

SIGNIFICANCE OF THE SIMULTANEOUS OCCURRENCE OF CONNECTIVE TISSUE DISEASE AND AGAMMAGLOBULINAEMIA*

BY

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During the past 6 years Good and his co-workers have made extensive studies of 37 patients with agammaglobulinaemia. Eighteen are male children with the congenital form of the disease, and nineteen are adults of both sexes with acquired agammaglobulinaemia. The classical criteria of the disease, an absence of gamma globulin and circulating antibody secondary to the lack of plasma cells, were present in all these patients. Some of those with agammaglobulinaemia also show abnormalities in the beta-2 globulins. When the amount of gamma globulin in the agammaglobulinaemic patients was measured by immunochemical methods, it was found that none had an absolute lack of gamma globulin, but all had it in only minute amounts. The congenital cases have less than the acquired ones; the lowest amount found was 1 mg. per cent.

An observation which has been of extreme interest to us has been the occurrence of connective tissue disease in twelve (one-third) of our patients. Rheumatoid arthritis, atypical arthritis, and tenosynovitis resembling rheumatoid arthritis, and one case of diffuse fibrinoid disease involving the blood vessels throughout the body has been found in these twelve patients. Dermatomyositis, juvenile rheumatoid arthritis, and scleroderma have been reported in agammaglobulinaemic patients in the literature (Good and Varco, 1955; Bruton, 1952; Hayles, Stickler, and McKenzie, 1954; Grant and Wallace, 1954; Van Gelder, 1957; Hanson, 1961).

Of our twelve patients with connective tissue disease, eight have classical rheumatoid arthritis, according to the diagnostic criteria of the American Rheumatism Association (Table, opposite). Six are adults with the acquired form of the disease and

two are congenital cases. Three other children with congenital agammaglobulinaemia would be classified as having probable rheumatoid arthritis. Four of our eleven patients with arthritis have developed characteristic subcutaneous rheumatoid nodules, located near the elbow on the extensor surface of the forearm. Biopsy has revealed a histological picture which is typical of the rheumatoid nodule save for the absence of plasma cells (Fig. 1, opposite).

The rheumatoid factor was not detected by Vaughan* in our patients. An attempt to inhibit rheumatoid agglutination by sera from three of our patients also gave negative results. However, all the agammaglobulinaemic sera from our patients, with or without connective tissue disease, had a distinct ability to enhance rheumatoid agglutination reactions. In order to determine whether or not the agglutination enhancement was due to small amounts of rheumatoid factor, euglobulin precipitates were prepared and studied. Neither agglutination nor inhibition of agglutination was seen in the fractionated specimens.

In our patients with arthritis indistinguishable from rheumatoid arthritis, x-ray examination revealed minimal juxta-articular demineralization of the bones and slight narrowing of the joint spaces. However, we are aware of another case of congenital agammaglobulinaemia with arthritis resembling rheumatoid arthritis which shows erosions on x-ray (Smythe, 1961).

The genetic background of patients with protein abnormalities and connective tissue disease has increasingly drawn the attention of the clinical investigator. It soon became apparent that the congenital form of agammaglobulinaemia was a sex-linked recessive condition involving male children. The acquired form appears to occur in either sex at

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TABLE

SYMPTOMS OF RHEUMATOID ARTHRITIS IN EIGHT PATIENTS WITH AGAMMAGLOBULINAEMIA

Sex	Male	Female	Male	Male	Male	Male	Male	Female	
Age (yrs)	7	33	58	5	4	9	10	44	
Symptoms	Morning stiffness	++	+++	++++	++	±	++	+	++
	Pain on motion or tenderness ..	+++	++	+++	+++	+++	++++	++++	+
	Swelling in one joint	++++	++++	++++	++++	++++	++++	++++	++
	Swelling in at least one other joint	++++	++++	++++	+++	+++	+++	+++	++
	Symmetrical joint swelling ..	++	++	+++	+	++	++	-	++
	Subcutaneous nodules	++	+	-	-	-	-	-	+
	X-ray changes typical of rheumatoid arthritis. Decalcification	+	+	±	-	-	-	-	-
	Agglutination test	-	-	-	-	-	-	-	-
	Poor mucin precipitate from synovial fluid	+	+	Not studied	+	Not studied	Not studied	Not studied	Not studied
	Characteristic histological changes in joints	++	Not studied	Not studied	+	Not studied	Not studied	Not studied	Not studied
Characteristic histological changes in nodules	++	++	Not studied	-	-	Not studied	Not studied	++++	

