

GEOGRAPHICAL DISTRIBUTION, DIAGNOSIS AND TREATMENT OF HUMAN FASCIOLIASIS: A REVIEW

J.G. ESTEBAN, M.D. BARGUES & S. MAS-COMA

Departamento de Parasitología, Facultad de Farmacia, Universidad de Valencia,
 Av. Vicente Andrés Estellés s/n, 46100 Burjassot - Valencia, Spain

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SUMMARY: In recent years multidisciplinary studies have furnished additional knowledge on different aspects of human fascioliasis caused by *Fasciola hepatica*. Today, the overall conception we have about this parasitic disease is pronouncedly different from only a few years before. The present exhaustive review compiles a total of 7071 human cases reported from 51 countries in all continents in the last 25-year period: Europe, 2951; America, 3267; Asia, 354; Africa, 487; Oceania, 12. The real number of human cases is undoubtedly much greater than that reported. A global analysis of the geographical distribution of human cases shows that the expected correlation between animal and human fascioliasis only appears at a basic level. High prevalences in humans do not seem to be necessarily related to areas where fascioliasis is a great veterinary problem. The major health problems are found in Andean countries, northern Africa, the Near East and western Europe. For human fascioliasis diagnosis, there are several types of techniques, although some suggestive clinical presentation aspects may be useful. Direct parasitological techniques, indirect immunological tests and other non-invasive diagnostic techniques are presently used for human fascioliasis diagnosis. New biological data introduce the importance of quantitative coprological data analyses in epidemiological surveys, as well as in posttreatment (and future postvaccination) monitoring. Besides eggs in coprological analyses, adults and eggs may be also found elsewhere by means of other invasive techniques: obtaining duodenal fluid, duodenal and biliary aspirates; surgery (laparotomy, cholecystectomy, sphincterotomy); histological examination of liver and/or other organ biopsy materials. Serological, intradermal and stool antigen detection tests have been developed. Immunological techniques present the advantages of being applicable during both periods of the disease, but fundamentally during the invasive or acute phase, as well as to the other situations in which coprological techniques may present problems. At any rate, immunological techniques offer other types of problems related mainly to sensibility and specificity. Different serological tests have been used for human diagnosis. Almost all these techniques concern the detection of circulating antibodies and only a very few are designed to detect circulating antigens and immune complexes. Several serological techniques have recently proved to be also useful for monitoring post-treatment evolution. Non-invasive diagnostic techniques which can be used for human diagnosis are radiology, radioisotope scanning, ultrasound, computed tomography and magnetic resonance. No new drugs have been developed during the last 15 years for fascioliasis treatment, and drug resistance in *F. hepatica* has already been reported to affect the efficacy of the drugs against immature stages in animals. For human fascioliasis, many drugs were used in the past that have now been more or less abandoned. Emetine derivatives (Emetine, Dehydroemetine), the classic drugs, were used widely and continue to be used today, but they cause a variety of toxic manifestations. Bithionol has been considered the drug of choice for years despite its long treatment course. At any rate, there was no consensus about the therapy of choice for human fascioliasis until very recently when Triclabendazole has proved its efficacy. Other drugs used for human fascioliasis have been Chloroquine, Hexachloro-para-xytol, Niclofolan, Metronidazole, Albendazole, Mebendazole, Rafoxanide, and Prednisone. Worth mentioning is that *Fasciola* may be the only genus of trematode that has practically no response to Praziquantel.

KEY WORDS: *Fasciola hepatica*, human fascioliasis, geographical distribution, diagnosis, treatment, review.

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INTRODUCTION

The liver fluke species *Fasciola hepatica* (Linnaeus, 1758) (Trematoda: Fasciolidae) is well known because of its veterinary importance related to the great production and economic losses it causes in livestock, mainly sheep and cattle (BORAY, 1982). The review by CHEN & MOTT (1990) was the first paper in which the public health importance of human fascioliasis began to be emphasized, owing to the high number of human cases recorded in the 1970-1990 period: 2594 infected persons from 42 different countries covering all continents.

However, in recent years multidisciplinary studies have furnished additional knowledge on different aspects of human fascioliasis. Today, the overall conception we have about this parasitic disease is pronouncedly different from only a few years before (MAS-COMA, BARGUES & ESTEBAN, 1998).

This paper presents an exhaustive review of three aspects of human fascioliasis where important changes have very recently been introduced: geographical distribution of human case reports, diagnosis and treatment.

GEOGRAPHICAL DISTRIBUTION

Human cases have been reported from countries in Europe, America, Asia, Africa and Oceania. Major reviews on human infection by *F. hepatica* have been carried out by FACEY & MARSDEN (1960), CHEN & MOTT (1990) and more recently MAS-COMA *et al.* (1998) and MAS-COMA, BARGUES & ESTEBAN (1998). Numbers of clinical cases of *F. hepatica* reported as well as of infected persons identified during epidemiological surveys have been significantly increasing since 1980.

The present exhaustive review compiles a total of 7071 human cases reported from 51 countries in all continents in the last 25-year period. These cases have been detected by parasitological methods (either by finding eggs in the stool or bile, or adult worms at surgical operation or at autopsy), by serological tests, by parasitolo-

gical and/or serological methods, by pathohistological examinations of sections of liver and other organs, by non-invasive techniques detecting a parasite stage and by clinical presentation. In several cases the diagnostic technique was not mentioned.

At any rate, care must be taken with these data. Our personal experience shows that numerous cases are diagnosed but only noted in non-published internal documents, reports or university theses, or published in local journals of very limited diffusion (i.e., Bolivia - see MAS-COMA *et al.*, 1995). Another problem arises because of human fascioliasis not being a disease of obligatory declaration (i.e., Spain - see SORRIBES *et al.*, 1989). Other limitations are related to the different methodologies used. Difficulties also appear when analysing detailed results of several community-based or epidemiological surveys. Finally, as the infection may be asymptomatic, and the symptoms and signs are not pathognomonic, the number of human cases is undoubtedly much greater than is reported.

