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CONSIDERATIONS ON THE USE OF CEPHAL RIDINE
IN HUMAN PATHOLOGY

Minerva Medica
(Medical Minerva)
Vol. 57, No. 47, pages 2161-2175, 1966

N. Dioguardi and G. Ideo

It is the purpose of this report to present a mostly practical clinical contribution to the knowledge of the activity of a new antibiotic, a semi-synthetic derivative of cephalosporine C which is obtained through biosynthesis from microorganisms belonging to the genus Cephalosporium (14, 38, 39).

The production of substances endowed with an antibiotic activity by organisms of this kind [genus] was brought out for the first time in Sardinia by Giuseppe Brotzu (9, 16) in the course of research undertaken to identify new antibiotics of natural origin.

The study of metabolites with the antibiotic action of Cephalosporium was then continued in Great Britain and seven new substances with antibiotic action were isolated (10, 19, 21). The most active among them turned out to be Cephalosporium P, Cephalosporium N ("synnematin"), which acts primarily through gram-negative germs (8, 36), and Cephalosporium C (27). The central nucleus of the latter is 7-aminocephalosporanic acid, similar to the nucleus of penicillin, [that is] 6-aminopenicillanic acid (2, 15, 28) (Figure 1).

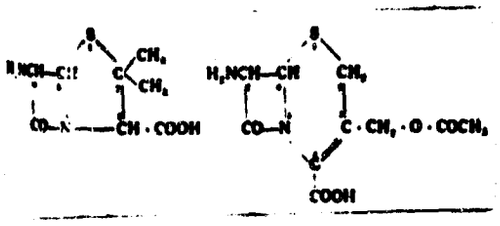

Figure 1. 6-amino-penicillanic acid and 7-amino-cephalesporanic acid.

The nucleus of cephalosporine C can currently be synthesized (5, 37, 38, 39, 42) and, by means of a number of substitutions, either in position 7, or at the expense of the acetoxylic group in position 3, it was possible to obtain a very large number of compounds. Many of these compounds, which proved to be active in vitro, on the other hand turned out to have a rather modest activity in vivo, since they are easily hydrolyzable in position 3 by means of organic esterases (11, 18, 25, 33).

Substituting the acetoxylic group in position 3 with pyridine, the organic esterases cannot split the compound since there is no longer any esterasic bond.

Among the various components synthesized with this criterion in mind, the Research Division of Glaxo synthesized cephaloridine by introducing the 7-thyenyl-acetic radical into position 7: /This resulted in/ the internal salt of 7-/2-thyenyl)-acetamido/-3-(1-pyridilmethyl)-3-cephem-4-carboxylic acid (7, 12) (Figure 2).

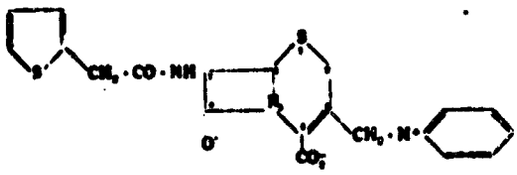

Figure 2. Cephaloridine = internal salt of 7-/(2-thyenyl)-acetamido/-3-(1-pyridilmethyl)-3-cephem-4-cargoxylic acid.

Cephaloridine acts through a bactericidal effect (7, 32) upon gram-positive and gram-negative microorganisms, whereas it is inactive toward fungi, protozoa, helminths, as well as aerobacter aerogenes, pseudomonas pyocyanea; it is hardly active toward mycobacterium tuberculosis (32, 41).

It is an antibiotic which resists penicillinase and the bacterial resistance without manifestations of crossed resistance with penicillin (1, 3, 6, 7, 13, 30, 43).

On the basis of laboratory investigations and on the basis of the first clinical applications (24, 40), cephaloridine appears to be perfectly well tolerated and absolutely devoid of any toxic effects when administered in clinical doses.

The maximum concentration in the human blood, after intramuscular administration of a dose of 0.5 g is reached after the first hour (3-10 gamma/cc) and the average stay /of this concentration in the blood/ may vary from 4-5 hours; however, during the 8th hour, we still find gamma 1-2/cc in a circle (32); cephaloridine is eliminated completely through the kidneys and the form of urinary elimination occurs without any modifications, since it has been demonstrated that it reveals a distinct stability with respect to intra-organic metabolic transformations.

In the course of clinical use, it has proved to be very active in a number of different affections which sometimes resisted treatment with other antibiotics (17, 20, 22, 23, 40).

After this introduction we would like to present the practical results derived from this antibiotic in a rather varied group of case histories, such as we found it at the special medical pathology institute of the University of Cagliari.

Since it is known that antibiotics develop a toxic action on the level of numerous organs and apparatuses, including first of all the liver and the kidney, we also directed our attention to the possible influence of the antibiotic we are studying here upon the functional activities of the liver cell.

Case Histories

Our research involved 65 patients who revealed various affections which we can group as follows:

(1) Affections involving the kidneys and the urinary tracts, nine cases;

(2) Affections of the respiratory system: 32 cases;

(3) Septic affections of the liver and of the bile ducts: eight cases;

(4) Cardiac affections: four cases;

(5) Miscellaneous affections: 12 cases.

In tables 1, 2, 3, 4, and 5 we show the diagnoses for each group of affections in detail.

(1) Therapy plan. Cephaloridine was administered at the rate of 1-3 g per day as attack dose and this was reduced after a period of time varying from one case to the next, to the maintenance dose of 1 g per day.

Along with this antibiotic, as well as all of the other antibiotics considered in this study, we also administered abundant doses of vitamins of the B group.

(2) Research plan. In order to evaluate the therapeutic effect of the

administration of cephaloridine in all of the patients treated here, we took into consideration not only the fever curve, the [blood] pressure and the pulse, but also the speed of sedimentation, the number of leucocytes, the leucocytary formula and the mucoproteins. In lung patients we dosed the quantity of the expectorate and we made numerous x-ray checks.

Accurate controls were performed on the urine in patients suffering from diseases of the urinary apparatus. In patients with diseases of the circulatory system we also examined the antistreptolysinic index. In patients with diseases of the bile ducts we attached particular importance to tests that would express the progress of the retentive state; we evaluated not only the behavior of bilirubinemia but also that of alkaline phosphatase, cholesterol, and the gamma and alpha$_2$ globulins; the latter were studied by means of electrophoresis on acetylcellulose.

For the purpose of bringing out any possible negative effect of the antibiotic upon the liver cell, we also made a study of the synthetic activities of the liver in all of these patients who were treated with cephaloridine; here we used the following tests: seric albuminemia dosage by means of electrophoresis, dosage of the prothrombinic activity (in icterus patients only after the addition of vitamin K), as well as dosage of the V factor, the VII factor, and cholinesterase.

As far as the evaluation of the liver's secretion capacity is concerned, we used the study of the elimination of bromosulfonphthaleine, of Cardio-Green, and of bilirubin in all of its fractions.

The study of the behavior of glycemia, azotemia, and cholesterolemia then completed our research.

Results

Affections of the urinary tracts. The response to the action of cephaloridine was truly one of the most effective and prompt (Table 1).