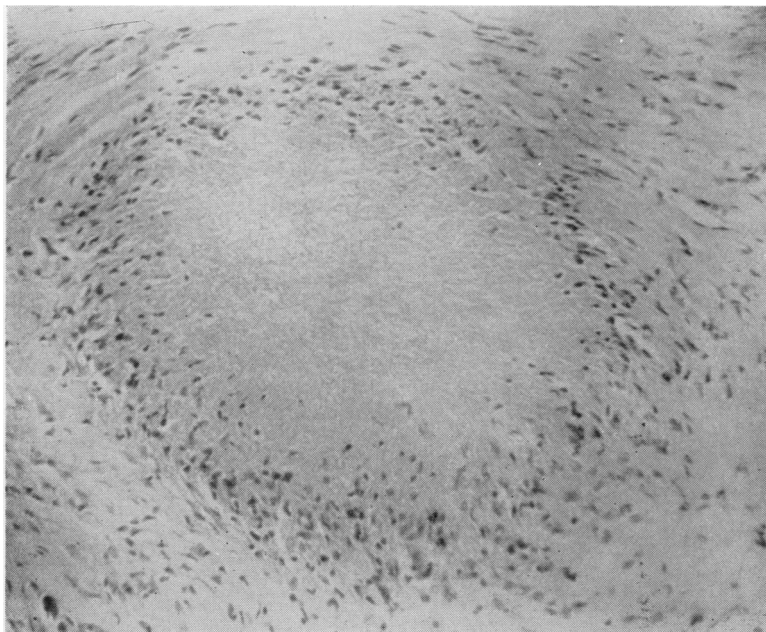


Fig. 1.—Subcutaneous nodule from a patient with acquired agammaglobulinaemia and rheumatoid arthritis. Except for the absence of plasma cells, the nodule is a typical histological specimen of a rheumatoid nodule.

any age. Waldenström (1961) has presented evidence that acquired agammaglobulinaemia is also genetically transmitted, albeit differently from the congenital type. Several recent reports have described the genetic background of patients with connective tissue disease, both with and without agammaglobulinaemia. Ziff, Schmid, Lewis, and Tanner (1958) found that patients with rheumatoid arthritis had a significant number of relatives in their immediate family who showed no clinical evidence of connective tissue disease, but had significant levels of rheumatoid factor in the sera. Kunkel (1959) found that, in a few families, disseminated lupus erythematosus and hypergammaglobulinaemia were associated. Rodnan (1959) described a patient with rheumatoid arthritis who showed very low levels of gamma globulin, and found rheumatoid arthritis in several members of the same family.

The families of two adults in our series with acquired agammaglobulinaemia and rheumatoid arthritis were investigated, and both showed an extraordinarily high incidence of rheumatoid arthritis. One family is shown in Fig. 2. On the other hand, the families of children with congenital agammaglobulinaemia and rheumatoid arthritis do not appear to include an unusual number of cases of connective tissue disease.

The immunological deficiency in agammaglobulinaemia is the basis of the clinical stigmata that occur in these patients. They are unable to manifest immediate hypersensitivity. Delayed hypersensitivity appears to be intact, although it cannot be quantitated by present methods. Certain clinical states such as atopic eczema occur in these patients; we have not been able to induce in them the production of demonstrable amounts of reagin antibodies, and the ability to produce reagins in demonstrable amounts by current methods may not be related to the development of atopic eczema. Although the defences of patients with agammaglobulinaemia towards several viral diseases appear normal, they seem to be inordinately susceptible to others. Two patients in this series succumbed to viral hepatitis with seemingly no ability to fight the disease.

