Read before the Swedish Society of Ophthalmologists at its Annual Meeting, June 5, 1948, in Gothenburg.

pathogenesis of many cases of iridocyclitis, scleritis and phlyctenular conjunctivitis are still obscure, and as these diseases are very frequently met with in association with joint diseases, it might be of interest to analyse the nature and frequency of eye symptoms in joint diseases in order thus to attempt to elucidate the pathogenic conditions.

The clinical pictures of concurrent eye and joint diseases have been described both in synoptic form and on the basis of original materials (Franceschetti, 1946; Sorsby and Gormaz, 1946; Edström, 1937), but aetiological and pathogenic outlines have not been drawn.

The incidence and symptomatology of concurrent eye and joint diseases will first be recapitulated in brief, the main stress being laid on the features relevant to the present investigation.

The medical ("rheumatic") joint diseases complicated by eye symptoms (Table I) comprise 2 groups: acute diseases (rheumatic fever, gonorrhoeal arthritis, and simple, urethritic polyarthritis or Reiter's disease) and chronic diseases (primary chronic polyarthritis, Still's disease, and ankylopoietic spondylo-arthritis or Pierre Marie-Strümpell-Bechterew's disease). Uritic arthritis is—with some reservation—included among the acute diseases.

TABLE I

Incidence (per cent.) of eye symptoms complicating joint diseases

	Conjunctivitis	Iritis	Sicca-syndrome
<i>Acute joint diseases</i>			
Rheumatic fever	5-10	4-5	—
Gonorrhoeal arthritis	10	5	—
Reiter's disease	80	10	—
Uritic arthritis	—	2	—
<i>Chronic joint diseases</i>			
Primary progressive chronic polyarthritis	—	2-5	10
Still's disease... ..	—	20	—
Ankylopoietic spondylo-arthritis ... (Bechterew-Strümpell-Marie)	—	15-50	—

In Denmark the most frequent form of joint disease is rheumatic fever with about 4,000 fresh cases annually. Next in frequency follows primary chronic polyarthritis with 3-400 fresh cases annually and a total of about 8,000 cases. All the other joint diseases are far less frequent. Gonorrhoeal arthritis is a rare phenomenon since the introduction of sulphonamide and penicillin treatment. Before the era of chemotherapy 1 to 5 per cent. of the gonorrhoea cases were complicated by joint diseases (Heerfordt, in 1909, collected 191 joint cases among 2,300 patients with gonorrhoea). The triad of polyarthritis, non-specific urethritis, and conjunctivitis (Reiter, 1916) has been observed with increasing frequency in many countries during and after the second world war (Skydsgaard, Haar, Paronen, whose material is the largest so far) and may be found also in women (Zewi found 6 women among 10 cases in 1947). In Paronen's abundant Finnish material (1948), comprising 325 cases of Reiter's disease, the syndrome was complete in 70 per cent., while joint symptoms were present in 98 per cent., eye symptoms in 90 per cent., and urethritis in 79 per cent. Initial dysentery-like gastro-enteric symptoms were found in 96 per cent.

Still's disease (1897) is a variety of chronic polyarthritis (peri-arthritis) affecting children, chiefly girls. In addition to chronic iridocyclitis, often with zonular keratitis, the disease is associated with polyadenitis and enlargement of the spleen, and the general condition is affected (Friedländer, Ejler Holm, Blegvad, Poulsen).

Uratic arthritis and ankylopoietic spondylitis being also fairly rare, the joint diseases of the most immediate importance in this connexion are rheumatic fever, primary chronic polyarthritis, and Reiter's disease.

All the above joint diseases, except uratic arthritis, may be included under the heading of infective arthritis. The arthrosis group, on the other hand, is not associated with eye symptoms. The articular symptomatology is characterized by being polyarticular. Ankylopoietic spondylitis begins in the sacro-iliac joints, whence it proceeds up through the joints of the vertebral column.

The eye symptoms in these joint diseases comprise in the main three distinct groups: (1) endogenous conjunctivitis, including episcleritis and scleritis, (2) iritis and iridocyclitis, and (3) the sicca-syndrome. In rare cases may be added optic neuritis and ocular palsies.