TABLE 1
SUMMARY TABLE OF CASE HISTORIES FOR AFFECTIONS
INVOLVING THE KIDNEYS AND THE URINARY TRACTS

(a) N.	(b) Paziente	(c) Forma morbosa	(d) Cefaloridine g. x 24 h. (g)	Durata trattamento (giorni)	(h) Sfebbramento dopo giorni	(e) VES (I.K.) prima (i)	dopo (j)	(f) Leucociti prima	dopo	(k) Risultato	(l) Commenti
1	M. L. (1)	Glomerulonefrite acuta	1	21	2	37,5	34	8.400	4.800	Ottimo (m)	-
2	Z. G. (2)	Pielonefrite specifica con infetto piogeno sovrapposto	1	18	9	100	90	7.500	6.100	Buono (n)	-
3	M. V. (3)	Pielonefrite acuta	1,5	9	2	49,5	18,5	9.800	6.600	Ottimo	-
4	M. E. (4)	Neoplasia prostatica; ritenzione urinaria	1	11	3	42,5	30	8.300	6.200	Ottimo	-
5	F. D. (5)	Cistopielite	2	10	3	37	28	11.500	9.000	Ottimo	-
6	C. S. (6)	Ipertermia conseguente ad esame urologico	1,5	8	2	62,5	26,5	12.500	8.000	Ottimo	-
7	A. L. (7)	Glomerulonefrosi acuta	1	11	3	35	27	10.000	9.200	Buono	-
8	B. L. (8)	Glomerulonefrite acuta	1	11	8	45	25	12.000	7.000	Buono	-
9	M. L. (9)	Cistite acuta in soggetto sofferente per paralisi flaccida agli arti inferiori con disturbi degli sfinteri per ernia discale	1,5	10	2	80	95	9.700	6.500	Ottimo	-

Legend: a--number; b--patients' initials; c--form of disease; d--cephaloridine; e--VES [sedimentation rate] (Kats index); f--leucocytes; g--duration of treatment (days); h--fever drop after number of days; i--before; j--after; k--result; l--comments; m--excellent; n--good; 1--acute glomerulonephritis; 2--specific pyelonephritis with superposed infected pyogen; 3--acute pyelonephritis; 4--prostatic neoplasic; 5--cystopyelitis; 6--hyperthermia following urological examination; 7--acute glomerulonephritis; 9--acute cystitis in subject suffering from flaccid paralysis of the lower limbs, with disorders in sphincters due to discal hernia.

The germs which were recognized most frequently here as being responsible for the infection were: Coli and enterococcus.

Figure 3 describes the time of fever drop from the beginning of the therapy pursued in the nine cases considered here. From this we can deduce that the fever drop occurred during a period of time which can vary from a minimum of 2 to a maximum of 9 days.

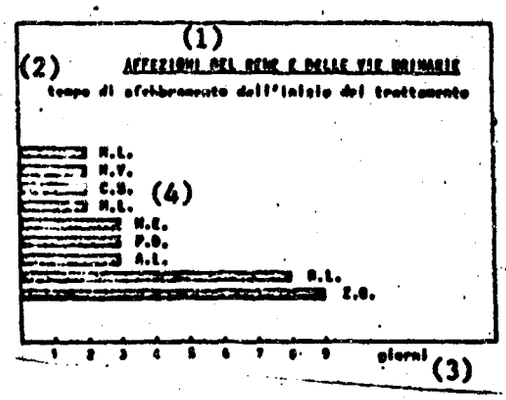

Figure 3. Legend: 1--affections of the kidneys and urinary tracts; 2--time of fever drop from beginning of treatment; 3--days; 4--patients' initials.

It might be worth while to point out here one case of renal tuberculosis with superposed infected pyogen, combined with a finding of Koch bacillus which was rather amply positive in the urine; in this case the temperature was particularly resistant to the specific treatment because of a cystopyelitis superposed by pyogens.

The use of cephaloridine brought the temperature down within 9 days; as the disease continued and for the period of time during which we were possible to observe the patient directly, the temperature turned out to be rather modest although it was a little more than 37.3-37.4° C; this was accompanied by a completely negative urine report in the sense of the pyogenic process (figure 4).

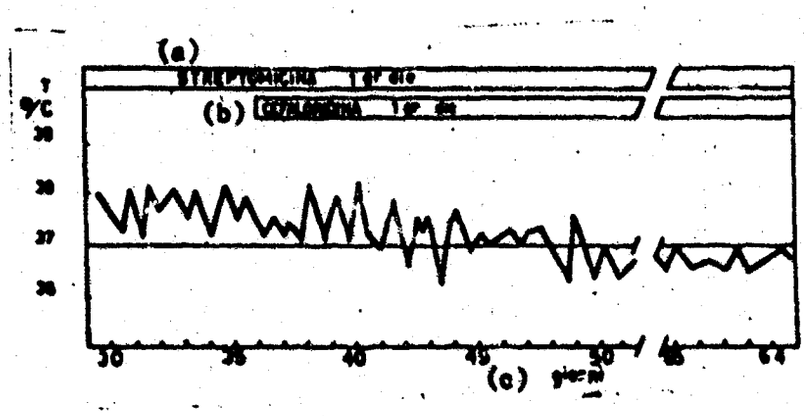

Figure 4. Z.G.: renal tuberculosis with superposed infected pyogen. Legend: a--streptomycin 1 g/day; b--cephaloridine, 1 g/day; c--days.

The antibiotic dose used in these disease forms was about 2 g during the attack phase and 1 g during the maintenance phase.

Affections of the Respiratory System. The affections of the respiratory system are represented above all by patients suffering from bronchial pneumonia and bronchitis, often complicated by an asthmatic ailment. Here our case histories were relatively more numerous and this gave us a better chance to use our antibiotic (Table 2).

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TABLE 2

SUMMARY TABLE OF CASE HISTORIES FEATURING AFFECTIONS OF THE RESPIRATORY SYSTEM, TREATED WITH CEPHALORIDINE

(a) N.	(b) Paziente	(c) Forma morbosa	(d) Cefaloridina g. x 24 h. (g)	(d) Durata trattamento (giorni)	(h) Febbre scomparsa dopo giorni	(e) VES (U.K.) prima (i)	(e) VES (U.K.) dopo (j)	(f) Leucociti prima (i)	(f) Leucociti dopo (j)	(k) Risultato	(l) Osservazioni
1	S. G. (u)	Bronchite asmatica	1	15	7	5	6	11.000	4.800	Ottimo (m)	–
2	M. S. (u)	Bronchite asmatica	1	13	4	52	48	9.100	7.800	Ottimo	–
3	N. G. (u)	Bronchite asmatica	1	8	—	50	35	9.000	8.900	Buono (n)	–
4	C. C. (v)	Bronchite cronica	1	12	7	29	21	14.000	9.900	Ottimo (q)	Gi[illegible] tra[illegible] senza di[illegible] co[illegible] pen[illegible]
5	F. I. (w)	Broncopolmonite	2	7	1	37	26	7.700	6.500	Ottimo	–
6	P. A. (w)	Broncopolmonite	1,5	7	1	52	46	10.300	8.800	Ottimo (r)	Tr[illegible] tata [illegible] cede[illegible] [illegible] alta[illegible] [illegible] otti[illegible] ri[illegible] ltata
7	S. G. (w)	Broncopolmonite	1,5	18	4	16	3	14.600	7.200	Ottimo	–
8	G. C. (x)	Broncopolmonite in paziente con neo polmonare	1	8	2	79	66	18.000	14.200	Ottimo (s)	In[illegible] [illegible] pa[illegible] [illegible] tr[illegible] [illegible] C. F
9	F. A. (y)	Broncopolmonite in portatore di istiocitoma	1	7	6	90	85	8.000	7.800	Ottimo	–
10	U. P. (u)	Bronchite asmatica	1	15	—	52	40	5.500	5.600	Discreto	–
11	N. C. (u)	Bronchite asmatica	1	8	1	16	12	—	—	Ottimo	–
12	S. L. (v)	Broncopolmonite	1,5	12	4	82	43	13.000	8.800	Ottimo (t)	[illegible] [illegible] [illegible] [illegible]
13	P. G. (z)	Pleurite metapneumonica in soggetto cirrotico	1	12	5	84	81	3.600	3.300	Buono	–
14	M. (aa)	Polmonite e sepsi	1,5	10	3	104	65	8.000	6.800	Ottimo (t)	[illegible] [illegible] [illegible] [illegible]
15	U. S. (bb)	Bronchite cronica in paziente con neoplasia epatica	1	25	(p) Febbre diminuita ma non scomparsa	51	62	5.900	6.200	Scarso (o)	–
16	P. M. (cc)	Bronchite acuta	1,5	7	—	43	25	8.600	8.400	Buono	–
17	S. C. (w)	Broncopolmonite	1,5	15	4	16	3	14.000	8.000	Ottimo	–
18	A. S. (cc)	Bronchite cronica	1	8	2	27	11	9.500	6.400	Ottimo	–
19	P. P. (dd)	Broncopolmonite con complicanza pleuritica	1	13	12	54	26	8.000	7.400	Buono	–
20	P. G. (ee)	Bronchite cronica; enfisema polmonare; cuore polmonare cronico	1	15	—	2	1	8.000	7.200	Ottimo	–
21	S. [illegible] (w)	Broncopolmonite	1	15	2	84	40	14.000	9.300	Ottimo	–
22	A. M. (w)	Broncopolmonite	1,5	10	4	66	50	22.000	9.200	Ottimo	–
23	P. L. (w)	Broncopolmonite	1,5	10	2	45	25	8.500	6.500	Ottimo	–
24	F. G. (ff)	Polmonite	1	13	3	48	30	16.000	8.000	Ottimo	–
25	V. C.	Broncopolmonite	1,5	4	1	56	30	9.000	6.000	Ottimo	–
26	M. P.	Broncopolmonite	1,5	8	3	32	22	11.500	6.000	Ottimo	–
27	G. P.	Broncopolmonite (w)	1,5	10	2	42	10	12.000	6.000	Ottimo	–
28	B. U.	Broncopolmonite	1,5	14	4	82	70	14.000	6.200	Ottimo	–
29	G. M.	Broncopolmonite	1,5	14	5	—	—	—	—	Ottimo	–
30	A. B. (gg)	Bronchite	1	6	2	—	—	—	—	—	–
31	B. R. (w)	Broncopolmonite	2	15	2	—	—	—	—	Ottimo	–
32	B. G. (w)	Broncopolmonite	2	12	3	—	—	—	—	Ottimo	–

