peritoneal cavity on the fifteenth postoperative day grew *E. coli* on culture. Severe bacterial infection, in particular *E. coli* infection, would seem to be associated with jaundice. Such a causal relationship was noted in the present series of cases of peritonitis complicating acute appendicitis.

The available biochemical evidence points to an obstructive pattern of jaundice without signs of extra-hepatic block. This indicates that the jaundice is of the cholestatic type: and, as suggested by Eley et al. (1965), this is possibly a hepatotoxic effect of the infecting organism, which was *E. coli* in most of the previously recorded cases and in 8 out of 9 of the present series.

Anæmia, which is a well-known accompaniment to any severe infection, has been an incidental finding in some of the cases recorded in this paper and also in other cases of infection with jaundice described by Bellmore (1963), Beckett and Ward (1965), and Arthur and Wilson (1967). This anæmia is usually ascribed to toxic depression of the bone-marrow, and there was certainly no suggestion of a hæmolytic effect in the present cases.

We thank Mr. R. B. Wright and the staff of the surgical division of the Southern General Hospital for permission to study patients under their care and for help and encouragement in the preparation of this paper.

REFERENCES

Arthur, A. B., Wilson, B. D. R. (1967) *Br. med. J.* i, 539.
Beckett, A. G., Ward, J. D. (1965) *ibid.* ii, 644.
Bellmore, C. (1963) *Med. J. Aust.* i, 381.
Bernstein, J., Brown, A. K. (1962) *Pediatrics, Springfield*, **29**, 873.
British Medical Journal (1963) i, 494.
— (1965) i, 743.
Eley, A., Hargreaves, T., Lambert, H. P. (1965) *ibid.* ii, 75.
Hamilton, J. R., Sass Kortsak, A. (1963) *J. Pediat.* **63**, 121.
Kunelis, C. T., Peters, J. L., Edmondson, H. A. (1965) *Am. J. Med.* **38**, 359.
Lancet (1966) i, 367.
McKenzie, C. G. (1964) *Br. med. J.* ii, 1558.
Pritchard, J. A., Adams, R. (1957) *Surgery Gynec. Obstet.* **105**, 626.
Tashiro, Y., Zinninger, M. (1946) *Archs Surg., Chicago*, **53**, 545.
White, M., Dennison, W. M. (1958) Surgery in Infancy and Childhood; p. 240. Edinburgh.
Wright, R. B. (1963) *Lancet*, ii, 475.

RHEUMATIC SYMPTOMS AND SEROLOGICAL ABNORMALITIES INDUCED BY ORAL CONTRACEPTIVES

GILES G. BOLE, JR. MITCHELL H. FRIEDLAENDER
C. KENT SMITH

FROM THE RACKHAM ARTHRITIS RESEARCH UNIT, DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN, U.S.A.

Summary Eight women, 21–29 years of age, noted rheumatic symptoms (or exacerbation of symptoms) during use of oral-contraceptive drugs. Six of these patients had episodes of thrombophlebitis before or during administration of these agents. In each case antinuclear antibodies were detected in serum during drug use and disappeared from serum in the five patients who permanently discontinued oral contraceptives. L.E. cells were detected in six patients while on therapy and disappeared in all but one case when the drug was withdrawn. Serum-IgM levels were elevated in five patients during drug use. IgG and IgA levels, rheumatoid-factor activity, and acute-phase proteins were not consistently affected by these agents. In four cases underlying rheumatic disease is suspected; two have Raynaud's disease and two have no laboratory or clinical evidence of disease. This preliminary study indicates that, in the evaluation of women suspected of having rheumatic disease, information on the use of oral contraceptives is required before clinical and laboratory findings can be interpreted.

