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COMPLEMENT DEFICIENCIES

Anete Sevciovic Grumach*

The evaluation of Complement deficiencies (CD) in man has lead to increased knowledge about the biological activity of this System that would not have ocurred by means of ''in vitro'' observations.

Complement Deficiencies were first described in healthy animals and humans, during decade of 1960 and the protective function of the complement system was not considered important (1).

In the beginning of 1970, inherited and acquired CD were associated with severe bacterial infections and auto-immune diseases. The defense function was established after the description of a C3 deficient patient presenting with severe bacterial infections, similar to hypogammaglobulinemic patients (2). The frequencies for complement components deficiencies are listed in Table I according to several authors. National surveys for Immunedeficiencies detected less than 1% of primary ID patients with CD in Japan and Sweden (3, 4), while in our experience this number approximates 5% (Figure 1) (5).

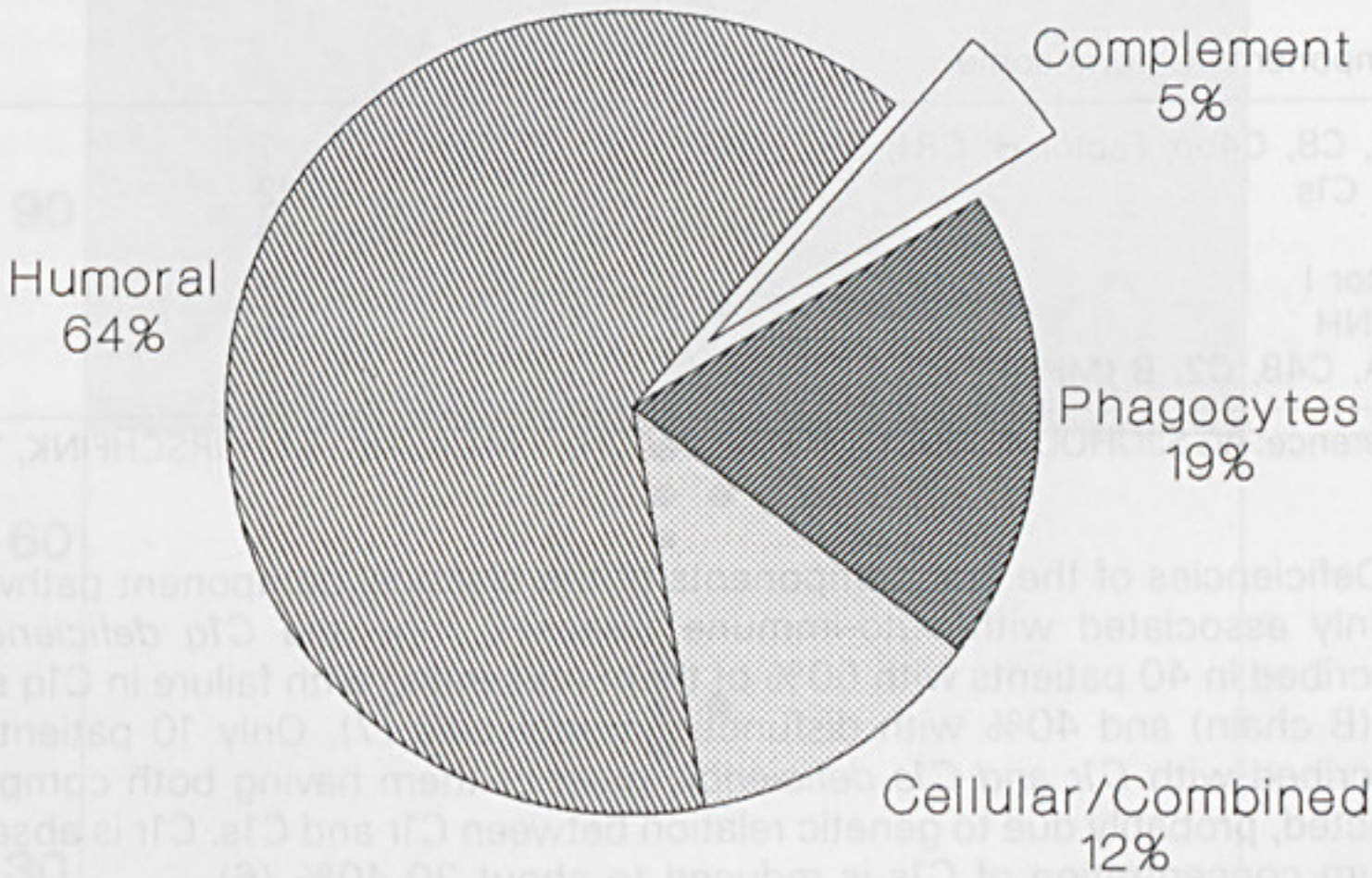

FIG. 1 Primary immunodeficiencies in Dept. of Pediatrics, Faculty of Medicine, University of São Paulo (n = 140)