Many haematological abnormalities also have been found, including recurrent neutropenia, persistent neutropenia, lymphopenia, eosinopenia, haemolytic anaemia, hypersplenism, and thymic tumour.

The known facts may be woven into a pattern which, if not definitive, may indicate a working hypothesis of the cause of connective tissue disease in the agammaglobulinaemic patient, and thus, perhaps, of the cause of some forms of connective tissue disease.

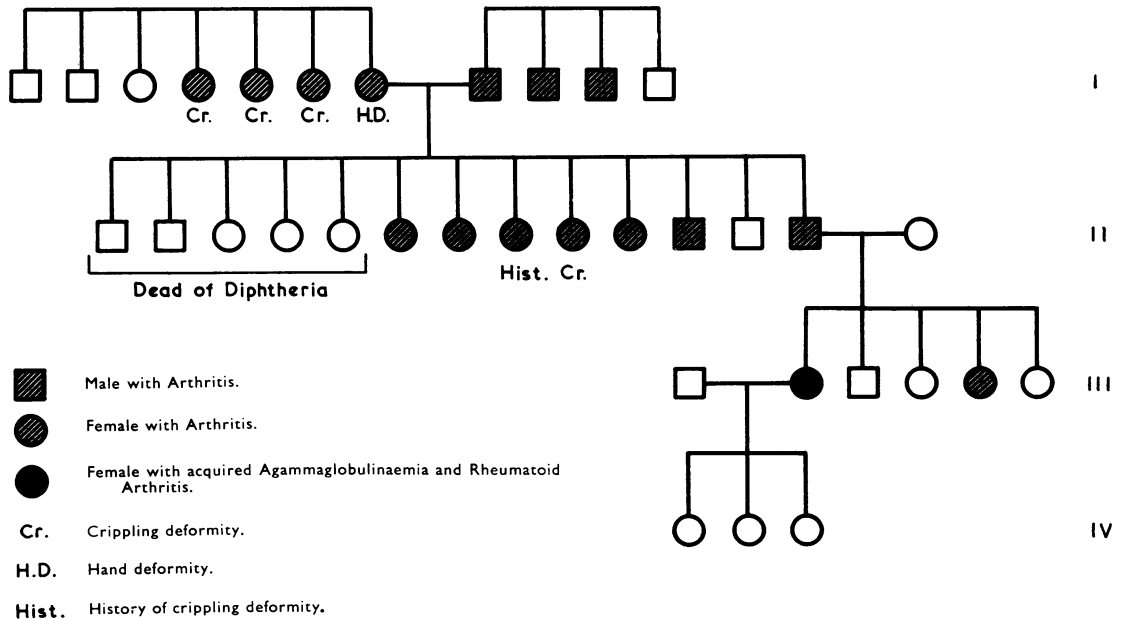


Fig. 2.—Family of a female patient with acquired agammaglobulinaemia and rheumatoid arthritis.

Connective tissue disease appears in patients with a familial background of the clinical or subclinical symptoms. The diseases themselves are featured by remissions and exacerbations, manifested by increases in acute-phase phenomena and, in some cases, by the development of abnormal proteins, which appear to be of the nature of antibodies. These antibodies have some of the characteristics of those which have been shown to occur in viral disease. Some suggestive, but unsubstantiated, experiments by Moolten and Clark (1953) have indicated a virus aetiology for the production of some of the connective tissue diseases; to this the agammaglobulinaemic patient may provide an important clue. Agammaglobulinaemia is an overt manifestation of mesenchymal tissue dysfunction. If the aetiological factor in connective tissue disease is an infectious agent, such as a virus, it may be passed from generation to generation in a latent, or provirus, form. This may alter the chromosomal pattern so that at times subclinical manifestations, such as the rheumatoid factor, L.E. cell factor, or false positive Wassermann factor, are produced. With normal defence mechanisms, the aetiological agent is more likely to remain in a quiescent form. However, in our series of agammaglobulinaemics, the normal defence mechanisms are not intact. This would allow trigger mechanisms to set off the chain of events which converts the agent from inactivity to activity, leading to the clinical manifestation of connective tissue disease. The disease itself may represent a direct response of the host to this agent, or it may be a hypersensitivity reaction to the agent in which the mechanisms of delayed allergy are operative, or, finally, it may be a response to the agent of another type of cellular hypersensitivity, similar but not identical to delayed allergy.