Introduction

DESPITE increased interest in adverse biological effects of oral-contraceptive agents, rheumatic complications received comparatively little attention. Pimstone (1966) reported an exacerbation of systemic lupus erythematosus in one patient; when the oral contraceptive was withdrawn she remained in remission (Pimstone 1968). Schleicher (1968) found the L.E.-cell phenomenon in ten apparently healthy young women who were receiving oral contraceptives; L.E.-cell tests were negative 4–8 weeks after the drugs were withdrawn. The apparent frequency of this finding has been disputed (Dubois et al. 1968). The development of rheumatic complaints in one group of women taking oral contraceptives and followed up in a planned-parenthood clinic has been interpreted by Gill (1968) as being no greater than that reported in population surveys.

In view of these reports, and the fact that pregnancy can ameliorate rheumatoid arthritis or exacerbate systemic lupus erythematosus, the development of rheumatic complaints and serological abnormalities in temporal relationship to the administration of oral contraceptives may be of interest.

Patients and Methods

Case 1 was suspected of having an adverse reaction to an oral contraceptive agent and cessation of therapy was advised. Subsequently, during 1967, seven other cases were identified at random from a hundred and sixty-seven women aged 15–45 who were attending the arthritis clinics at this institution. The development of thrombophlebitis (in six) and a history of the development or exacerbation of rheumatic complaints (in all patients) led to discontinuation of oral-contraceptive drugs. The women were taking, or had taken, one or more of the following (U.S.A. proprietary names unless otherwise indicated): 'Ovulen' (ethynodiol diacetate 1 mg. and mestranol 0·1 mg.); 'C-Quens' (mestranol 0·08 mg. and chlormadinone acetate 2 mg., 'Sequens' in U.K.); 'Ortho-Novum' (norethindrone 2 mg. and mestranol 0·10 mg., 'Orthonovin' in U.K.); 'Provest' (medroxyprogesterone 10 mg. and ethinylœstradiol 0·05 mg.); 'Enovid-E' (norethynodrel 2·5 mg. and mestranol 0·1 mg., 'Conovid E' in U.K.); 'Norlutin' (norethindrone 15 mg.).

These patients had been seen at intervals of 1–3 months in the arthritis clinics and venous blood specimens had been obtained from each individual during and after treatment with oral contraceptives. All women except one returned for special follow-up evaluation 3–16 months after they stopped taking anovulatory drugs. Patient 7 (a physician) sent a serum specimen and a detailed history of her condition during the previous 12 months.

Special laboratory tests carried out simultaneously on treatment and post-treatment sera included the following: detection of antinuclear antibodies, by indirect immunofluorescent technique using cryostat sections of mouse liver as substrate (Friou 1967); L.E.-cell tests, by the two-stage indirect method (Snapper and Nathan 1955); rheumatoid-factor activity, by an F II latex-fixation procedure (Singer and Plotz 1956); quantitative estimation of IgG, IgA, and IgM, acid-soluble α_1-glycoprotein, α_2-macroglobulin, and transferrin, by radial immunodiffusion using commercially available reagents (Behringwerke AG); C-reactive protein, by a capillary precipitation procedure; and serum-lipids (Bole 1962).

Results

Clinical Findings

Each patient was given a detailed clinical examination

TABLE I—VARIATION IN RHEUMATIC SYMPTOMS AND JOINT FINDINGS BEFORE, DURING, AND AFTER USE OF ORAL-CONTRACEPTIVE DRUGS

Case	Age	Drug	Months used		Rheumatic complaints in relation to oral contraceptives				Follow-up mo. off oral contraceptives
			Total	To onset of symptoms	Before	On	Off	Back on	
1	24	Ovulen ..	10	6	0	V	0	..	16
2	27	C-Quens, ortho-novum	4	0·5	0	V	−F	..	15
3	25	Ortho-novum	6	5	V	S	−F	..	6
4	21	Provest, ortho-novum	30	16	0	S	0	..	8
5	23	Ovulen ..	6	2	0	V	0	..	4
6	26	Enovid-E, ortho-novum	27	26	0	S	0	+F	3
7	29	Norlutin, ortho-novum	8	2	0	V	−F	+S	13
8	22	Ovulen ..	1·5	1	S	S	−S	..	6