Legend: a--number; b--patients' initials; c--form of disease; d--cephaloridine; e--VES /sedimentation rate/ (Katz index); f--leucocytes; g--duration of treatment (days); h--fever drop after number of days; i--before; j--after; k--result; l--comments; m--excellent; n--good; o--poor; p--fever decreased but did not disappear; q--already treated earlier with penicillin, without results; r--treated earlier with other antibiotics, without results; s--not sensitive to penicillin, tetracycline, CAF; t--not sensitive to other antibiotics; u--asthmatic bronchitis; v--chronic bronchitis; w--bronchial pneumonia; x--bronchial pneumonia in patient with recent lung infection; y--bronchial pneumonia in carrier of histiocytoma; z--metapneumonic pleuritis in cirrhotic subject; aa--pneumonia and sepsis; bb--chronic bronchitis in patient with hepatic neoplasia; cc--acute bronchitis; dd--bronchial pneumonia with pleuritic complications; ee--chronic bronchitis; lung emphysema; chronic pulmonary heart; ff--pneumonia; gg--bronchitis.

The fever drop time for the patients is described in Figure 5 and ranges from a minimum of 1 day to a maximum of 12 days.

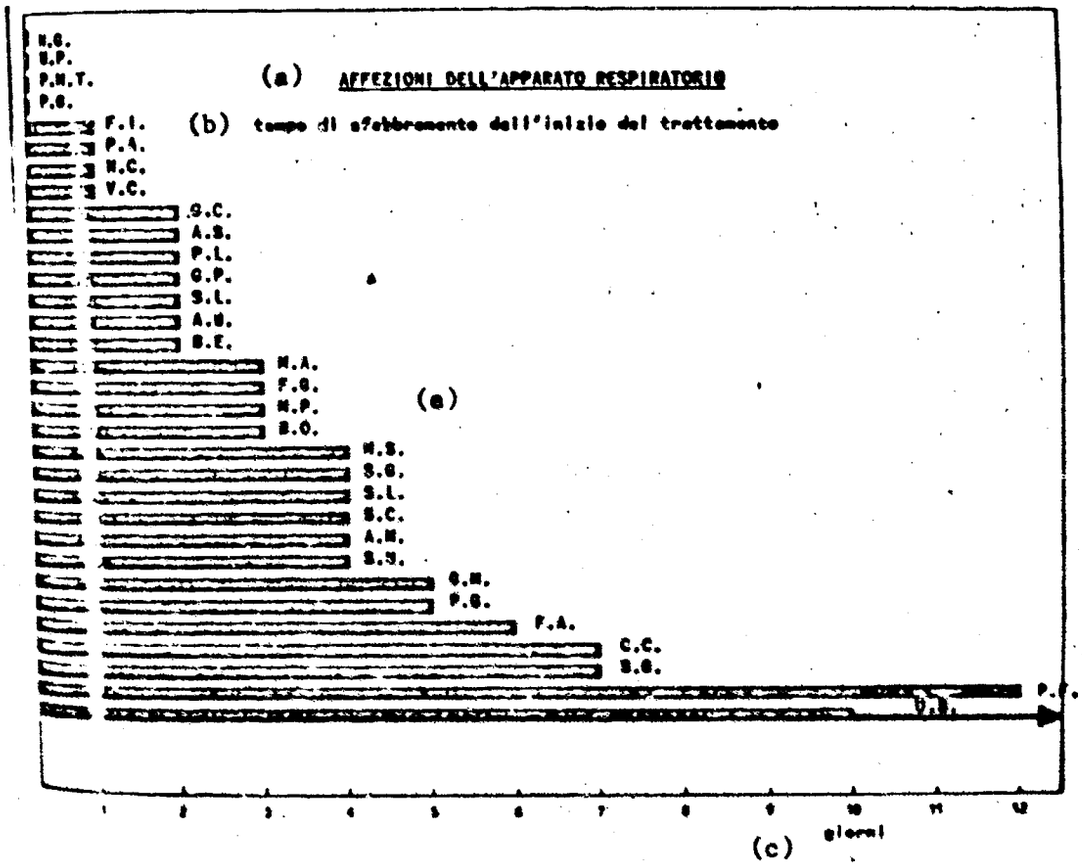

Figure 5. Legend: a--affections of the respiratory apparatus; b--time of fever drop from beginning of treatment; c--days; e--patients' initials.

We are also describing here a case of residual fever which turned out to be not susceptible to cephaloridine treatment.

Figure 6 shows an example of a bronchial pneumonia episode which was resolved due to the effect of the antibiotic in a very evident fashion. The expectorate, which increased during the first few days, parallel to the transition from the hepatization phase to the resolution phase, decreased quite definitely, and then disappeared within a week. All of the other constants followed the favorable course of the disease.

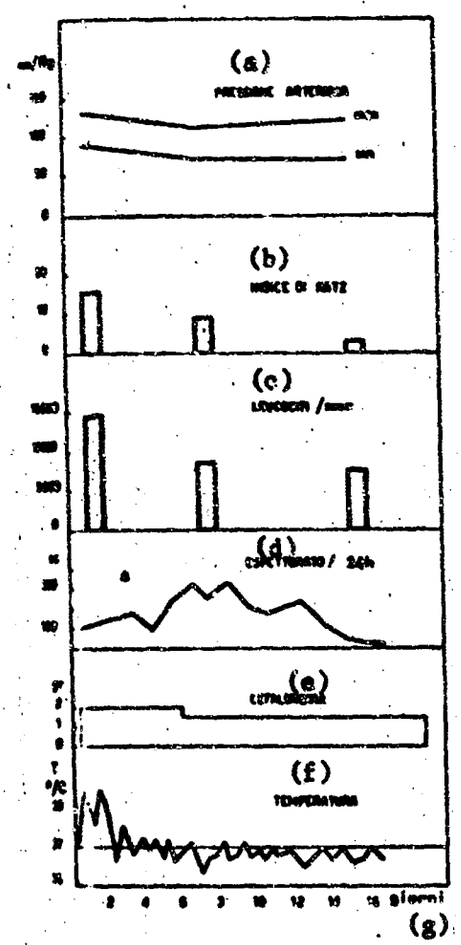

Figure 6. S. G.: bronchial pneumonia. Legend: a--arterial [blood] pressure; b--Katz index; c--leucocytes/cubic mm; d--expectorate [sputum] /24 hours; e--cephaloridine; f--temperature; g--days.