A global analysis of the distribution of human cases shows that the expected correlation between animal and human fascioliasis only appears at a basic level. Although it is true that the major sources of the infection, domestic herbivorous mammals, are widely distributed in the world and human infection is not rare in these areas (CHEN & MOTT, 1990), high/low human prevalences are not related to high/low animal prevalences, respectively. Thus, high prevalences in humans do not seem to be necessarily related to areas where fascioliasis is a great veterinary problem. In Europe there is a concentration of human cases in the western countries of France, Spain and Portugal, whereas animal fascioliasis is, because of climatic conditions, more linked to northern countries in which human cases are only sporadic. Similarly, in South America hyperendemics and mesoendemics are found in Bolivia and Peru, whereas the veterinary problem is mainly known in countries such as Uruguay, Argentina and Chile in which only sporadic cases or hypoendemic areas are found. In Australia livestock fascioliasis is well known, whereas human cases are only sporadic. Such geographic differences be-

tween human and animal fascioliasis are related to differences in human dietary habits, as well as to economic and hygienic-sanitation conditions.

Human reports in Europe

A total of 2951 human cases diagnosed in European countries are compiled in Table 1. Up to 19 countries are involved, although for convenience (according to literature data) countries recently created are included in the former USSR, former Czechoslovakia and former Yugoslavia. It is worth mentioning that no recent report on fascioliasis was found from Hungary despite the several severe outbreaks of human infection recorded there between 1959 and 1970 (KOBULEJ, 1981/82). According to Table 1, France, Portugal, the former USSR (including its Asian part), Spain and the UK are the countries including most of the cases. In all other countries cases appear to be very sporadic.

France is considered an important human endemic area (ANONYMOUS, 1988). The first large modern epidemic of human fascioliasis occurred in 1956 (COUDERT & TRIOZON, 1958). Between 1950 and 1983, 3297 cases from published reports have been catalogued (GAILLET *et al.*, 1983). Most cases were reported from the areas of Lyon, Bretagne Nord - Pas de Calais and Sud-Ouest. Recent reports on Sud-Ouest France refer to more than 300 cases (LABORDE, 1985; GIAP, 1987; RIPERT *et al.*, 1987). At any rate, cases compiled in the present review only refer to published reports; the paper by DANIS, NOZAIS & CHANDENIER (1985), which reports on 5863 human cases recorded from only 9 hospitals between 1970 and 1982, demonstrates that published data largely underestimate the real situation. The French Mediterranean island of Corsica maintains a low hypoendemia (GITARD *et al.*, 1965; GIL-BENITO *et al.*, 1991).

The disease is also important in Portugal, with the northern part of the country as a marked endemic area.

Country (area)	No. of cases	Diagnostic method				References (according to numbers in References section)
		Parasitological	Serological	Clinical	Unknown	
Austria	6	4	2			53, 54, 296, 473, 489
Belgium	14	10	4			77, 142, 186, 304, 419
Bulgaria	1	1				472
former Czechoslovakia	2	2				214
France	1129	133	715	16	265*	15, 27, 31, 61, 83, 93, 98, 99, 100, 104, 106, 107, 111, 117, 120, 121, 139, 140, 154, 158, 160, 165, 210, 212, 248, 258, 272, 303, 306, 311, 321, 336, 350, 374, 389, 391, 392, 397, 404, 406, 408, 420, 421, 422, 428, 446, 467, 479, 480, 486
France (Corsica)	20	3	15		2*	146, 161, 216, 217
Germany	4	4				101, 315, 445
Greece	1	1				43
Ireland	1	1				155
Italy	7	6	1			66, 370, 465, 478
The Netherlands	1	1				481
Poland	39	37	2			65, 206, 263, 287, 338, 386, 458, 485
Portugal	1115	210	142		763**	4, 119, 124, 150, 255, 331, 417, 430, 431, 432, 433
Rumania	14	14				64, 157, 470
Spain	288	123	103	2	60**	8, 11, 12, 13, 19, 20, 21, 34, 44, 45, 47, 57, 58, 79, 108, 109, 110, 118, 130, 134, 135, 136, 148, 162, 201, 205, 207, 208, 211, 241, 261, 265, 322, 323, 324, 340, 343, 346, 349, 353, 358, 360, 361, 367, 369, 379, 388, 423, 456, 457, 474, 501
Sweden	2	1	1			185
Switzerland	15	14	1			28, 153, 220, 320, 405, 447, 462
UK	93	25	28		40*	30, 48, 49, 85, 88, 164, 235, 260, 266
former USSR	195	195				22, 74, 273, 283, 294, 400, 424, 425
former Yugoslavia	4		1		3*	102, 335, 454
TOTAL	2951	785	1015	18	1133	

Table 1.— Human reports in Europe. * = by parasitological and/or serological tests; ** = by parasitological, serological and/or clinical diagnosis.

ROMBERT & GRACIO (1984) report on 77 cases and Sampaio Silva (in CHEN & MOTT, 1990) refers to 561 cases in only three communities in northern Portugal. In a recent report, SAMPAIO SILVA *et al.* (1996) refer to 1011 cases diagnosed in the laboratory of Porto between 1970 and 1992. Cases reported in Portugal include those in residents from 3 islands, Madeira, Azores and Cape Verde (ROMBERT & GRACIO, 1984; ABREU *et al.*, 1996; MENDONÇA *et al.*, 1996).

In Spain, according to the review by SORRIBES *et al.* (1989, 1990), human fascioliasis appears to be underestimated and mainly distributed in northern Spain (autonomous communities of the Pais Vasco, Castilla-León, Cantabria, Navarra and Rioja).