Chromosomal location of most complement component genes have been determined. C4A and C4B genes are located near MHC and this association is related to a higher susceptibility to auto-immune diseases. (1) (TABLE II)

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TABLE I
PREVALENCE OF COMPLEMENT DEFICIENCIES

Component	Prevalence
C2	1:10.000 /1:30.000 (caucasians)
C4	complete: rare incomplete: 1:250
C6	1:60.000 (caucasians)
C7	1:25.000 (japanese)
C9	1:1.000 (japanese)
C1-INH	1:150.000

References: Sjöholm AG 1990 (1); SC. ROSS & P. DENSEN, 1984 (8) CD WEST 1989 (13)

TABLE II
CHROMOSOMAL LOCATION OF COMPLEMENT COMPONENTS

Components	Chromosome
C1q, C8, C4bp, Factor H, CR1, CR2, DAF	1
C1r, C1s	12
C3	19
Factor I	4
C1-INH	11
C4A, C4B, C2, B (MHC)	6

Reference: AG SJÖHOLM, 1990 (1); AS GRUMACH, FFM CASTRO & M KIRSCHFINK, 1992 (6)

Deficiencies of the first components of the classical component pathway are mainly associated with auto-immune diseases. Inherited *C1q deficiency* was described in 40 patients with 60% of them presenting with failure in C1q synthesis (B chain) and 40% with disfunctional molecule (7). Only 10 patients were described with *C1r and C1s deficiency*, most of them having both components affected, probably due to genetic relation between C1r and C1s. C1r is absent and serum concentration of C1s is reduced to about 20-40% (6).

C4 is codified by two polymorphic genes, inside MHC, which originate from two isotipic, C4A and C4B. *Complete deficiency of C4* requires inheritance with allele nulls in both C4 loci. Only 16 cases have been described to date (7,8). Nevertheless, single null alleles are common in both loci, frequently resulting in heterozygotic deficient persons. About 60% of the human population have four active genes, so, partial C4 deficiency is one of the most common human immunodeficiencies (1). *Partial C4 deficiency* is associated with HLA-DR3 and greater susceptibility to Systemic Lupus Erythematosus (SLE). (9)

Severe and early Systemic Lupus Erythematosus was described in C4A deficient patients and bacterial meningitis caused by *H. influenzae* in children was related to C4B deficiency. C4A is envolved with the manipulation of immunecom-

plexes and C4B is linked to the polyssacharides present in bacterial surfaces (9). *C2 deficiency* is also associated with Systemic Lupus Erythematosus Lupus as are C1 and C4, but 25% of C4 deficients are healthy.

C3 deficiency was described in only 16 patients. One patient, a boy, was followed in our Department of Pediatrics (São Paulo, Brazil). The diagnosis was confirmed with the collaboration of Prof. Wilmar Dias da Silva. The clinical manifestations were present early in his life in the form of recurrent infections: pneumonia, otitis, meningitis and pioarthritis. The inheritance was autossomic codominant, with C3 intermediate levels in other relatives (Figure 2) without symptoms (10). This complement component, as C4, presents a electrophoretic polymorphism with slow and fast patterns as shown in Figure 3.