Figure 7 describes the case of an apyretic patient suffering from chronic bronchitis accompanied by an asthmatic ailment with abundant excretions, treated with cephaloridine. The favorable development in this case was manifested not only by the decrease in the kinetic symptomatology of the respiratory tract, but also by a reduction in the number of asthmatic attacks and above all by the reduction of the expectorate practically down to zero.

The antibiotic dose used in these patients varied between 1-2 g.

Affections of the liver and the bile ducts. The affections of the liver and the bile ducts are represented by patients with septic affections of the liver, patients who are carriers of primary or secondary angiocholitis or of cyst suppurated by echinococcus (Table 3).

TABLE 3
SUMMARY TABLE OF CASE HISTORY OF SEPTIC AFFECTIONS
OF THE LIVER AND THE BILE DUCTS, TREATED WITH CEPHALORIDINE

N. (a)	Pazienti (b)	Forme morbose (c)	(d) Cefaloridina g. x 24 h.	Durata trattamento (giorni) (g)	Febbre scende dopo giorni (h)	(e) VES (U.K.) prima (i)	VES (U.K.) dopo (j)	(f) Leucociti prima (i)	Leucociti dopo (j)	Risultato (k)	Commenti (l)
1	D. E.	Colangite acuta (r)	1	10	1	20	13	9.400	7.800	Ottimo (m)	-
2	C. R.	Colelitiasi; thr. intestinale (s)	1	10	Febbricola residuale (p)	16	19	9.200	8.700	Scarso (o)	-
3	P. E.	Epatite cronica ascitogena colecistopatica (t)	1	9	4	136	119	11.000	5.000	Buono (n)	-
4	L. F.	Epato-colangite (u)	1	8	3	41	20	9.500	6.300	Ottimo	-
5	D. L.	Epatite acuta con colangite (v)	1	15	2	20	13	9.400	8.000	Ottimo	-
6	P. G.	Epatite cronica; colecistite acuta (w)	1	15	2	87	57,5	6.000	5.500	Buono	Incerto (q)
7	M. C.	Cisti da echinococco epatica suppurata (x)	1,5	15	13	60	40	9.500	7.000	Ottimo	-
8	D. M.	Stato iperfermico protratto in colecistectomizzata; calcificazioni epatiche multiple; empiema polmon. acuto (y)	2,5	25	12	57	89	18.000	7.500	Ottimo	-

Legend: a--number; b--patients' initials; c--form of disease; d--cephaloridine; e--VES [sedimentation rate] (Katz index); f--leucocytes; g--duration of treatment (days); h--fever drop after number of days; i--before; j--after; k--result; l--comments; m--excellent; n--good; o--poor; p--residual fever; q--not sensitive to other antibiotics; r--acute cholangitis; s--cholelithiasis; t--chronic ascitogenic cholecystopathic hepatitis; u--hepato-cholangitis; v--acute hepatitis with cholangitis; w--chronic hepatitis; acute cholecystitis; x--suppurated hepatic cyst [cystitis] due to echinococcus; y--protracted hyperthermic state in cholecystectomized [female] patient; multiple liver calcifications, acute pulmonary empyema.

The germs [viruses] isolated in this part of our group of case histories were enterococcus, bacterium Coli, and staphylococcus.

One case of cholelithiasis in a subject who was also a carrier of intestinal tuberculosis, did not respond to the antibiotic.

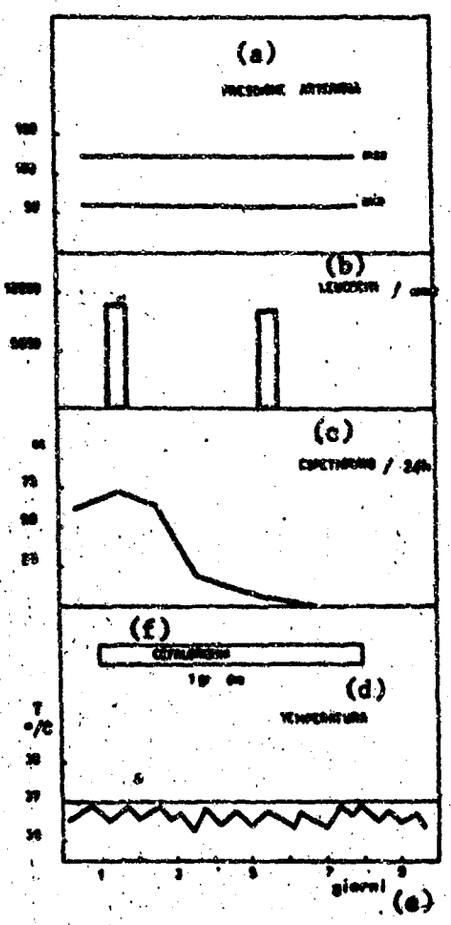

Figure 7. N. G.: asthmatic bronchitis. Legend: a--arterial [blood] pressure; b--leucocytes/cubic mm; c--expectorate/24 hours; d--temperature; e--days; f--cephaloridine, 1 g per day.

Figure 8 shows the fever drop time for the patients in this group of case histories.

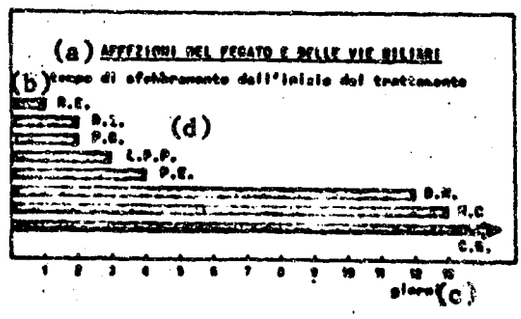

Figure 8. Legend: a--affections of the liver and the bile ducts; b--time of fever drop from beginning of treatment; c--days; d--patients' initials.

We also think it interesting to point out the case of a 38-year old female patient who revealed a radiological picture and a symptomatology which led to a diagnosis of "multiple liver abscesses in a subject already cholecystectomized" (see the x-ray picture of the liver in Figure 9).

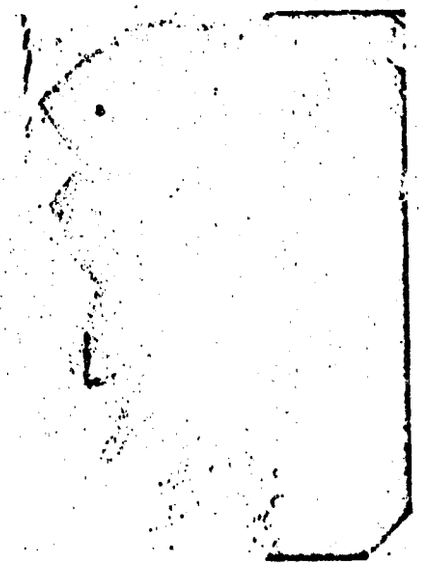

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Figure 9. Patient D. M. [female]: Direct liver x-ray.

After a period of treatment at the institute with antibiotics, our female patient was discharged although she still had some fever but maintenance treatment was administered with the antibiotic. After about 10 days, she developed a rather bad pain in the right shoulder; the attending physician interpreted this as scapulohumoral periarteritis; she was treated with a dose of prednisone at the rate of 100 mg per day. After 6 days of treatment,

she had recurrent high fever, intensive pain in the right half of the chest, and her excretion [sputum] was purulent in nature (Figure 10). We then instituted cephaloridine therapy at the rate of 3 g per day for a period of 10 days and 2 g during the following days; within 4 days the fever dropped, along with the symptomatology. The fever disappeared completely by the 14th day; simultaneously, the leucocytosis returned to normal (Figure 12). The lung picture, in turn, after 20 days revealed a complete cleansing, with success in the symphysis of the costo-phrenic corner [angle] (Figure 11).