Concerning the former Soviet Union, almost all reported cases were from its southern Asian republic, Tadzhik, near the Afghanistan border (KHASHIMOV & KAMARDINOV, 1975; KAMARDINOV, 1985; RAKHMAMOV, 1987). The findings of SADYKOV (1988) suggest that high prevalences can exist in the Samarkand region: between 1 and 14 flukes were found in each liver at post-mortem in 81 inhabitants in 1968-1986; deaths were not due to fascioliasis, which was detected incidentally.

In the UK, 44 human cases (mostly in 3 localities) were reported in the first half of 1969, compared with only 2 cases during 1968 (ANONYMOUS, 1969).

Countries such as Hungary and Turkey, with less than 100 documented cases, are considered by WHO (1995)

but are not included in Table 1 because no report references could be found.

Human reports in America

Human cases diagnosed in American countries are compiled in Table 2. Whereas in North and Central American countries cases can be counted, this is not the case in South America where several countries present large endemics.

In North America, human fascioliasis appears to be only very sporadic in the U.S.A. and Canada. In Mexico, 53 cases had been reported before the period here analysed (FLORES & GARCIA, 1960; ALVAREZ-CHACON *et al.*, 1992).

In Central America, fascioliasis is a human health problem in the Caribbean Islands, above all in zones of Puerto Rico and Cuba. In Cuba, in Pinar del Rio Province more than 10000 people were infected between 1947 and 1948 (MITTERPAK, 1968) and a new outbreak involving 81 subjects occurred in 1995 (PEREZ *et al.*, 1997), and in Villa Clara Province an outbreak involved more than 1000 subjects in 1983 (see GONZALEZ *et al.*, 1985, 1987; DIAZ *et al.*, 1990). On the mainland, only Costa Rica and Guatemala appear in the records. A total of 16 human cases have been diagnosed in Guatemala up to the present (AGUILAR & CIFUENTES, 1993). It is clear that studies on other countries are needed. In countries such as the Dominican Republic and El Salvador, fewer than 100 cases

Country (area)	No. of cases	Diagnostic method				References (according to numbers in References section)
		Parasitological	Serological	Clinical	Unknown	
Argentina	85	85				116, 215, 316, 366, 390, 451
Bolivia	2001	993	872	111	25	29, 90, 180, 181, 254, 328, 460
Brazil	44	44				25, 26, 68, 133, 225, 387, 436
Canada	1				1*	375
Chile	204	90	1	5	108**	18, 35, 36, 37, 39, 40, 41, 97, 301, 438, 439, 440, 463
Costa Rica	57	1	56			24, 122, 345
Cuba†	361	222	78		61§	5, 152, 175, 183, 222, 223, 227, 339, 347, 381, 382, 415
Ecuador	1	1				14
Guatemala	16	10	6			9
Haiti	1		1			476
Mexico	15	5	10			7, 23, 267, 354
Peru	397	291		106		80, 115, 289, 290, 332, 344, 384, 414, 459, 477
Puerto Rico	19	19				78, 81, 308, 410, 411
Uruguay	60	8		8	44¶	6, 114
USA	4		4			239, 357, 394
Venezuela	1	1				2
TOTAL	3267	1770	1028	230	239	

Table 2.— Human reports in America. † = an outbreak in 1983 involved more than 1000 subjects; * = by parasitological and/or serological tests; ** = by serological and/or clinical diagnosis; § = data from a report of the Ministry of Health, method not mentioned; ¶ = by parasitological and/or clinical diagnosis.

have been documented (WHO, 1995) but are not included in Table 2 because no report references could be found.

In South America, human fascioliasis is a serious problem in Bolivia and Peru, and probably also in Ecuador.

In Bolivia, although sporadic cases are known in different parts of the country (MAS-COMA *et al.*, 1995), the human hyperendemic concerns only the Northern Altiplano zone, between the Lake Titicaca and the valley of the city of La Paz, at 3800-4100 m altitude. There, prevalences in given communities are as high as 72% and 100% in coprological and serological surveys, respectively (HILLYER *et al.*, 1992; MAS-COMA *et al.*, 1995; BJORLAND *et al.*, 1995; ESTEBAN *et al.*, 1997a,b; ANGLES *et al.*, 1997; STRAUSS *et al.*, 1997a) including about 350000 infected individuals and a human population of around 1 million people at risk, according to estimations made by HILLYER & APT (1997).

In Peru, human cases have been detected in the whole country, with mesoendemics and hyperendemics in given zones. The high human prevalences in Arequipa (PICOAGA, LOPERA & MONTES, 1980), Mantaro valley (up to 60% of children presenting eggs in faeces - BENDEZU, 1969; STORK *et al.*, 1973), Cajamarca valley (up to a 50% in the rural population and more than 20% in Cajamarca city by coprological methods - COSME-CONTRE-RAS *et al.*, 1971; KNOBLOCH, 1985; KNOBLOCH *et al.*, 1985; C. NAQUIRA, Lima, 1995, pers. comm.), and the Puno region (general prevalence of 15.6%, with 37% in children - SANCHEZ, APARICIO & HURTADO, 1993; C. NAQUIRA, Lima, 1995, pers. comm.) are worth mentioning; global estimations refer a rural population of almost 8 million people at risk (WHO, 1995).

Concerning Ecuador, general characteristics of the country suggest a situation similar to that known in Peru, although unfortunately there is a total lack of concrete data. Only one case of *F. hepatica* infection, reported in

a man who had returned to Germany from Ecuador, could be found (AHRENS & BERNING, 1968). However, according to WHO (1995), about 1% of the total rural population living in the endemic areas at risk, or approximately 20000 people, are estimated to be infected.

In Chile, human fascioliasis is hypoendemic in the Valparaíso and Viña del Mar zones, as well as in Regions V, VI and VII (SUBERCASEAUX *et al.*, 1985; APT *et al.*, 1993). In countries like Argentina, Uruguay, Brazil, Colombia, and Venezuela, human fascioliasis appears to be focal in distribution and sporadic, with less than 100 cases reported (WHO, 1995). No paper concerning human cases in Guyana, Surinam, French Guiana and Paraguay was found. At any rate, the example of Bolivia must not be forgotten. This country did not even appear in the WHO list according to the review by CHEN & MOTT (1990) and has recently proved to include the highest hyperendemic zone of the whole world. This situation was already known before 1990, but the information could only be found in unpublished reports, internal documents or papers in local journals of very restricted diffusion (MAS-COMA *et al.*, 1995).