Iritis may be found in association with any one of the above seven joint diseases, at frequencies varying from 2 to 50 per cent. It is most rare in association with uratic arthritis (2 per cent.), primary chronic polyarthritis (2 to 5 per cent.), gonorrhoeal

arthritis and rheumatic fever (4 to 5 per cent.), but more frequent in Reiter's disease (10 per cent.) and ankylopoietic spondylitis (15 to 50 per cent.) (Comroe, Heerfordt, Paronen). The nature of the iritis in the acute joint diseases is chiefly acute, serous, with no essential characteristic, and in the chronic diseases chiefly chronic, though with acute exacerbations. In ankylopoietic spondylitis there is found an abundant exudation of fibrin into the anterior chamber. Still's disease may be associated with zonular keratitis.

Conjunctivitis occurs as a characteristic symptom only in the acute joint diseases, ranging in frequency from 10 to 80 per cent. (80 per cent. in Reiter's disease, 10 per cent. in gonorrhoeal arthritis, and 5 to 10 per cent. in rheumatic fever). Clinically it may have the form of a more or less superficial phlyctenular conjunctivitis or episcleritis (Heerfordt's subconjunctivitis epibulbaris) or a more diffuse bilateral conjunctivitis with limited secretion.

The sicca-syndrome (Sjögren's disease) is a characteristic occurrence only in primary chronic polyarthritis, with a frequency of 10 per cent. (Stenstam and Stig Holm, 1947). The clinical picture, described in detail by Sjögren (1933-40) and placed in relation to Plummer-Vinson's syndrome and ariboflavinosis (Godtfredsen, 1947) will not be discussed further. It should be remembered, however, that the disease is a generalized systemic affection of the secretory structures in the upper respiratory and alimentary tracts, lacrimal glands, pancreas and vaginal glands, with humoral changes (hyperglobulinaemia). The symptomatology is characterized by keratoconjunctivitis sicca, xerostomia, atrophic rhinitis, histamine-refractory achylia and desquamatory colpitis.

Even though from 2 to 50 per cent. of the joint diseases mentioned here are complicated by different eye symptoms, the total number of cases is rather limited, because the frequently occurring joint diseases most rarely show eye complications, whereas the reverse is the case for the rarer joint diseases (ankylopoietic spondylitis, Still's disease, and Reiter's disease). However, in the Eye Department of the Municipal Hospital, Copenhagen, we recently found that by systematic fractional urine examination ("two- or three-tube test") with inspection for fibres in all iritis cases we may discover a number of otherwise overlooked cases of Reiter's disease. Likewise the ophthalmologists will no doubt diagnose a greater number of ankylopoietic spondylitis cases by bearing this disease in mind when seeing iritis patients who have difficulty in pushing the chin forwards to the chin support of the slit-lamp, owing to the reduced mobility of the cervical part of the vertebral column.

PATHOGENESIS

The pathogenesis of the joint diseases mentioned in the present paper, is by no means fully elucidated, and there is no agreement in the literature. The most current views (Comroe, Cecil) are those summarised below.

Rheumatic fever is presumably an allerge-toxic reaction to infection with haemolytic streptococci, a hypothesis that is supported by the antistreptolysin titre, which is increased in 80 per cent. of the cases (> 200) (Kalbak; Winblad). In gonorrhoeal arthritis there is found gonococcaemia, and cultivation of gonococci from synovial fluid was performed before the gono-complement fixation reaction became positive. Reiter's disease, which originally was supposed to be due to a spirochaete, is still aetiologicaly obscure. The most recent literature ventilates the possibility of a virus, which, however, it has not yet been possible to cultivate. Reiter's disease often has an initial gastro-enteric stage, after which the characteristic triad manifests itself, probably released by an allerge-toxic agent. In uratic arthritis the essential feature is the pathological purine metabolism with increased serum uric acid values, and thus the pathogenesis differs from those of the other joint diseases. As for the three chronic joint diseases the aetiology is unknown, but is presumably infective and possibly—like Reiter's disease—of a virus nature with an allerge-toxic pathogenesis. Constitutional, possibly endocrine factors, are likely to play a part (Lövgren, 1945). This may explain the pronounced sex difference: primary chronic polyarthritis and Still's disease are most frequent among women, whereas Reiter's disease and ankylopoietic spondylitis are most frequent among men (Paronen; Sorsby and Gormaz).

In primary chronic polyarthritis 10 per cent. of the cases have increased antistreptolysin titre, which is only slightly above the normal findings (6 per cent., Kalbak). The agglutination test for haemolytic streptococci, on the other hand, yields increased values in 80 per cent. (Kalbak, 1946), a finding which has supported the theory of the aetiological importance of haemolytic streptococci. However, the most recent investigations (Wallis, 1947) seem to show that the agglutination reaction is not specific, but a more general indication of an abnormal serum instability (similar to the conditions which may give a positive Takata reaction). The agglutination test gives a negative reaction in ankylopoietic spondylitis.