V = Vascular or musculoskeletal symptoms.
S = Symptoms associated with objective signs of synovitis in 2 or more joints.
Increase in symptoms (+S) or findings (+F).
Decrease in symptoms (−S) or findings (−F).

by one or more of us before oral-contraceptive agents were discontinued. At the special follow-up examination the medical record was reviewed and additional details were asked for if required. Tables I and II summarise the clinical findings in all eight cases. Four of the patients had taken more than one oral-contraceptive agent; these agents are listed in the order in which they were used in each case. Two patients (cases 6 and 7) elected on their own to resume ortho-novum when they had been off the drug for 3 and 13 months, respectively. At the time of the special follow-up case 6 had been on ortho-novum for 8 months and case 7 had been back on the drug for 2 months. Each of these patients had been seen and examined during the period that they were off oral contraceptives. None of the eight patients were treated with adrenocorticosteroids. The only anti-inflammatory drug that these patients received was aspirin 2·4–4·0 g. per day.

The rheumatic complaints and clinical findings are shown in table I. These included a history of persistent arthralgias, myalgias, and articular or general morning stiffness in all cases. Objective signs of synovitis in two or more joints developed in four patients during the period of treatment with oral contraceptives. In case 3 subjective musculoskeletal stiffness was noted before the use of oral contraceptives. Case 8 had had Raynaud's disease and episodes of migratory polyarthritis involving all peripheral joints for $2^1/_2$ years before the use of ovulen. Based upon current clinical and laboratory findings this patient is felt to have systemic lupus erythematosus. Joint findings disappeared once oral contraceptives were withdrawn, but

TABLE II—VASCULAR ABNORMALITIES PRESENT BEFORE, DURING, AND AFTER USE OF ORAL-CONTRACEPTIVE DRUGS

Case*	Raynaud's phenomenon in relation to oral contraceptives				Phlebitis in relation to oral contraceptives	
	Before	On	Off	Back on	Before	On
1	0	0	0	..	+	+
2	0	0	0	..	+	+
3	0	0	0	..	0	+
4	0	0	0	..	0	0
5	0	0	0	..	0	+
6	0	+	0	+	0	0
7	+	×	÷	×	+	0
8	+	×	+	..	0	+

Increase (×) or decrease (÷) in symptoms or findings.
* Blood-pressure less than 140/90 mm. Hg in all cases.

Raynaud's phenomenon has persisted, and balding over the temples has developed. Cases 6 and 7 elected to resume ortho-novum and in each case vascular and musculoskeletal symptoms recurred. Two patients (cases 2 and 7) became pregnant after discontinuing anovulatory drugs; these were planned pregnancies. Case 2 noted an increase in multiple arthralgias, myalgias, and morning stiffness during the last 4 months of pregnancy, and prompt remission after delivery. In contrast, case 7 noted no increase in symptoms during pregnancy, but did note postpartum return of Raynaud's phenomenon when ortho-novum was resumed.

The incidence of vascular abnormalities in these patients is summarised in table II. Peripheral blood-pressure was normal in each patient during the entire period of observation. Patient 7 noted the onset of unilateral Raynaud's phenomenon 2 months before she started taking oral contraceptives. Both cases 7 and 8 experienced a dramatic increase in Raynaud's phenomena during administration of these drugs. Symptoms decreased in case 7, but did not change in case 8 after stopping anovulatory therapy. Patient 6 developed Raynaud's phenomenon after 26 months of treatment with enovid-E, and improved strikingly when the drug was withdrawn, as did patient 7. In these two patients (cases 6 and 7) there was a definite increase in vascular symptoms when they resumed oral contraceptives. Three of these young women had a documented history of thrombophlebitis before use of these drugs. Five of the eight patients had thrombophlebitis while taking oral contraceptives, and this was the primary reason for discontinuing therapy in each instance. In no case was pulmonary embolism either suspected or documented.