Human reports in Asia

In Asia an additional problem appears because of the overlapping distribution, from the Near East to the Far East, of *F. hepatica* and *F. gigantica*, including intermediate forms which are traditionally referred to as *Fasciola* sp. That is why in several papers the liver fluke is not noted at species level and numerous reports speak only of «fascioliasis». Although HASHIMOTO *et al.* (1997) have recently demonstrated by means of molecular techniques that intermediate forms may be ascribed to *F. gigantica*, at least in Japan, nothing can be assured for other Asian countries. Consequently, human cases

Country (area)	No. of cases	Diagnostic method				References (according to numbers in References section)
		Parasitological	Serological	Clinical	Unknown	
China	41	41				159, 259, 307, 313, 464, 483, 487, 502, 503
India	3	3				87, 297
Iran	244	18	226			50, 192, 193, 234, 284, 342, 356, 398
Israel	2	2				143, 443
Japan	13	8	4	1		16, 17, 156, 203, 228, 262, 270, 293, 442, 466, 469, 496
Saudi Arabia	2	2				92
Korea	15	8	1		6*	123, 125, 127, 128, 232, 256, 285, 286, 305, 373
Thailand	6	6				103, 126, 282, 372, 475, 491
Turkey	25	25				46, 52, 63, 129, 163, 226, 276, 277, 278, 365, 482, 499
Yemen	3	3				355, 402, 444
TOTAL	354	116	231	1	6	

Table 3.— Human reports in Asia. * = by parasitological, serological and/or clinical diagnosis.

diagnosed in Asian countries and compiled in Table 3 refer to all reports in which *F. hepatica* is specifically noted and those in which the causal species is not specifically reported. At any rate, reports concerning Japan in which the *Fasciola* species is undetermined have been also included in Table 3.

Only a few cases have been described in Asia, including several countries among which Iran is worth mentioning because of the recent estimates which suggest more than 10000 human cases (see BAHAR *et al.*, 1990; MASSOUD, 1990; POURTAGHVA *et al.*, 1990; WHO, 1995) and a population of about 6 million at risk (WHO, 1995). Countries such as Cambodia, Irak, Israel, Lebanon, Nepal, the Philippines, the Syrian Arab Republic, and Viet Nam are considered as presenting less than 100 documented cases by WHO (1995) but are not included in Table 3 because no references on the reports could be found.

Human reports in Africa

Only a few human cases have been reported from African countries (Table 4), although studies carried out up to the present are evidently insufficient for a significant overview. Moreover, in some parts of Africa overlapping infections may occur with both *F. hepatica* and *F. gigantica*. *F. hepatica* appears to be more restricted in northern Mediterranean countries such as Morocco, Algeria and Tunisia (MAAMOURI *et al.*, 1968; CHEN & MOTT, 1990; AYADI *et al.*, 1991; KHALLAAYOUNE *et al.*, 1991; AYADI, MAKNI & BEN SAID, 1997), as well as in southern Zimbabwe and South Africa (PANTELOURIS, 1965), and it is the species present at high altitude in Kenya and Ethiopia (BERGEON & LAURENT, 1970), whereas *F. gigantica* is present in most of the African continent, from the Nile Delta in the north to the Cape Provinces of South Africa in the south (BORAY, 1982).

The most human cases have been reported from Egypt (ARAF & LASHEN, 1993; EL-SHAZLY, EL-DESOKY & EL-FEKY, 1991; EL-SHAZLY *et al.*, 1991; FARAG *et al.*, 1979, 1986, 1988; FARID *et al.*, 1986, 1990, 1993; FARID,

KAMAL & WOODY, 1988; MANSOUR *et al.*, 1983; OSMAN, HELMY & MEGEHED, 1995; OSMAN *et al.*, 1995; RAGAB & FARAG, 1978; SALEM, ABOU BHASHA & FARAG, 1987; HAMMOUDA *et al.*, 1995, 1997), probably due to *F. gigantica*, since it appears to be the only species in domestic animals in this country (CHEN & MOTT, 1990). The *Fasciola* species involved remains undetermined in most reports, although sometimes *F. hepatica* is specified (FARID, 1971; FARID *et al.*, 1977; ABOU-BASHA *et al.*, 1989; EL-SHABRAWI *et al.*, 1997). Fascioliasis has appeared as an emerging health problem in Egypt during the last few years. Liver fluke infection in humans has been found in almost all governorates of Lower Egypt and even in some governorates of Upper Egypt (EL-KHOBY, 1997). An increasing number of human infections with both *Fasciola* species have been diagnosed in the Nile delta, one province of Upper Egypt, and the city of Alexandria. Some rural areas may be considered endemic, with prevalence rates varying between 7% and 17% (FARAG, 1997). The population at risk is 27.7 million people and the number infected is at least 830000 (WHO, 1995).

Countries such as Ivory Coast, Madagascar, Mali, and Mozambique, with less than 100 documented cases, and Ethiopia, with 100-1000 cases, are considered by WHO (1995) but are not included in Table 4 because no references of the *F. hepatica* reports could be found.

Human reports in Oceania

Concerning Oceania, there are only 12 human reports from Australia and none in New Zealand (see Table 5), despite the important livestock production and the high prevalences in sheep and cattle (BORAY, 1969; CHEN & MOTT, 1990).

DIAGNOSIS

For human fascioliasis diagnosis, there are several types of techniques, although some suggestive clinical presentation aspects may be useful.