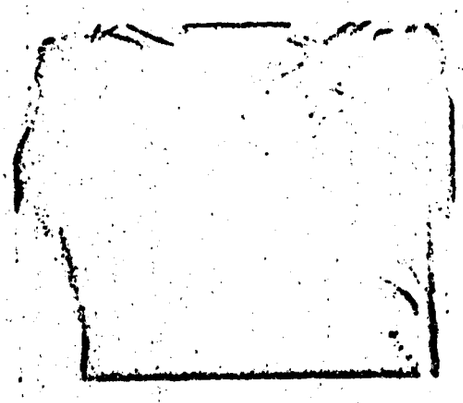

Figure 10. Female patient D.M.: chest x-ray prior to cephaloridine therapy.

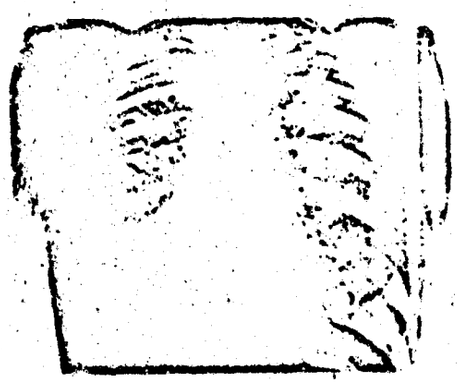

Figure 11. Female patient D.M.: x-ray of chest after cephaloridine treatment.

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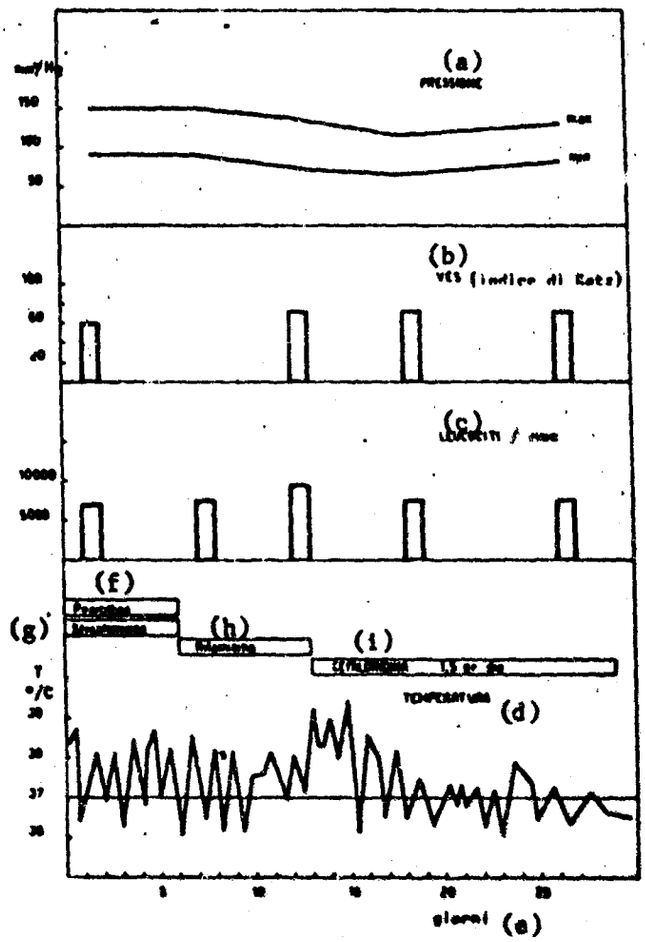

Figure 12. D.M.: hyperthermic state in cholecystectomised [male] patient; liver calcifications; acute pulmonary empyema. Legend: a--[blood] pressure; b--VES [excretion rate per second] (Katz index); c--leucocytes/cubic mm; d--temperature; e--days; f--penicillin; g--streptomycin; h--rifamycin; i--cephaloridine, 1.5 g/day.

An equally brilliant result was obtained in the group of affections of the bile ducts. Figure 13 describes the behavior of signs imputable to the inflamation process going on in the bile tract; we can observe a definite improvement induced by antibiotic therapy with cephaloridine, as demonstrated by the reduction in the temperature, the VES [sedimentation rate per second or speed of elimination of secretions], the mucoproteins, and the alpha$_2$ globulins.

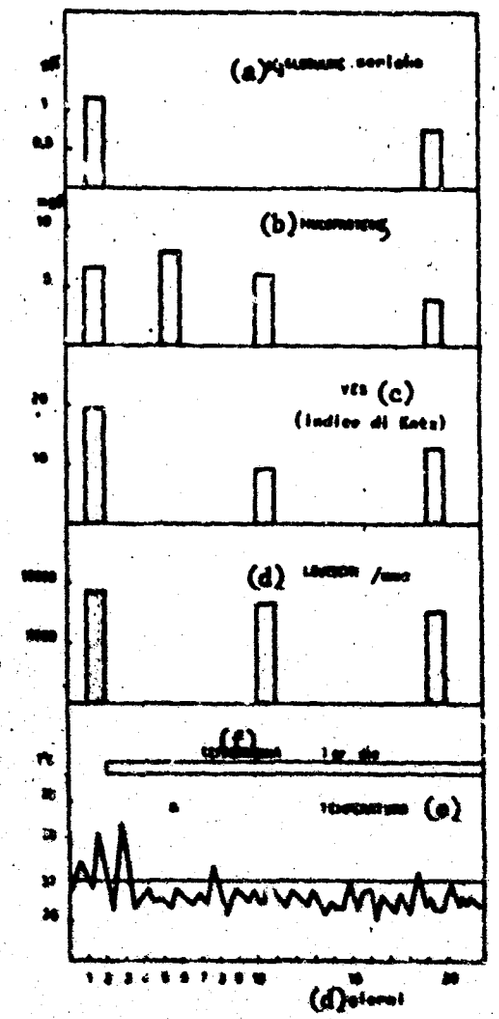

Figure 13. D.E.: acute cholangitis. Legend: a--seric alpha$_2$ globulins; b--mucoproteins; c--VES (Katz index); d--leucocytes/cubic mm; e--temperature; d--days; f--cephaloridine, 1 g/day.

The signs of bile retention also definitely improve, along with the regression in the inflammation process. This was expressed by the reduction in the bilirubinemia, the cholesterolemia, and the alkaline phosphatase, as well as the behavior of the color excretion tests (BSF and Cardio-Green), which were performed the moment the bilirubinemic level had become compatible with the performance of these tests (Figure 14).