Clinical evaluation of each of these patients indicated that the eight constituted a heterogeneous group—incipient rheumatic disease (three cases), possible systemic lupus erythematosus (case 2), possible rheumatoid arthritis (case 4), definite systemic lupus erythematosus (case 8), and asymptomatic inactive rheumatic aortic and mitral valvular heart-disease (case 5). Raynaud's phenomena was present in two women (cases 6 and 7) without other signs of progressive disease. In cases 1 and 3 no evidence of disease was found during the follow-up period.

Case-report (Case 1)

This 24-year-old housewife gave a history of right saphenous vein ligations after an episode of thrombophlebitis at age 18. She had otherwise been in excellent general health, and first took ovulen in July, 1966. An episode of nausea and vomiting led to discontinuation of therapy in December, 1966. She resumed the drug in January, 1967, and a routine white-blood-cell count (W.B.C.) was found to be 3400 per c.mm. Arthralgias developed and leukopenia persisted (W.B.C. 1800 per c.mm.). The patient noted diffuse morning stiffness, and reported symmetrical swelling in the small joints of the hands and episodic swelling of the right knee. She was seen at another hospital in April, 1967, where leukopenia (W.B.C. 2800 per c.mm.) was again demonstrated, and L.E. cells and antinuclear antibodies were detected in the serum. Other routine blood tests were normal. She had a brief febrile illness and was referred to the arthritis unit at this institution for evaluation. At that time (May, 1967) she complained of multiple arthralgias and myalgias. There was evidence of a resolving superficial thrombophlebitis in the right calf. Total W.B.C. was again 1800 cells per c.mm. in late April, 1967; otherwise the clinical examination was within normal limits. L.E.-cell and antinuclear-antibody tests were positive. The patient was advised to discontinue ovulen. This was the only drug that she was taking. Over the next 6 weeks the leukopenia (W.B.C. 9600 per c.mm.,

TABLE III—ANTINUCLEAR ANTIBODIES, L.E.-CELL PHENOMENA, AND RHEUMATOID-FACTOR ACTIVITY IN PATIENTS RECEIVING ORAL-CONTRACEPTIVE AGENTS

Case	Antinuclear antibodies*			L.E. cells			Rheumatoid factor		
	On	Off	Back on	On	Off	Back on	On	Off	Back on
1	+	0	..	+	0	..	0	0	..
2	+	0	..	+	0	..	0	1/160	..
3	+	0	..	+	0	..	0	0	..
4	+	0	..	0	0	..	0	0	..
5	+	0	..	+	0	..	0	0	..
6	+	..	0	+	..	+	0	..	0
7	+	..	+	0	..	0	0	..	0
8	+	+	..	+	+	..	1/320	1/1280	..

*Positive 1/8 serum dilution.

hæmatocrit 43%), L.E. cells, and antinuclear antibodies disappeared; and by July, 1967, the patient was again symptom-free. Total W.B.C. (8400–8700 per c.mm.) and negative L.E.-cell and antinuclear-antibody tests were recorded in February and May, 1968, and at the time of requested follow-up evaluation in July, 1968. History, physical examination, and all laboratory tests have remained normal for the 15 months after withdrawal of oral contraceptives.

Laboratory Findings

Antinuclear antibodies were detected in the sera of all eight patients during administration of oral contraceptives (table III). The pattern of nuclear fluorescence was of mixed type (homogeneous, speckled, peripheral) in most of the mouse-liver sections. No individual pattern predominated, but the nuclear pattern did change when the serum was diluted. Five patients' sera were negative after drug withdrawal. These tests were done on specimens obtained from individual patients 6 weeks to 16 months after stopping oral contraceptives. In two patients who elected to resume drug therapy, one was positive at 2 months (case 7) and the other negative at 8 months (case 6). The patient with systemic lupus erythematosus (case 8) continued to have detectable antinuclear antibodies in her serum 6 months after stopping ovulen. Six patients had positive L.E.-cell tests while on anovulatory drugs (identification of one typical L.E. cell was considered positive). Follow-up sera were negative, except for the patient with systemic lupus erythematosus (S.L.E.), who remained off the drug, and the patient who had resumed oral contraceptives (case 6). Rheumatoid factor was detected in the sera in cases 2 and 8.