Country (area)	No. of cases	Diagnostic method				References (according to numbers in References section)
		Parasitological	Serological	Clinical	Unknown	
Algeria	6	3		3		149, 229, 240
Egypt	442	286	104	26	26*	3, 42, 167, 168, 169, 170, 171, 188, 189, 190, 193, 196, 197, 198, 230, 231, 238, 319, 337, 362, 364, 399, 426, 427, 429
Morocco	1	1				441
Tunisia	36				36*	55, 56, 314
Zimbabwe	2	2				67, 383
TOTAL	487	292	104	29	62	

Table 4.— Human reports in Africa. * = by parasitological and/or serological tests.

Country (area)	No. of cases	Diagnostic method				References (according to numbers in References section)
		Parasitological	Serological	Clinical	Unknown	
Australia	12	10	2			141, 224, 300, 318, 395, 471, 492, 493
TOTAL	12	10	2			

Table 5.— Human reports in Oceania.

Direct parasitological techniques, indirect immunological tests and other non-invasive diagnostic techniques are presently used for human fascioliasis diagnosis.

Parasitological examinations

Parasite stages may be looked for not only in faeces. Besides eggs in coprological analyses, adults and eggs may also be found elsewhere by means of other invasive techniques.

COPROLOGICAL TECHNIQUES

Coprological examination by finding the parasite eggs in faeces is still the main method for diagnosis. However, several situations may be taken into account:

- **Eggs in transit:** people ingesting infected domestic animal livers (mainly cattle, sheep and pig) a short time before may reflect «false» fascioliasis when the fluke eggs are found in their stools (STORK *et al.*, 1973; RAGAB & FARAG, 1978; CAMPO *et al.*, 1980); in such cases, diagnosis requires placing the patient on a liver-free diet and performing repeated follow-up stool examinations;
- **Acute phase:** in man, the incubation phase (from a few days to 2-3 months) is shorter than the prepatent period (at least 3-4 months), so that infected humans may present clinical findings long before eggs could be found in the stools, making egg finding in faeces as an early diagnosis tool impossible; thus, coprological techniques become useful only after 3-4 months postinfection;
- **Egg output dynamics:** in man, egg output number (in livestock the absence of a direct relationship between number of flukes present and number of eggs shedded is well known) and dynamics (egg production oscillations in trematodes in general throughout their life span is also well known) are unfortunately unknown, so that different possibilities such as intermittent and very low egg shedding, above all in cases of only one or a few fluke adults as well as in old infections, may not be excluded; multiple and repeated follow-up stool examinations are needed in such cases;
- **Ectopic infections:** many ectopic locations are not digestive-related and consequently eggs cannot be found

in stools; moreover, a sexually mature ectopic fluke has never been found, so that eggs are presumably never produced;

- **Immature flukes:** except in human endemic regions, man is generally believed to be a non-suitable host for *F. hepatica*; consequently, in non-human endemic areas the possibility of hepatic infections by flukes unable to attain maturity in human subjects cannot be disregarded; eggs could never be found in such subjects.

Up to the present, qualitative techniques were usually applied for human fascioliasis coprological diagnosis. Techniques were never considered concerning their adaptability to furnish good quantitative results. However, recent studies by BARGUES *et al.* (1996) have proved that eggs shed by humans may be viable and thus humans contribute to the disease transmission at least in hyperendemic areas. This new fact introduces the importance of quantitative data analyses in epidemiological surveys, as well as in posttreatment (and future postvaccination) monitoring.

Qualitative techniques

Techniques ranging from a simple direct smear to different concentration methods (i.e., RITCHIE, 1948; SAPERO & LAWLESS, 1953; BLAGG *et al.*, 1955; LUMBRE-RAS, CANTELLA & BURGA, 1962; KNIGHT *et al.*, 1976; MUÑOZ *et al.*, 1987) have been used for the diagnosis of human chronic *F. hepatica* infection.

Egg concentration has been achieved by flotation and sedimentation techniques (ASHTON *et al.*, 1970; STORK *et al.*, 1973; RAGAB & FARAG, 1978; FARAG *et al.*, 1979; BENDEZU, FRAME & HILLYER, 1982; BOLBOL, 1985; KNOBLOCH *et al.*, 1985; MUÑOZ *et al.*, 1987; SAMPALIO SILVA in CHEN & MOTT, 1990; HILLYER *et al.*, 1992; ESTEBAN *et al.*, 1997a,b). The sedimentation technique appears to be more accurate and sensitive than flotation techniques, as most of the hyperosmotic solutions distort the eggs (BORAY, 1969).

A comparative study of 3 techniques (MUÑOZ *et al.*, 1987) was made on the basis of 15 known human cases of *F. hepatica* infection (6 stool samples per patient, one daily): the gravity sedimentation method modified by MUÑOZ *et al.* (1987) (Fast Sedimentation Method -

FSM); the Teleman centrifugation technique (TM); and the standard Gravity Sedimentation (GS). With TM, eggs of the parasite were only found in 33.3% of the cases, in contrast with 100% for GS and FSM. A more detailed study of the last two revealed that FSM, besides being easier and faster to perform, permitted ova detection in all the patients through the examination of a single sample, while GS only reaches 73.3% of the cases considering the 6 samples. The respective indexes of positive over performed readings were 92.2% for FSM and 20.6% for GS. Adding growing quantities of eggs (5 by 5) to negative samples, a complementary study on the sensibility of FSM was conducted and pointed out that 15 ova were enough to allow 100% of the positive readings.

According to KNOBLOCH *et al.* (1985), rapid sedimentation (using 20 g faeces on each of 3 consecutive days), although inconvenient, seemed to be largely more sensitive than the merthiolate-iodine-formaldehyde concentration method (MIFC) (using 1 g of faeces in a single examination) or the Enterotest, according to BEAL *et al.* (1970) (single examination of duodenal fluid). Among five concentration techniques compared by AKAHANE *et al.* (1975), the recovery rates of eggs in the sediment using 0.5 g faeces were: formalin-ether method, 5.3%; HCl-ether method, 7.8%; Weller-Darmin's modification method, 37.7%; citrate buffer-Tween 80-ether method, 25.3%; and AMS III (Tween 80) method, 30.5%.