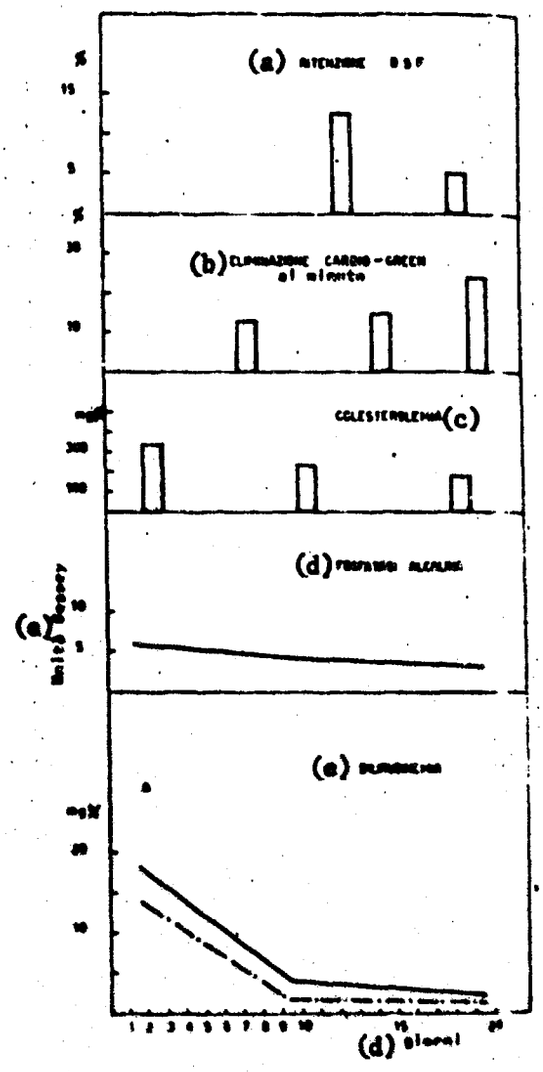

Figure 14. D.E.: acute cholangitis. Legend: a--retention; b--Cardio-Green elimination, per minute; c--cholesterolemia; d--alkaline phosphatase; e--bilirubinemia; d--days; e--bessey units.

On the basis of the data collected, we can say that cephaloridine can penetrate membranes which are rather purely permeable for other antibiotics, with a good coefficient of concentration. This fact became evident, for example, in a case of suppurated cystic echinococcosis, which responded to treatment in a truly exceptional fashion.

Figures 15 and 16 show the x-rays for bladder expansion due to echinococcosis [voluminous echinococcosis cyst], in an antero-posterior and lateral projection; Figure 17 shows the stratigraphic picture after [right beyond] the pneumoperitoneum.

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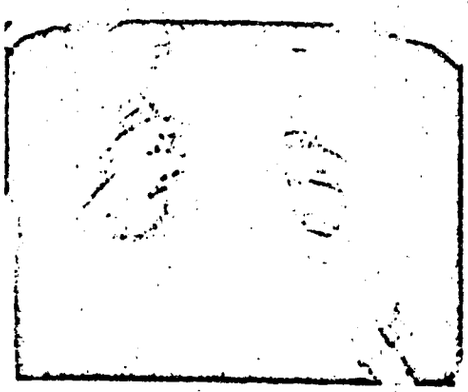

Figure 15. Patient M.C.: suppurated hepatic echinococcosis cyst; chest x-ray in standard projection.

Figure 16. Patient M.C.: suppurated hepatic echinococcosis cyst; chest x-ray in lateral projection.

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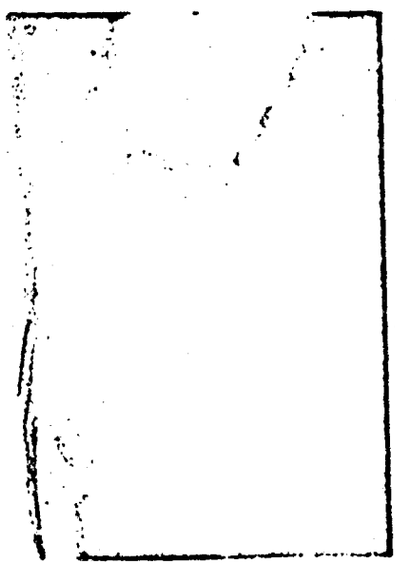

Figure 17. Patient M.C.: suppurated hepatic echinoccosis cyst; stratigraphic image after [beyond] pneumoperitoneum.

The evolution of the geric constants and the temperature, which had turned out to be very little or not at all sensitive to other antibiotics, are summarized in Figure 18.

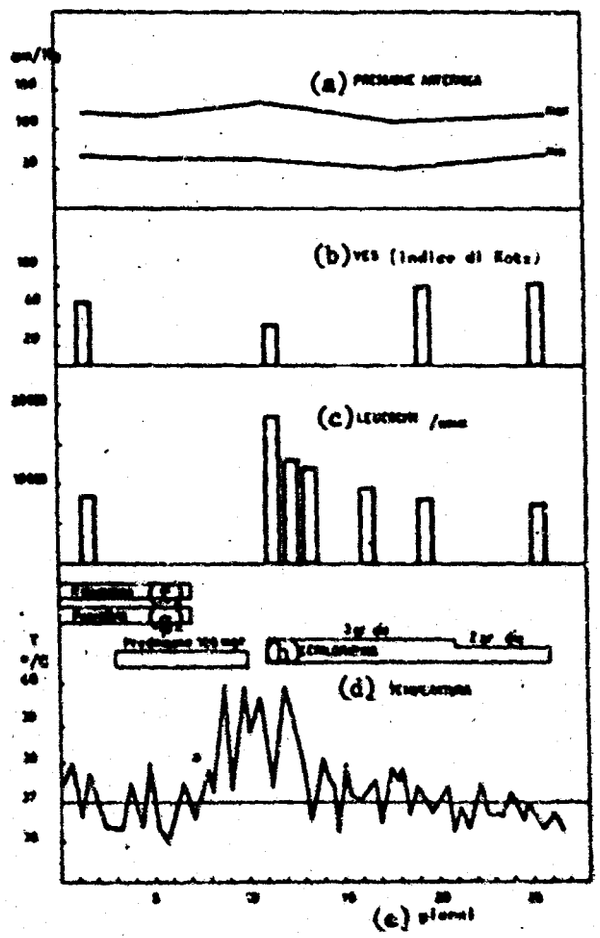

Figure 18. M.C.: suppurated hepatic echinococcosis cyst. Legend: a--arterial pressure; b--VES (Katz index); c--leucocytes per cubic mm; d--temperature; e--days; f--rifamycin; g--penicillin; h--cephaloridine, 3 g/day; 2 g/day.

Heart diseases. The case histories for the septic heart diseases (Table 4 and Figure 19), although rather scarce here, nevertheless do enable us, on the basis of one case which we followed particularly long and which had been treated with many other antibiotics to no avail, to state that cephaloridine is useful also in these disease forms.

TABLE 4
SUMMARY TABLE OF CASE HISTORIES OF BACTERIAL CARDITIS TREATED WITH CEPHALORIDINE

N. (a)	Paziente (b)	Forma morbosa (c)	(d) Cefaloridina g. x 24 h.	Durata trattamento (giorni) (g)	Febbricitante dopo giorni (h)	(e) VES (I.K.) prima (i)	dopo (j)	(f) Leucociti prima (i)	dopo (j)	Risultato (k)	(l)
1	D. A.	Endocardite reumatica (r)	1	13	[illegible]	35	22	7.400	6.800	Ottimo	
2	R. S.	Endocardite batterica (q) da S. viridans	2	25	7	90	90	10.000	5.000	Ottimo (m)	Insensibile altri antibiotici (q)
3	M. E.	Pericardite acuta, bronchite cronica (t)	1	13	11	15	7	7.200	6.800	Buono (n)	
4	P. F.	Pericardite acuta (u)	1	17	Febbricola residuale (p)	90	85	8.000	7.100	Discreto (o)	—

Legend: a--number; b--patients' initials; c--form of disease; d--cephaloridine; e--VES [sedimentation rate] (Kats index); f--leucocytes; g--duration of treatment (days); h--fever drop after number of days; i--before; j--after; k--result; l--comments; m--excellent; n--good; o--discreet; p--residual fever; q--not sensitive to other antibiotics; r--rheumatic endocarditis; q--bacterial endocarditis due to S. viridans; t--acute pericarditis, chronic bronchitis; u--acute pericarditis.

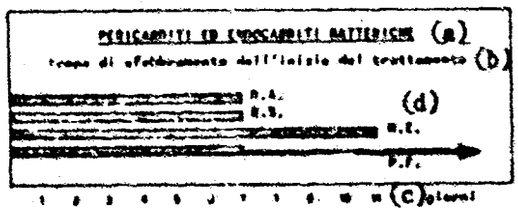

Figure 19. Legend: a--bacterial pericardites and endocardites; b--time of fever disappearance from beginning of treatment; c--days; d--patients' initials.