Slight increases in IgM levels were found in five of the patients while on oral contraceptives (table IV). The increase persisted in the two patients who resumed drug therapy (cases 6 and 7) and in two who remained off therapy. The patient with S.L.E. also had increased levels of IgG. Acid-soluble α_1-glycoprotein, α_2-macroglobulin, and transferrin were normal in most cases during and after use of oral contraceptives. Transferrin levels tended to increase in those patients who remained off drug therapy. Determinaton of the concentration of acute-phase proteins in each patient at different time points after drug withdrawal could account for this variation in response. C-reactive protein was detected in serum from cases 2 and 7 during drug therapy, in case 6 after resumption of drug, and in follow-up serum from case 8. Total serum-cholesterol in the eight patients ranged between 157 and 336 mg. per 100 ml. during therapy, and, except for cases 3 and 8, the levels decreased by 10–30% after drug withdrawal. Serum triglyceride and phospholipid levels tended to parallel the changes noted for cholesterol.

TABLE IV—IMMUNOGLOBULIN LEVELS IN PATIENTS RECEIVING ORAL CONTRACEPTIVES*

Case	IgG (mg./ml.)			IgA (mg./ml.)			IgM (mg./ml.)		
	On	Off	Back on	On	Off	Back on	On	Off	Back on
1	11·6	12·0	..	2·1	1·3	..	2·6	0·8	..
2	9·4	14·5	..	2·5	3·4	..	1·7	1·9	..
3	7·4	9·1	..	0·9	1·4	..	1·1	1·4	..
4	9·5	8·0	..	1·0	1·8	..	1·0	0·7	..
5	18·0	12·9	..	2·4	1·8	..	3·4	2·6	..
6	9·5	..	8·8	1·3	..	1·4	3·4	..	3·4
7	13·9	..	11·9	0·9	..	1·1	2·8	..	2·4
8	20·9	30·4	..	1·3	2·2	..	3·1	2·9	..

* Normal range (mg./ml.) IgG 7·0–16·0, IgA 0·9–2·6, IgM 0·5–2·3.

Discussion

In these eight patients, rheumatic symptoms, synovitis, Raynaud's phenomenon, and positive serological tests seem to have been associated with the administration of oral contraceptive drugs. In a small series such as this, it is not possible to differentiate between incipient rheumatic disease and induction of illness in a healthy person. An association between œstrogens/progestogens and rheumatic disease is not a new finding, and the influence of pregnancy on rheumatoid arthritis (Hollander 1966) and systemic lupus erythematosus (Mund et al. 1963) continues to be of theoretical and practical significance. Oral contraceptives have been used as a treatment for rheumatoid arthritis (Blais and Demers 1962, Rotstein et al. 1962) but the results were equivocal.

Of interest in the light of our findings is the report of exacerbation of symptoms in two of seventeen patients with rheumatoid arthritis (Rotstein et al. 1962), and the report of Pimstone (1966). Gill (1968) has reported that the prevalence (0·66%) of rheumatoid arthritis in women taking oral contraceptives and followed up in a birth-control clinic population (84% Negro, 16% White) was no greater than that noted in other population surveys. Indirect comparisons of this type are difficult to interpret. In Gill's (1968) series the incidence of definite, probable, or possible rheumatoid arthritis in 3014 females increased from 2·98 per 1000 to 6·63 per 1000 in the two years after initiation of oral-contraceptive therapy in these women. This exceeded by more than 50% the rate of increased incidence of rheumatoid arthritis with age calculated from other population survey data (Lawrence 1961, U.S. Public Health Service 1966).