The cellophane faecal thick-smear technique (Kato-Katz) according to KATO & MIURA (1954) and KATZ, CHAVES & PELLEGRINO (1972) has also been used (KREMER & MOLET, 1975; HILLYER *et al.*, 1992; BJORLAND *et al.*, 1995; ESTEBAN *et al.*, 1997a,b). This technique has the advantages of being rapid, having low cost, and being reproducible (CHEN & MOTT, 1990). Although it has been estimated as presenting a relatively low sensitivity which limits its clinical application, opinions differ on this aspect. Moreover, this appears to be a very useful quantitative technique.

According to HILLYER & APT (1997), cup sedimentation using tap water (the simplest and cheapest) was more sensitive than formol-ether concentration, which was more sensitive than the Kato-Katz thick smear. At any rate, different results have been found in large epidemiological surveys (ESTEBAN *et al.*, 1997a, b).

Quantitative techniques

In fact, all concentration techniques may be used for egg count if started from a known stool volume. Such techniques have already been used quantitatively in human fascioliasis (STORK *et al.*, 1973; BENDEZU, FRAME & HILLYER, 1982; KNOBLOCH *et al.*, 1985; MUÑOZ *et al.*, 1987; SAMPAIO SILVA in CHEN & MOTT, 1990).

At any rate, the cellophane faecal thick-smear technique (Kato-Katz) appears to be the most appropriate, taking into account time needed, its very low cost and its sensibility, at least in epidemiological surveys (ESTEBAN

et al., 1997a, b). Comparative studies are presently under way to ascertain the value of the different techniques for quantitative purposes.

OTHER ADULT AND EGG FINDING TECHNIQUES

Other direct techniques are based on adult and/or egg finding in locations other than faeces. Duodenal fluid obtained with the Enterotest of BEAL *et al.* (1970) as well as duodenal and biliary aspirates may present fluke eggs (KNOBLOCH *et al.*, 1985; CHEN & MOTT, 1990), mainly after the administration of colecistoquinine by intravenous infusion (0.01 ml/kg) (GOMEZ-CEREZO *et al.*, 1997).

Adult flukes and/or eggs may be found in the bile ducts and gall bladder at surgery (laparotomy, cholecystectomy, sphincterotomy) in patients suspected of *F. hepatica* infection or in patients with cholangitis, cholelithiasis or obstructive jaundice of unknown cause (LORTAT-JACOB *et al.*, 1960; NICHOLAS, 1970; SALEMBIER, 1974; DIPPON & WIDMER, 1976; FARID *et al.*, 1977; ACOSTA-FERREIRA, VERCELLI-RETTA & FALCONI, 1979; ZHU, XIA & DONG, 1979; MORETO & BARRON, 1980; PEÑA SANCHEZ *et al.*, 1982; PARICHATIKANOND & SARASAS, 1984; URIBARRENA *et al.*, 1985; WONG *et al.*, 1985; CHI *et al.*, 1986; DUAN *et al.*, 1986; HONG *et al.*, 1986; ABOU BASHA *et al.*, 1989; RIVERO & MARCIAL, 1989; COSME *et al.*, 1990; VEERAPPAN *et al.*, 1991; ATALAY *et al.*, 1993; ARJONA *et al.*, 1995; GUÇLU, DIK & AGAOGLU, 1995; KUMAR, GAUTAM & CHATURVEDI, 1995; RIEDTMANN *et al.*, 1995; DIAS *et al.*, 1996). Up to 12 flukes (BANNERMAN & MANZUR, 1986; BELGRAIER, 1976; COSME *et al.*, 1979; COULAUD *et al.*, 1970; DAN *et al.*, 1981; ZHENG *et al.*, 1986) have been removed at laparotomy with clinical recovery. In one unusual case, 19 dead flukes were found in T-tube drainage from the common bile duct (ZHENG *et al.*, 1986). Between 1 and 14 flukes were found in each liver at post-mortem in 81 inhabitants of the Samarkand region in 1968-1986 (SADYKOV, 1988).

Histological examination of liver and/or other organ biopsy materials may occasionally reveal egg granulomas or fluke sections (COURAUD *et al.*, 1975; ACOSTA-FERREIRA, VERCELLI-RETTA & FALCONI, 1979; ZHU, XIA & DONG, 1979; SAPUNAR *et al.*, 1992; KIM, CHUNG & CHO, 1994; ARJONA *et al.*, 1995; EL-SHABRAWI *et al.*, 1997; RICARDO *et al.*, 1997; TCHIRIKHTCHIAN *et al.*, 1997). Nevertheless, with an adequate index of suspicion, the diagnosis of *F. hepatica* infection should be established in most cases without having to perform surgery or liver biopsy.

Immunological techniques

For human fascioliasis, serological, intradermal and stool antigen detection tests have been developed. Im-

munological techniques present the advantages of being applicable during both periods of the disease, but fundamentally during the invasive or acute phase, and to the other situations in which coprological techniques may present problems (see above). At any rate, immunological techniques offer other types of problems related mainly to sensibility and specificity.

SEROLOGICAL TESTS

During the recent decades, different serological tests have been used for human diagnosis. Almost all of these techniques concern the detection of circulating antibodies and only a very few are designed to detect circulating antigens and immune complexes. Several serological techniques have recently proved to be also useful for monitoring post-treatment evolution.

For diagnosis

Serological diagnostic tests may detect antibodies or circulating antigens and immune complexes. Molecular biology techniques have recently been developed for *F. hepatica* detection in both snails and definitive animal hosts. These may be applied to human diagnosis in the near future.