Common to the above joint diseases—except uratic arthritis—is thus the fact that the pathogenesis seems to be an allerge-toxic reaction to a primary infectious agent, the aetiology of which is

clear for rheumatic fever (haemolytic streptococci) and gonorrhoeal arthritis. The aetiology of the other joint diseases is obscure; the possibility of a virus infection is present.

The clinical picture and the course of these joint diseases with and without associated eye signs being otherwise alike (Stenstam; Holm) we may suppose that the pathogenesis of the eye signs is the same as that of the joint symptoms, being thus of an allerge-toxic nature. This hypothesis is supported by the clinical picture of the eye symptoms. Phlyctenular conjunctivitis, or episcleritis, corresponds exactly to the eye signs in well-known allergic conditions, such as serum disease, sulphonamide allergy and tuberculin allergy. The histopathological picture of the phlyctenules is the same in these diseases, presenting an aggregation of polymorphonuclear leucocytes, small lymphocytes, and epithelioid cells, sometimes polynuclear, reminiscent in structure of Aschoff's nodules in the myocardium and the rheumatic nodules in the skin demonstrated in rheumatic infection (Edström and Osterlind). The iritis attending the joint disease resembles the monosymptomatic primary iritis, the aetiology of which is to an increasing extent believed to be allerge-toxic (Duke-Elder, 1947). Bjorn Foss' experimental work on anaphylactic iritis (1947) tends in the same direction. The pathogenesis of the sicca-syndrome may vary. Both hormone-biological factors and avitaminosis may play a part; but in the great majority of the sicca cases associated with primary chronic polyarthritis, the infective pathogenesis with an allerge-toxic reaction is the most likely one.

DISCUSSION

That the eye may be affected in the joint diseases mentioned above is probably due to various factors, of which a few will be pointed out. It has been shown that the blood-synovial barrier of the joints and the blood-aqueous barrier of the eye exhibit the same conditions of permeability for the substances involved in the inflammatory processes. In experimental streptococcaemia in animals (Angevine and Rothbard, 1940) the ciliary processes of the eye and the synovia of the joints were the places where the streptococci by preference elicited inflammatory changes.

Human clinical medicine does not, however, bear out the animal experimental findings. Thus among 72 cases of streptococcaemia, Sylvest (1946) found 6 with eye signs (iritis, vitreous body abscess, and conjunctivitis), but without joint symptoms, which were present in one-third of the remaining cases.

The primary infective agent is unknown in several of the concurrent eye and joint diseases reported in this paper, but

known in gonorrhoeal arthritis, and is presumably haemolytic streptococci in rheumatic fever (where 80 per cent. had increased streptolysin-titre). For primary acute iritis without joint symptoms, on the other hand, the significance of haemolytic streptococci is doubtful since the antistreptolysin titre does not here differ from the normal (Björk, 1947).

The supposed allerge-toxic processes resulting in concurrent eye and joint diseases seem to bear no relation to allergic constitution and heredity, since these patients do not to any conspicuous extent present otherwise well-known allergic symptoms, such as vasomotor rhinitis, hay fever and urticaria.

It should be pointed out that many of the above concurrent eye and joint diseases have a more generalized character, presenting signs in other organs or systems as well, *e.g.*, the cardiac complications in rheumatic fever, the generalized glandular affection in Sjögren's syndrome, the polyadenitis and the splenic enlargement in Still's disease, the urethritis in Reiter's disease, etc. This generalized symptomatology has clinico-topographic points of resemblance to various characteristic diseases where not only the eyes and the joints are affected, but also the skin and the mucous membranes around the orifices of the body—the so-called pluri-orificial location (with conjunctivitis, stomatitis, affection of the external genitalia, *e.g.*, balanitis, vulvo-vaginitis)—and where the pathogenesis is supposed to be allerge-toxic on an infective basis.

The most important diseases with cardinal signs constituting a more or less constant tetrad of signs from eyes, joints, skin, and oral and genital mucous membranes have been set out in Table II, grouped according to the supposed aetiology (bacteria, virus, unknown, intoxication). The frequently protean clinical pictures will not be discussed in detail, but brief mention may be made of the following facts. Stevens-Johnson's syndrome (1922) is a special form of manifestation of exudative erythema multiforme* with concurrent skin exanthema of cockade-like eruptions increasing to bullous dermatitis, as well as stomatitis, conjunctivitis, and balanitis, more rarely polyarthritis (Edmund; Jersild; Ustvedt, 1948). A similar clinical picture is met with in the exceedingly rare Behcet's syndrome (Tage Jensen, Bechgaard), where, however, the skin lesion may be more of the character of erythema nodosum. Furthermore there is found a recurrent iritis with hypopyon, aphthous stomatitis, and genital affection. Analogous pictures are seen when foot-and-mouth disease affects humans (Bojén). Acute disseminated erythematous lupus is likewise a rare and severe disease (V. Mortensen; Cordes

* Recently discussed by J. E. Wolff (1949. in *Brit. J. of Ophthalm.*, 33, 110.