Our findings support those of Schleicher (1968) who reported that some women develop positive L.E.-cell tests while taking anovulatory drugs. Two of our patients had negative L.E.-cell tests, and the patient with S.L.E. continued to be L.E.-cell positive after the drug was withdrawn. Dubois et al. (1968) tested sera from thirty apparently healthy women who were taking ovulen or 'Syntex' (chlormadinone acetate 0·5 mg.). L.E.-cell tests were negative in all cases; antidesoxyribonucleoprotein antibody and rheumatoid factor was detected in two separate patients. Larger groups of women with and without symptoms must be investigated before the effect of oral contraceptives on these serological tests can be determined. Our patient population is not comparable with those of Schleicher (1968), Dubois et al. (1968), or Gill (1968), but the findings do suggest that in certain individuals the use of oral contraceptives can induce positive tests for antinuclear antibodies and L.E. cells. In case 8 these tests remained positive in the presence of active S.L.E. and were not influenced by withdrawal of oral contraceptives. The high incidence of thrombo-

phlebitis in this small group of young women may also point to a tendency to respond abnormally to synthetic œstrogen/progestogen drugs.

In the evaluation of women suspected of having early rheumatic disease, specific information on the use of oral contraceptives is required before the clinical and laboratory findings can be properly interpreted. A case-selected prospective study of this problem in a healthy and a rheumatic disease population is now in progress.

We thank Miss Susan Christensen and Mr. Scott Himes for their expert technical assistance. This study was supported in part by a National Institute of Arthritis and Metabolic Disease grant AM 06206 and the Michigan Chapter, Arthritis Foundation, U.S.A.

Requests for reprints should be addressed to G. G. B.

REFERENCES

Blais, J. A., Demers, R. (1962) *Arthr. Rheum.* **5**, 284.
Bole, G. G. (1962) *ibid.* p. 589.
Dubois, E. L., Strain, L., Ehn, M., Bernstein, G., Friou, G. J. (1968) *Lancet*, ii, 679.
Friou, G. J. (1967) Laboratory Diagnosis in Rheumatic Disease; p. 136. Boston.
Gill, D. (1968) *J. chron. Dis.* **21**, 435.
Hollander, J. L. (1966) Arthritis and Allied Conditions; p. 606. Philadelphia.
Lawrence, J. S. (1961) *Ann. rheum. Dis.* **20**, 11.
Mund, A., Simson, J., Rothfield, N. (1963) *J. Am. med. Ass.* **183**, 917.
Pimstone, B. L. (1966) *S. Afr. J. Obstet. Gynæc.* **4**, 62.
— (1968) *Lancet*, i, 1153.
Rotstein, J., Gilbert, M., Cunningham, C., Estrin, I., Pincus, G. (1962) *Arthr. Rheum.* **5**, 655.
Schleicher, E. (1968) *Lancet*, i, 821.
Singer, J. M., Plotz, C. M. (1956) *Am. J. Med.* **21**, 888.
Snapper, I., Nathan, D. J. (1955) *Blood*, **10**, 718.
U.S. Public Health Service (1966) *U.S. publ. Hlth Serv. Publ.* no. 1431.

REPLACEMENT THERAPY IN HEREDITARY ANGIOEDEMA

SUCCESSFUL TREATMENT OF TWO PATIENTS WITH FRESH FROZEN PLASMA

R. J. PICKERING J. R. KELLY
R. A. GOOD H. GEWURZ

FROM THE RESEARCH LABORATORIES OF THE VARIETY CLUB HEART HOSPITAL, DEPARTMENTS OF PEDIATRICS, SURGERY, AND MEDICINE, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINNESOTA 55455

Summary The abnormality unique to hereditary angioedema (H.A.E.) which seems to be responsible for the episodes of œdema is the deficiency of a normally occurring serum-inhibitor of the esterase activity associated with the first component of complement. Since this deficiency has been suspected to be responsible for events which produce symptoms, it seemed reasonable to treat the symptoms by providing the patient with the deficient protein. Two patients with H.A.E., one with laryngeal œdema and one with persistent abdominal pain, were treated with fresh frozen plasma. Both improved subjectively during the infusion, and later had rapid, complete remission of symptoms. Objective evidence that this infusion provided the patients with effective inhibitor was shown by a measurable increase in inhibitor function, a significant decrease of free esterase activity in the serum, and a possible decrease of the in-vivo inactivation of C'4 after the infusion. It is suggested that the precedent set in the treatment of hæmophilia should encourage the use of fresh-plasma therapy for potentially life-threatening or painful episodes in H.A.E. until an effective purified form of the C'1-esterase-inhibitor becomes available.