Figure 20 represents a graphic recording of the temperature of a young [male] patient suffering from streptococcic endocarditis; this case had not responded to a long series of antibiotics. As we can see quite clearly from the graph, it was cephaloridine which ended the state of sickness in 6 days, after the disease had earlier appeared irreducible.

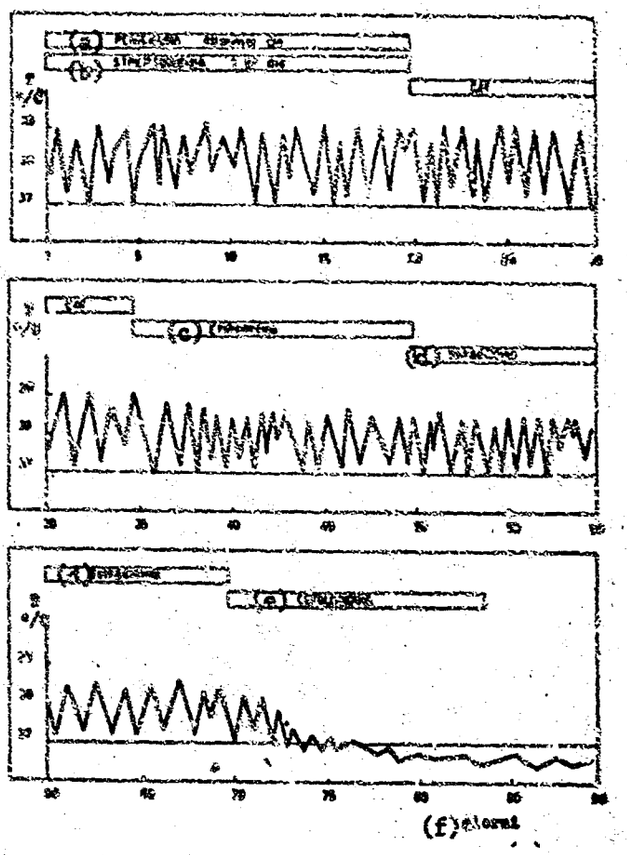

Figure 20. R.S.: bacterial endocarditis due to viridans. Legend: a--penicillin, 40 million per day; b--streptomycin, 1 g/day; c--Erythromycin; d--tetracycline; e--cephaloridine; f--days.

Miscellaneous affections. Data on the other cases treated here can be found in Table 5 and Figure 21. We can say that in most of these cases we were able to end the fever within 3-4 days. Only 1 case of chronic tonsillitis and a hyperthermic state in a cholecystectomized male patient did not respond to the treatment.

One portion of our cases did not respond to antibiotic treatment initiated upon admission in an absolute fashion, with respect to the fever curve profile. However, these cases, upon further investigation, turned out to consist of affections not susceptible to antibiotic treatment.

Study of liver cell functional tests and other blood-chemistry constants. Our investigation was aimed primarily at the synthetic and detoxicating activities of the liver.

TABLE 5

SUMMARY TABLE OF CASE HISTORIES INCLUDING MISCELLANEOUS AFFECTIONS TREATED WITH CEFNALORIDINE

N. (a)	Paziente (b)	Forma morbosa (c)	(d) Cefaloridina g. X 24 h.	Durata trattamento (giorni) (g)	Defebbramento dopo giorni (h)	(e) VES (Ka.) prima (i)	(e) VES (Ka.) dopo (j)	(f) Leucociti prima (i)	(f) Leucociti dopo (j)	(k) Risultato	(l) Commenti
1	V. M.	Tonsillite cronica (v)	1	11	Febbricola residuale	5	5	4.700	4.400	Scarso (q)	—
2	B. A.	Tonsillite cronica, malattia reumatica (w)	1	25	4	8,5	5	9.200	5.500	Ottimo (m)	—
3	R. E.	Tromboflebite arto inferiore destro (x)	1	6	2	34,5	28	15.000	12.700	Buono (n)	—
4	M. E.	Rinofaringite cronica (y)	1	14	3	19	10	4.400	5.600	Buono	—
5	P. I.	Appendicopatia cronica (z)	1	6	3	36	11	6.800	7.100	Ottimo	—
6	N. S.	Ipertermia in paziente colecistectomizzata (aa)	1	15	Febbricola residuale (p)	42	24	7.600	5.000	Discreto (o)	—
7	S. M.	Eritematodes (bb)	1	16		90	41	6.500	5.000	Buono (r)	Associata a rapida prednisonoterapia
8	Z. G.	Disterpnia in neurodistonico (cc)	1	11	Quadro febbrile invariato (t)	4	2	6.200	4.200	Nullo (s)	Insensibile qualsiasi antibiotico e chemioterapia
9	M. C.	Sprue nostrana (dd)	1	18	—	11	3	7.500	9.400	(o) Discreto	—
10	I. D.	Ipertermia sensibile a terapia con isoniazide e streptomicina (ee)	1	9	Quadro febbrile invariato	45	53	8.000	8.800	(u) Nullo	—
11	C. R.	Linfogranuloma maligno (ff)	1	15	Quadro febbrile invariato	108	104	7.600	7.600	Nullo	—
12	M. L.	Reticolosarcoma (gg)	1	15	Quadro febbrile invariato	56	48	6.900	3.700	Nullo	—

Legend: a--number; b--patients' initials; c--form of disease; d--cephaloridine; e--VES /sedimentation rate/ (Katz index); f--leucocytes; g--duration of treatment (days); h--fever drop after number of days; i--before; j--after; k--result; l--comments; m--excellent; n--good; o--discreet; p--residual fever; q--poor; r--associated prednisone therapy; s--not sensitive to any antibiotic or chemical therapeutic agent; t--unchanged fever picture; u--nothing; v--chronic tonsillitis; w--chronic tonsillitis, rheumatic disease; x--thrombophlebitis, right lower limb; y--chronic rhinopharyngitis; z--chronic appendicopathy; aa--hyperthermia in cholecystectomized /female/ patient; bb--erythematodes; cc--Dysthermia in neurodystonic /patient/; dd--sprue nostrana; ee--hyperthermia sensitive to therapy with isonazide and streptomycin; ff--malignant lymphogranuloma; gg--reticulosarcoma.

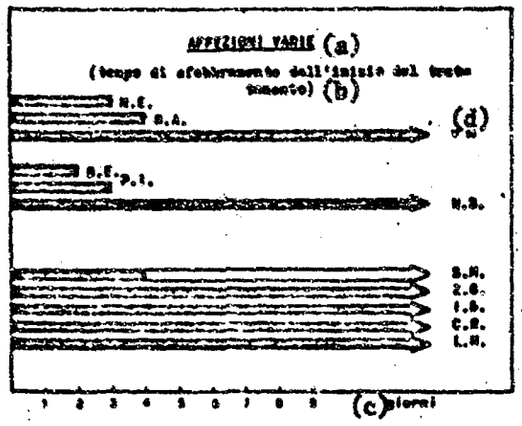

Figure 21. Legend: a--miscellaneous affections; b--time of fever disappearance from start of treatment; c--days; d--patients' initials.

The synthetic activities of the liver cell (albuminemia, cholinesterase, prothrombinic activities, V factor and VII factor) in all groups of patients studied revealed that they do not respond negatively to the administration of the antibiotic, even when the antibiotic is administered at high doses (Figure 22).