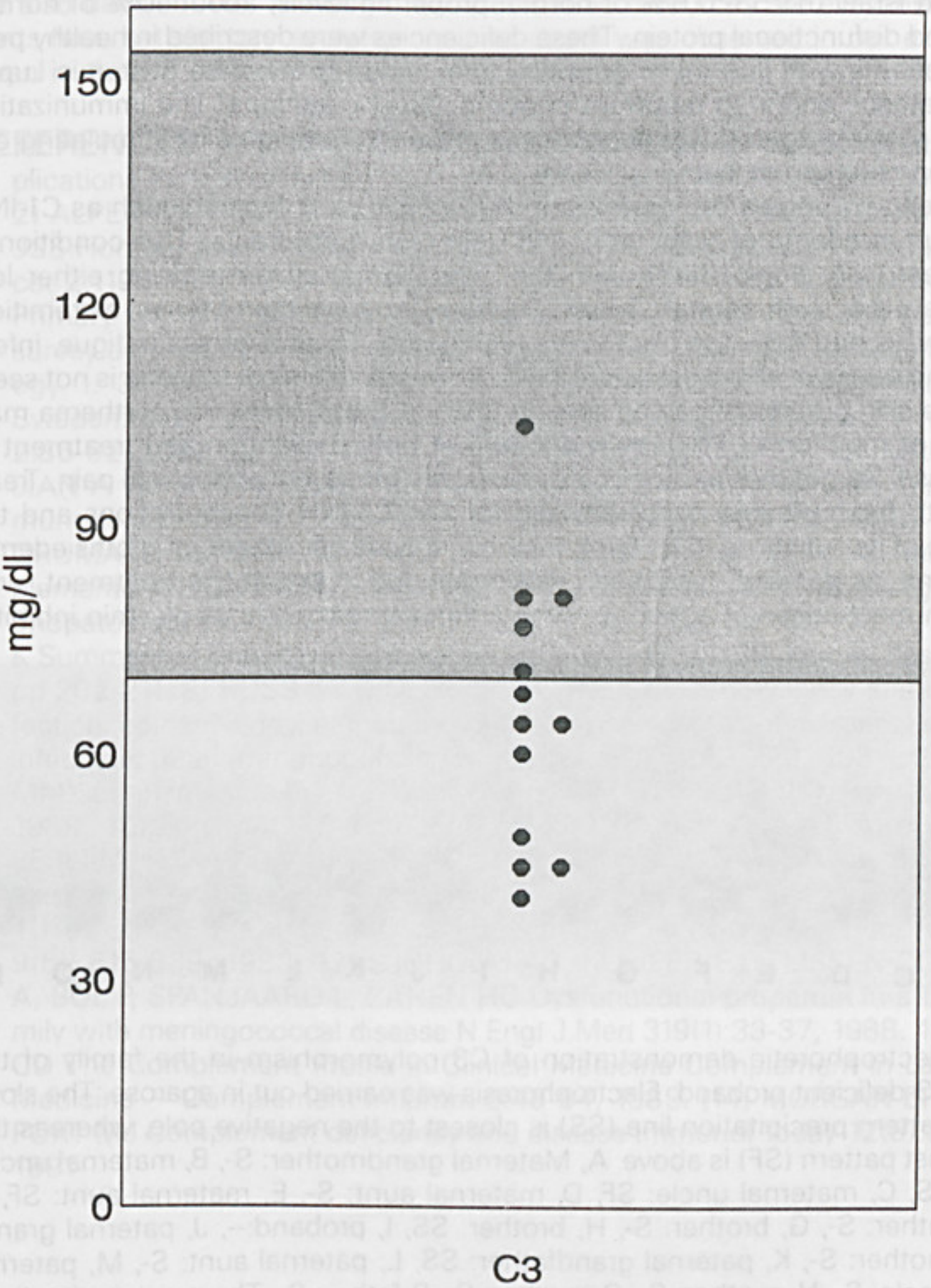

FIG. 2. C3 levels in relatives of homozygous C3 deficient patient, described by GRUMACH et al. (1988).

Association of C3 with IgG2 deficiency, resulting in severe infections was described recently. Some other patients had SLE and nephropathy associated with this condition (10).

Terminal components of complement system (C5-C8) are associated with recurrent infections due to *Neisseriae meningiditidis* and *gonorrhae*. These infections are caused by uncommon serogroups, frequently associated with septicemia in children over 10 years of age. Other diseases mediated by immune — complexes also can be associated. No clinical manifestation were described in C9 deficient states (8,11).

Absence of *Factor D* recently was found in a male patient with recurrent infections by *Neisseriae* (1).

Different types of *properdin* deficiency were reported in Scandinavia, the Netherlands and Israel (n=53):0.5% of normal properdin levels, about 10% of normal values and disfunctional protein. These deficiencies were described in healthy people, in patients with late meningoccocal infections (45%), with Systemic Lupus Erythematosus and with recurrent pneumococcal infections. The immunization of these patients against *Meningococcus* prevents meningitis by stimulating opsonization resulting in bacterial death (12).