Our laboratories are currently engaged in viral studies in patients with connective tissue disease. Tissues and their fluids have been inoculated into neonatal mice, rabbits, guinea-pigs, embryonic chick tissue culture, and cortisone-treated animals. As yet, no agent has been isolated from agammaglobulinaemics with arthritis, children with Still's disease, or adult rheumatoid arthritis. As we work with the techniques currently used in the detection of viruses, we realize that new and much more precise methods will have to be developed in the future.

Dr. Good's laboratory has been actively engaged in attempts to devise experimental models of immunological incompetence. So far it appears that three models may be useful and should be studied:

(1) Thymectomy in new-born rabbits produces animals which appear to be defective in producing circulating antibody (Archer and Pierce, 1961).

(2) 19 nor-testosterone given to chick embryos 5 days after the start of incubation interferes with the development of the bursa of Fabricius. The lymphoid tissue does not develop normally and at 6 weeks they have a poorly-developed thymus and relatively little splenic and lymphoid tissue. They are also deficient in the production of circulating antibody (Mueller, Wolfe, and Meyer, 1960; Papermaster, Friedman, and Good, 1961).

(3) Another approach is to produce tolerant mice in the accepted manner. If one takes these tolerant mice, *i.e.* C3H animals tolerant of A cells, and injects A cells into them, progressive destruction of the lymphoid tissue develops in the adults and they end up as runts with destroyed lymphoid organs (Martinez, Smith, and Good, 1961).

These creatures may, or may not, be models of immunological incompetence comparable in mechanism to the incompetence of human agammaglobulinaemia, but in each instance they have a highly disorganized lympho-reticulo-endothelial system and thus may be better examples of animals to manipulate than normal healthy animals when attempting to produce experimental models of collagen disease. This basic defect in agammaglobulinaemia certainly deserves continued investigation, and this relationship to rheumatoid disease may be an opening wedge, which will permit the development of more representative experimental laboratory models of connective tissue disease.

Summary

The authors have studied 37 agammaglobulinaemic patients from the genetic, clinical, and laboratory points of view. One-third of them developed connective tissue disease. The data permit a working hypothesis of the cause of connective tissue disease to be expounded. Three ways of producing immunologically incompetent animals are described. The significance of the past work in this field and a new experimental approach are discussed.

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Importance de l'occurrence simultanée d'une maladie du tissu conjonctif et de l'agammaglobulinémie

RÉSUMÉ

Les auteurs ont étudié 37 malades agammaglobulinémiques du point de vue génétique, clinique et de laboratoire. Un tiers d'entre eux ont développé une maladie du tissu conjonctif. Les données obtenues offrent une hypothèse pratique sur la cause de la maladie du tissu conjonctif. On décrit trois manières de produire l'incompétence immunologique chez des animaux. On discute l'importance des travaux antérieurs sur ce sujet et une nouvelle approche expérimentale.

Importancia de la aparición simultánea de enfermedad del tejido conectivo y de agammaglobulinemia

SUMARIO

Los autores estudiaron 37 pacientes agammaglobulinémicos desde el genético, clínico y laboratorio punto de vista. Un tercio de ellos desarrollaron enfermedad del tejido conectivo. Los datos obtenidos ofrecen una hipótesis respecto a la causa de la enfermedad del tejido conectivo. Tres modos de producción de la incompetencia inmunológica en animales son descritos. Se discute la importancia del anterior trabajo en esta materia y un nuevo acercamiento experimental.