Introduction

EPISODES of œdema in patients with hereditary angioedema (H.A.E.) may present the physician with an acute, potentially life-threatening process which, heretofore, he has been unable to prevent or modify. Patients with this disease have recurrent attacks of relatively painless, non-pruritic, non-pitting œdema which may involve any part of the body. If the mucosa of the intestinal tract or pharynx and larynx becomes involved, severe abdominal pain or fatal airway obstruction may result (Landerman 1962, Donaldson and Rosen 1966). The frequency of attacks and the course of each attack is completely unpredictable; they may occur once in a lifetime or once a week, and each attack may be as brief as a few hours or as long as a few days before it subsides spontaneously.

The biochemical abnormality which distinguishes this disorder from other forms of angioedema is the hereditary absence or functional deficiency of a normally occurring inhibitor of the esterase activity associated with the first component of complement (C'1) (Donaldson and Evans 1963, Rosen et al. 1965). The absence of this C'1-esterase inhibitor seems to permit the autocatalytic conversion of the inactive precursor to the active esterase, and to allow this esterase to react with its natural serum-substrates, which include the fourth (C'4) and the second (C'2) components of complement (Haines and Lepow 1964, Lepow et al. 1965). This latter interaction leads to enzymatic cleavage of C'4 and C'2, and could deplete the activities of these components in the serum (fig. 1) (Donaldson and Rosen 1964). It is this esterase so consistently found in serum of patients with active disease which may, through its enzymatic activity in vivo, lead to the production of the biologically active peptides responsible for development of the œdema (Donaldson and Rosen 1964).

Therapy is difficult to evaluate because of the unpredictable course of any one attack, but it is generally agreed, as emphasised in Landerman's review (1962), that attempts to interrupt the progress of œdema with a variety of medications including adrenaline, steroids, and antihistamines have been ineffective. In many instances there is no urgent need to intervene, since swelling of a hand, arm, or leg may be, at most, inconvenient. However, when œdema involves the face, with the possibility of progression to oral and laryngeal œdema, an effective means for interrupting the progress of the attack might prevent airway obstruction and the need for tracheotomy. In

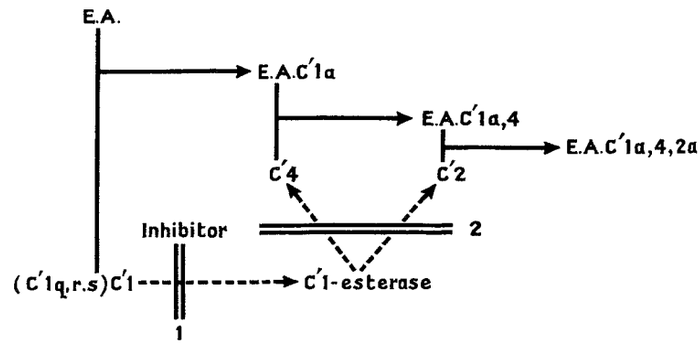

Fig. 1—A simplified representation of the sites of activity of C'1-esterase-inhibitor.

Inhibition at site no. 1 indicates an effect on the autocatalytic conversion of proesterase to esterase; there seems to be no effect on the spontaneous conversion step (Lepow et al. 1965). Activity at site no. 2 includes inhibition of esterase hydrolysis of a synthetic substrate N-acetyl-L-tyrosine ethyl ester.

Symbol E represents antigen; symbol A represents antibody.