Deficiency of *regulatory proteins* of the Complement System such as C1-INH may result in edema of respiratory and gastrointestinal tracts. This condition is called hereditary angioedema with the most common forms being either low C1-INH levels or dysfuctional C1-INH. The skin, mucosal membranes, extremities, face, airways and digestive tract may be envolved. Trauma, stress, fatigue, infections or no cause at all are associated with its onset. Classical urticaria is not seen, but some skin problems may be seen in 25% of these cases (i.e. erythema marginatum or multiform). Therapy is directed at both prevention and treatment of the disease. Sometimes narcotics are necessary for severe abdominal pain. Treatment with fresh plasma is not advised for low C1-INH concentrations and the presence of its substrate (C1). Tracheostomy may be necessary for glottis edema. Androgens, as danazol, have been recommended in preventive treatment, with unknown mechanism of action. Epsilon aminocaproic accid as plasmin inhibitor

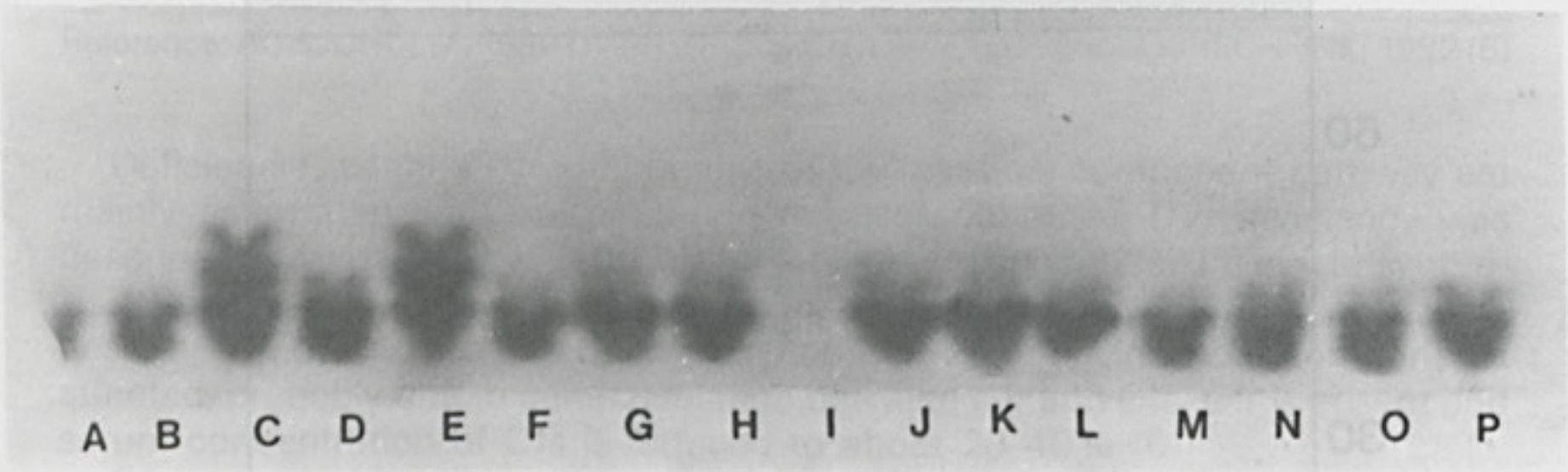

FIG. 3 Electrophoretic demonstration of C3 polymorphism in the family of the C3-deficient proband. Electrophoresis was carried out in agarose. The slow-pattern precipitation line (SS) is closest to the negative pole, whereas the fast pattern (SF) is above. A, Maternal grandmother: S-, B, maternal uncle: SS, C, maternal uncle: SF, D, maternal aunt: S-, E, maternal aunt: SF, F, father: S-, G, brother: S-, H, brother: SS, I, proband:--, J, paternal grandmother: S-, K, paternal grandfather: SS, L, paternal aunt: S-, M, paternal uncle: S-, N, mother: S-, O, mother: S-, P, father: S-. The precipitation lines shown in the lower part of the picture close to the negative pole present the slow pattern. One cm above is the fast pattern.

has been prescribed, with some adverse effects in muscles and by causing thrombosis (6,13).

Complement receptor deficiencies have been described for CR1, CR3 and CR4. CR1 and CR3 deficiencies were verified in SLE patients. CR3 and CR4 belong to a family of adhesion molecules, the integrins. The lack of beta 2 subunit of the dimeric molecule is associated with severe bacterial infections, due to impaired adherence of inflammatory cells to the endothelium and to impaired phagocytosis. This disease was named leukocyte adhesion deficiency. The clinical manifestations are late umbilical cord fall, bad cicatrization, severe bacterial infections, leukocytosis and injured leukocyte function (9), (6, 14).

In general, the treatment of complement deficiencies is restricted to environmental care, vaccination, fresh plasma and gammaglobulin when IgG subclasses are also deficient (6). Although few therapeutic resources are available, the patients have satisfactory evolution and no death was observed in our experience (even in the C3 deficient patient).

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