Antibody detection: Antibody detection is clearly the method of preference for the immunodiagnosis of fascioliasis. Among the advantages are the ease in obtaining antigen reagents, the ease of the test systems used, and the fact that infections can be detected early (by 1-2 weeks of infection). The disadvantages are the lack of commercially-available defined, specific antigens, combined with test systems (HILLYER, 1993). A consensus concerning the optimal test systems for the serologic analysis of human fascioliasis has been difficult to reach (STORK *et al.*, 1973; CHEN & MOTT, 1990). Thus each laboratory prepares its own reagents and test systems with the ensuing lack of uniformity, and consequently results obtained with the same technique vary according to authors. A large number of patients show parasite eggs in their stools despite being serologically negative, and serologic cross-reactions proved to be common (SAMPAIO SILVA *et al.*, 1996).

Different serological antibody-detecting techniques have been applied for human fascioliasis diagnosis:

– **Precipitation tests:** radial diffusion (RD) (i.e., SAMPAIO SILVA *et al.*, 1985); double diffusion (DD) (i.e., EVERALL, 1970; BULAJICC *et al.*, 1977; GARCIA-RODRIGUEZ, MARTIN & GARCIA, 1985; GARCIA-RODRIGUEZ *et al.*, 1985; MERCADO, CANALES & ATIAS, 1985; APT *et al.*, 1992, 1993); immunoelectrophoresis (IEP) and/or counter-immunoelectrophoresis (CIEP) (i.e., CAPRON *et al.*, 1964; STORK *et al.*, 1973; HILLYER, 1975, 1981; HILLYER & CAPRON, 1976; WATTRE, CAPRON & CAPRON, 1978; SAMPAIO SILVA, CA-

PRON & CAPRON, 1980; GARCIA-RODRIGUEZ, MARTIN & GARCIA, 1985; GARCIA-RODRIGUEZ *et al.*, 1985; MERCADO, CANALES & ATIAS, 1985; MAKLED *et al.*, 1988; MIKHAIL *et al.*, 1990; ASSMAR *et al.*, 1991; BACQ *et al.*, 1991; KODAMA *et al.*, 1991; ALVAREZ-CHACON *et al.*, 1992; APT *et al.*, 1992, 1993; YOUSSEF & MANSOUR, 1993); and metacercarial precipitin test (FARAG, EL-SAYAD & OSMAN, 1995);

– **Agglutination tests:** indirect haemagglutination (IHA) (i.e., CAPRON *et al.*, 1973; WATTRE, CAPRON & CAPRON, 1978; AMBROISE-THOMAS, DESGEORGES & BOUTTAZ, 1980; SAMPAIO SILVA, CAPRON & CAPRON, 1980; ROBERT *et al.*, 1981; JEDRZEJEWSKA & PLONKA, 1983; MANSOUR *et al.*, 1983; MONTEJO *et al.*, 1983; GARCIA-RODRIGUEZ, MARTIN & GARCIA, 1985; GARCIA-RODRIGUEZ *et al.*, 1985; MERCADO, CANALES & ATIAS, 1985; CONTRERAS & SALINAS, 1987; BACQ *et al.*, 1991; ALVAREZ-CHACON *et al.*, 1992; ARJONA *et al.*, 1995; AATY & HASHIM, 1996; AZAB & EL-ZAYAT, 1996);

– **Haemolysis tests:** complement fixation (CF) (i.e., CAPRON *et al.*, 1973; STORK *et al.*, 1973; BULAJICC *et al.*, 1977; PICOAGA, LOPERA & MONTES, 1980; CONTRERAS & SALINAS, 1987; WESSELY *et al.*, 1988; APT *et al.*, 1992, 1993, 1995);

– **Fluorescence tests:** immunofluorescence assay (IFA) (i.e., FRAGA DE AZEVEDO & COELHO ROMBERT, 1965; CAPRON *et al.*, 1973; STORK *et al.*, 1973; DEELDER & PLOEM, 1975; BULAJICC *et al.*, 1977; WATTRE, CAPRON & CAPRON, 1978; AMBROISE-THOMAS, DESGEORGES & BOUTTAZ, 1980; SAMPAIO SILVA, CAPRON & CAPRON, 1980; DAVEAU & AMBROISE-THOMAS, 1982; TELLO *et al.*, 1988; WESSELY *et al.*, 1988);

– **Radioisotope tests:** radioimmuno assays (RIST, RAST) (i.e., SAMPAIO SILVA *et al.*, 1985);

– **Enzymatic tests:** enzyme-linked immunosorbent assay (ELISA) (i.e., AMBROISE-THOMAS, DESGEORGES & BOUTTAZ, 1980; HILLYER, 1981; MARTYENKO & KLIMENKO, 1981; DAVEAU & AMBROISE-THOMAS, 1982; MARTYENKO, LYSENKO & VASIL'EV, 1982; ROMBERT & TRINCA, 1982; KAMARDINOV, 1984; KNOBLOCH, 1985; ESPINO *et al.*, 1987; WESSELY *et al.*, 1988; KHALIL *et al.*, 1989, 1990; SHAHEEN *et al.*, 1989; ASSMAR *et al.*, 1991; AGUILERA, ZULANTAY & APT, 1992; APT *et al.*, 1992, 1993, 1995; ESPINO, MILLAN & FINLAY, 1992; OSMAN *et al.*, 1992, 1995; YOUSSEF & MANSOUR, 1993; SHAKER *et al.*, 1994; HASSAN *et al.*, 1995; SAMPAIO SILVA *et al.*, 1996; CORDOVA *et al.*, 1997); enzyme-linked immunofiltration assay (ELIFA) (i.e., PAILLER *et al.*, 1990); enzyme-linked immuno-electrotransfer blot (EITB) (i.e., SANTIAGO & HILLYER, 1986; HILLYER & SOLER DE GALANES, 1988; HILLYER *et al.*, 1992; SILVA *et al.*, 1993; SHAKER *et al.*, 1994); and Falcon™ assay screening test-enzyme linked immunosorbent assay (FAST-ELISA) (i.e., HILLYER & SOLER DE GALANES, 1988, 1991; HILLYER *et al.*, 1992; BJORLAND *et al.*, 1995);

– **Anti-P₁ antibody tests:** automated assay of anti-P₁ antibodies (BEN-ISMAIL, CARME & GENTILINI, 1978; BEN-ISMAIL *et al.*, 1980, 1982).