TABLE II

Diseases with concurrent symptoms from eyes, joints, skin and mucous membranes

	Eyes	Joints	Skin	Mucous membranes (stomatitis, balanitis)
<i>Virus diseases or obscure aetiology</i>				
Reiter's disease	+	+	+	+
Stevens-Johnson syndrome ...	+	(+)	+	+
Behcet's syndrome	+	(+)	+	+
Foot-and-mouth disease	+	?	+	+
Acute disseminated erythematous lupus	+	+	+	+
Measles, chicken-pox	+	(+)	+	+
<i>Bacterial diseases</i>				
Gonococcal sepsis	+	+	(+)	+
Streptococcal sepsis	(+)	+	+	+
<i>Intoxications</i>				
Sanocrysin, arsenicals	+	(+)	+	+
Serum sickness	+	+	+	+

(+) means less significant.

and Aiken, 1947) with a polymorphous picture comprising the skin lesion, polyarthritis, lymphadenitis, endocarditis and pluri-orificial ulcerative mucosal affections.

Gonococcaemia and streptococcaemia have already been mentioned. The morphology of the exanthemata may here vary a great deal. Intoxications by heavy metallic salts, notably sanocrysin (*cf.* Sundelin, 1941) and arsenicals (arsphenamine) may cause exfoliative dermatitis, endogenous conjunctivitis, stomatitis, and varying joint symptoms, very much like exudative erythema multiforme (Edmund). The disseminated exanthema, polyarticular lesions, and mucosal symptoms of serum disease are well known.

CONCLUSION

It is hardly possible to draw any definite conclusions, because our knowledge of many of the clinical pictures mentioned above is still rather limited. But it appears from the present clinical

analysis that a group of the rheumatic joint diseases, which—except uratic arthritis—all belong to the type of infective arthritis, are to a certain extent associated with eye symptoms, chiefly of an allerge-toxic nature. The eye and joint disease may be presumed to have the same aetiology and pathogenesis, where either a definitely known or a supposed primary bacterial (or virus) infection releases the allerge-toxic symptoms. The many clinical points of resemblance to various generalized diseases located on the skin, the pluri-orificial mucous membranes, and the joints, where allerge-toxic pathogenesis is certain or likely, bear out the hypothesis of an allerge-toxic pathogenesis of concurrent eye and joint diseases in a more restricted sense.

The therapeutic consequences of the above lines will not be discussed further in this place. The underlying bacterial diseases respond to treatment with sulphonamide and penicillin, whereas this has no influence on the supposed virus diseases. Although histamine is only symptomatic of the allergic process, it may be of interest to attempt an anti-histamine treatment (benadryl, pyribenzamine, and antistine). This has been tried on iritis without joint symptoms (Lemoine, 1947) with encouraging results, which, however, need further testing. The favourable response of sanocrysin intoxications to BAL (Cohen, 1947; Edström, 1948) might perhaps prompt one to the use of BAL against some of the related diseases mentioned here.

SUMMARY

A clinical analysis is given of the incidence and symptomatology of concurrent eye and joint diseases. The medical joint diseases which are complicated by eye symptoms (phlyctenular conjunctivitis, scleritis, iritis, and kerato-conjunctivitis sicca) all belong to the type of infective arthritis, partly acute and partly chronic (rheumatic fever, gonorrhoeal arthritis, Reiter's disease, Still's disease, and ankylopoietic spondylitis). The pathogenesis is presumably the same for the eye disease and the joint disease, being probably an allerge-toxic reaction to a primary bacterial or virus infection. This hypothesis is borne out by clinical points of resemblance to various generalized diseases affecting joints, skin and pluri-orificial mucous membranes (conjunctivitis, stomatitis, and affection of external genitals), where an allerge-toxic pathogenesis is certain or likely—Stevens-Johnson's syndrome, Behcet's syndrome, foot-and-mouth disease, serum disease, acute disseminated erythematous lupus, and intoxication by heavy metallic salts, notably sanocrysin and arsenicals.