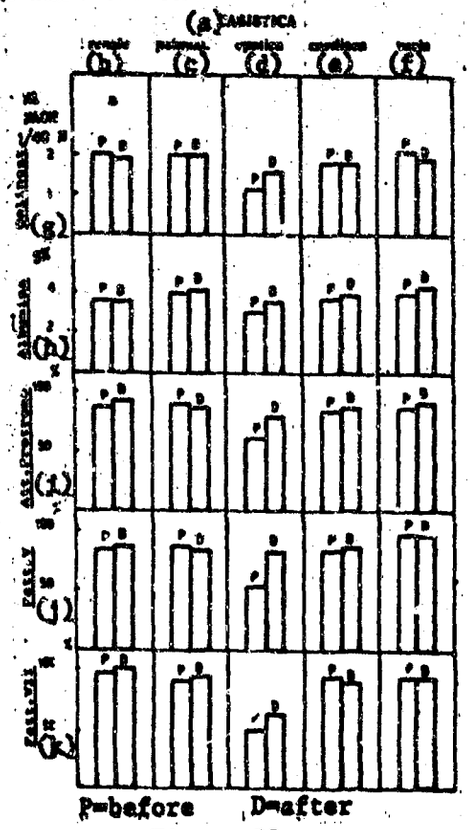

Figure 22

(Legend on following page)

Figure 22. Behavior of tests indicating synthetic capacities of liver cell, before and after treatment with cephaloridine. Legend: a--case histories; b--kidney; c--lung; d--liver; e--heart; f--miscellaneous; g--cholinesterase; h--albumin; i--prothrombinic activity; j--V factor; k--VII factor; P--before; D--after.

The excretion tests made on the liver (bilirubinemia, elimination of Cardio-Green, and of bromosulfonphthalein), azotemia, glycemia, and blood cholesterol revealed similar behavior (Figures 23 and 24).

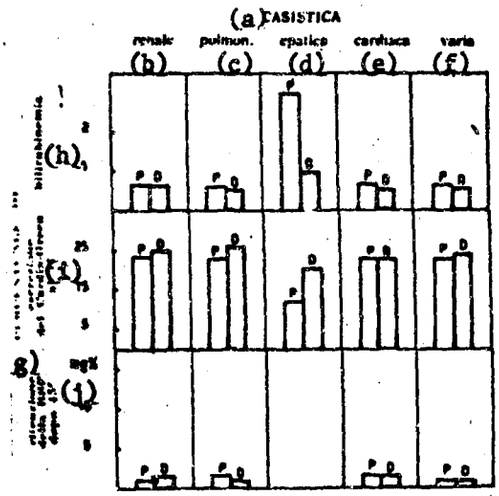

Figure 23. Behavior of excretory functions of liver, before and after administration of cephaloridine. Legend: a--case histories; b--kidney; c--lung; d--liver; e--heart; f--miscellaneous; g--percentages; h--bilirubinemia; i--excretion of Cardio-Green per /illegible/; j--retention of BSF after 45'; P--before; D--after;

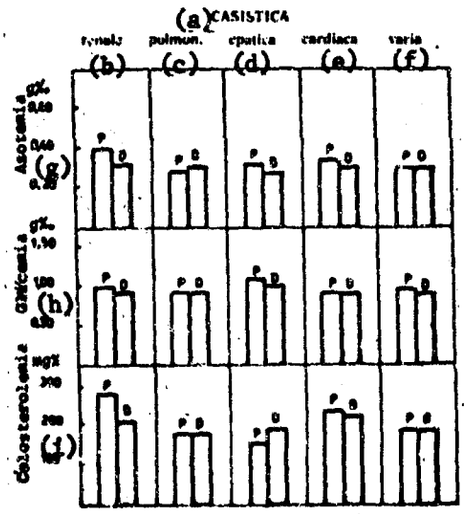

Figure 24 (Legend on following page)

Figure 24. Behavior of azotemia, glycemia, and cholesterolemia, before and after treatment with cephaloridine. Legend: a--case histories; b--kidney; c--lung; d--liver; e--heart; f--miscellaneous; g--azotemia; h--glycemia; i--cholesterolemia; P--before; D--after.

Cephaloridine does not induce modifications in the membrane of the liver cell. As a matter of fact, we were unable to demonstrate in any of the patients that there was a seric variation in the output enzymes (Figure 25).

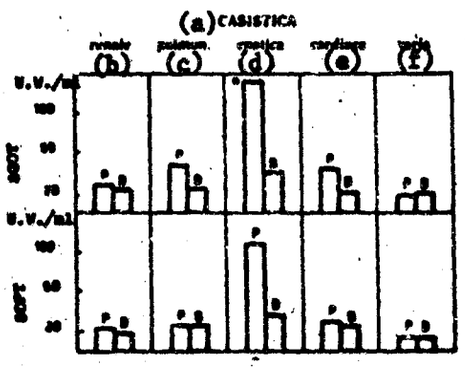

Figure 25. Behavior of seric transaminases before and after treatment with cephaloridine. Legend: a--case histories; b--kidney; c--lung; d--liver; e--heart; f--miscellaneous; P--before; D--after.

In Figure 26 we have the behavior of the speed [rate] of elimination of Cardio-Green and the percentage of retention of BSF before and after acute injection of 2 g of cephaloridine. This tells us that neither of the two tests expressing the excretory and detoxicating capacity of the liver is modified by the injection of antibiotic.

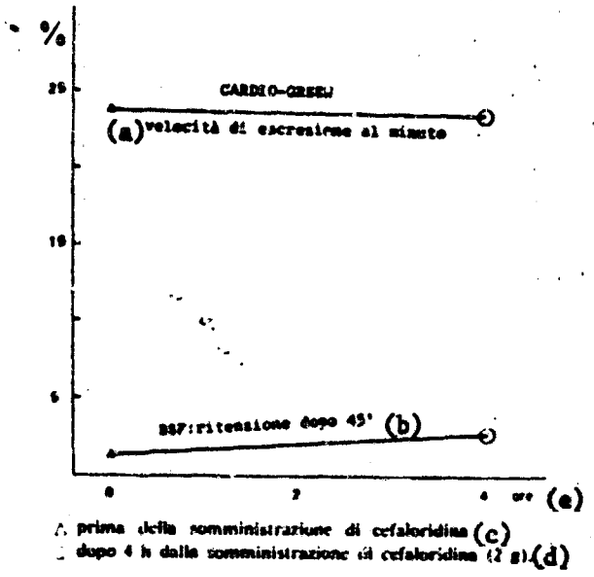

Figure 26. Influence of cephaloridine on rate of excretion of Cardio-Green and percentage of retention of BSF. Legend: a--rate of excretion per minute; b--BSF: retention after 45'; c--before administration of cephaloridine; d--4 hours after administration of cephaloridine (2 g); e--hours.

Conclusions

On the basis of the data reported here we can say that cephaloridine can be considered, without further ado, to be an antibiotic which acts promptly and which displays a rather high activity level; it also has an extremely low toxicity (29, 31, 34, 35, 37, 38).

In all of our case histories, we only had two cases which revealed signs of toxicity that could be related to the antibiotic; these signs were represented by glossitis, stomatitis, and esophagitis as well as some diarrheic discharge. But these manifestations disappeared completely the minute the therapy was discontinued.

This antibiotic did not interfere with the synthetic capacities of the liver cell in any of our cases. As regard the excretory capacity of the liver, we do know (4) that some antibiotics tend to compete with the excretion of bilirubin and also with respect to the excretion of colors (Cardio-Green, BSF); but the pharmaceutical which we used definitely did not produce any action along these lines.

Its truly remarkable activity with respect to kidney affections is explained by the excretion through that outlet. Cephaloridine is characterized by a high coefficient of distribution in the various organs and systems;

this justifies and explains the prompt effect also in affections located in the lungs, the liver, the heart, etc. (26).

Finally, we think we ought to emphasize here the rather high tendency of cephaloridine to diffuse across the inflamatory barriers, as was demonstrated by the excellent result obtained from its use in the case of a suppurated echinoccosis cyst. This is probably another reason for the brilliant result obtained during cases of bacterial endocarditis which had earlier been treated to no avail with other antibiotics which are less diffusible.

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