BIBLIOGRAPHY

- ANGEVINE, D. M. and ROTHARD, S. (1940).—*J. Exp. Med.*, **71**, 129.
- BLEGVAD, O. (1941).—Still's disease. *Acta Ophthalm.*, **19**, 219.
- BECHGAARD, P. (1940).—Behcet's syndrome. *Ugeskrift. f. Læger*, **102**, 1019.
- BJÖRK, A. (1947).—Ast in acute iritis. *Acta Ophthalm.*, **25**, 127.
- BOJLEN, K. (1941).—*Ugeskrift. f. Læger*, **103**, 497.
- CECIL (1942).—Text-book of Medicine. Saunders.
- COHEN (1947).—BAL and sanocrysin intoxication. *J. Amer. Med. Assoc.*, **133**, 749.
- COMROE, B. J. (1941).—Arthritis and allied conditions. Philadelphia.
- CORDÉS, F. C. and AIKEN, S. D. (1947).—Lupus erythem. diss. *Amer. J. Ophthalm.*, **30**, 1541.
- DUKE-ELDER, S. (1946).—*Trans. Amer. Ophthalm. Soc.*, **44**, 143.
- EDMUND, C. (1935).—Endogenous conjunctival affections. *Acta Ophthalm.*, Suppl. 7.
- EDSTRÖM, G. (1937).—*Ergeb. d. inn. Med. u. Kdhk.*, **52**, 439.
- and OSTERLIND, G. (1948).—Rheumatic episcleritis. *Acta Ophthalm.*, **26**, 1.
- FOSS, B. (1947).—Anaphylactic iritis. *Nordisk Med.*, **36**, 2276.
- FRANCESCHETTI (1946).—Rheumatic eye diseases. *Ophthalmologica*, **111**, 246.
- GODTFREDSSEN, E. (1947).—Sjögren's syndrome, Plummer-Vinson syndrome and ariboflavinosis. *Acta Ophthalm.*, **25**, 95.
- HAAR, M. (1945).—Reiter's disease. *Ibid.*, **23**, 143.
- HEERFORDT, C. F. (1909).—Subconjunctivitis epibulbar gonn. *Graefe's Arch.*, **72**, 344.
- HOLM, S (1948).—Kerato-conjunctivitis sicca. *Acta Ophthalm.*, **26**, 269.
- JENSEN, T. (1940).—Behcet's syndrome. *Ugeskrift. f. Læger*, **102**, 1023.
- JERSILD, M. (1945).—Erythema multiforme exudativum. *Ibid.*, **107**, 879.
- KALBAK, K. (1942).—O-streptolysin. Copenhagen.
- (1946).—Agglutination in rheumatic arthritis. *Nordisk Medicin.*, **31**, 1997.
- LEMOINE, P. (1947).—Iritis and allergy. *Arch. d'Ophtal.*, **7**, 161.
- LÖVGREN, O. (1945).—Intermediären Stoffwechsel bei chronisch polyarthritis. *Acta Med Sci.*, Suppl. **163**.
- PARONEN, I. (1948).—Reiter's disease. *Ibid.*, Suppl. **212**.
- POULSEN, A. G. (1947).—Still's disease. *Nordisk Medicin.*, **35**, 1963.
- SKYDSGAARD, H. (1943).—Reiter's disease. *Acta Ophthalm.*, **21**, 107.
- SJÖGREN, H. (1940).—Kerato-conjunctivitis sicca. *Ibid.*, **18**, 369.
- SORSBY, A. and GORMAZ, A. (1946).—Iritis in rheumatic affections. *Brit. Med. J.*, **1**, 597.
- STENSTAM, T. (1947).—Kerato-conjunctivitis sicca. *Acta Med. Sc.*, **127**, 130.
- SUNDELIN, F. (1941).—Sanocrysin treatment of rheumatoid arthritis. *Ibid.*, Suppl. **117**.
- SYLVEST, O. (1947).—Streptococcobacteriaemia. Copenhagen.
- USTVEDT, H. J. (1948).—Erythema multiforme exudativum. *Acta Med. Sc.*, **131**, 32.
- WALLIS, A. D. (1947).—*Amer. Jl. Med. Sc.*, **94**, 213.
- WINBLAD, S. (1941).—Antistreptolysin-titre. *Acta Path. et Microbiol. Sc.*, Suppl. **44**.
- ZEWI, M. (1947).—Morbus Reiteri. *Acta Ophthalm.*, **25**, 47.
-