The major problem of antibody-detecting techniques lies in their sensitivity and specificity, which are dependent on antigen type and on a lack of consensus concerning the optimal antigen to be used in the different tests (HILLYER, 1993; SAMPAIO SILVA *et al.*, 1996). However, several authors already agree today that crude *F. hepatica* antigens have less than optimal specificity because they may easily present cross-reactions with other helminthic infections such as paragonimiasis, schistosomiasis, hydatidosis, ascariasis, trichinellosis and filariasis (HILLYER, 1981; CHEN & MOTT, 1990; HONG *et al.*, 1990), as well as with hepatitis C virus infection (AATY & HASHIM, 1996).

Thus, the use of partially purified antigens in different serologic techniques has been enhanced in order to avoid cross-reactions and gain specificity and sensibility, i.e., CIEP (HILLYER & CAPRON, 1976), IFA (DAVEAU & AMBROISE-THOMAS, 1982), ELISA (DAVEAU & AMBROISE-THOMAS, 1982; KHALIL *et al.*, 1989, 1990; SHAHEEN *et al.*, 1989; APT *et al.*, 1995) and EITB (SANTIAGO & HILLYER, 1986).

Serological techniques using excretory-secretory (E/S) products of adult *F. hepatica* as antigen have been reported to have the highest sensitivity and specificity, and allow the differentiation among other human parasite infections: CIEP (HILLYER, 1981), IHA (AZAB & EL-ZAYAT, 1996), IFA (CAPRON *et al.*, 1973; BULAJIC *et al.*, 1977; DAVEAU & AMBROISE-THOMAS, 1982), and mainly ELISA (HILLYER, 1981; MARTYENKO & KLIMENKO, 1981; DAVEAU & AMBROISE-THOMAS, 1982; MARTYENKO, LYSENKO & VASILEV, 1982; ROMBERT & TRINCA, 1982; ESPINO *et al.*, 1987; KHALIL *et al.*, 1989; OSMAN *et al.*, 1995; SAMPAIO SILVA *et al.*, 1996; CORDOVA *et al.*, 1997), EITB (HILLYER & SOLER DE GALANES, 1988; HILLYER *et al.*, 1992; SILVA *et al.*, 1993; SHAKER *et al.*, 1994) and FAST-ELISA (HILLYER & SOLER DE GALANES, 1988, 1991; HILLYER *et al.*, 1992; BJORLAND *et al.*, 1995). IFA was reported to have 92–96% sensitivity in the acute phase of the infection (CAPRON *et al.*, 1973). ELISA was reported to have a sensitivity of 95% to 100%, a specificity of 93% to 97% and an accuracy of 96% to 98% (HILLYER, 1981; ESPINO *et al.*, 1987; SHAKER *et al.*, 1994; OSMAN *et al.*, 1995; SAMPAIO SILVA *et al.*, 1996). EITB was reported to have 100% sensitivity but unknown specificity (HILLYER *et al.*, 1992) and to be 100% sensitive and specific (SHAKER *et al.*, 1994). FAST-ELISA was reported to have 95% sensitivity but unknown specificity (HILLYER *et al.*, 1992). Some differences in the antibody responses to E/S antigens reported by different investigators may be due to different methods of antigen preparation and storage conditions, or varying times of blood collection during the course of infection (HILLYER, 1993; SAMPAIO SILVA *et al.*, 1996).

Specialists concentrate efforts in obtaining purified

E/S antigens and/or recombinant molecules to increase sensibility and specificity even more. By EITB, Fh12 is a potential marker for screening for *F. hepatica* in humans in areas of the world where schistosomiasis is absent (HILLYER *et al.*, 1988, 1992). The use of the recombinant protein (denoted rFh15) for serological screening of *F. hepatica* infections is in progress (HILLYER, 1993). A purified *Fasciola* 27 kDa cysteine proteinase was found to be a species-specific, sensitive antigen for an ELISA for the diagnosis of human fascioliasis (YAMASAKI, AOKI & OYA, 1989). CORDOVA *et al.* (1997) have recently isolated and characterized two purified *F. hepatica* cysteine proteinase antigens (26 kDa and 25 kDa), which are valuable as sensitive and specific antigens (mainly that of 25 kDa) for the diagnosis by ELISA of the human fascioliasis. Although yet to be ascertained in humans, the antibody response of sheep and rabbits to *F. hepatica* Glutathione S-transferase (FhGST) seemed promising (HILLYER, SOLER DE GALANES & BATTISTI, 1992; HILLYER, 1993). These studies suggest a combination of ELISA using *F. hepatica* E/S antigens followed by a Western Blot (EITB) to detect target candidate diagnostic antigenic polypeptides (HILLYER & SOLER DE GALANES, 1988, 1991; HILLYER *et al.*, 1992; HILLYER, 1993).

O'NEILL *et al.* (1998) isolated and purified a highly immunogenic cathepsin L1 cysteine proteinase which proved to be potentially useful for the sensitive and specific immunodiagnosis of human fascioliasis, after a comparative study of crude parasite extracts (liver fluke homogenates), E/S products, and purified cathepsin L1 (CL1) as antigens in ELISA to discriminate between seropositive (exposed) and seronegative (non-exposed) human individuals. According to STRAUSS *et al.* (1997b) and O'NEILL *et al.* (1998), a standardized diagnostic test for human fascioliasis, based on an ELISA which detects IgG4 responses to CL1, could be available to all diagnostic centres if sufficient quantities of recombinant CL1 can be produced.

Circulating antigen and immune complex detection:

A sensitive and immunologically specific antigen detection test is an important goal, since it should imply recent, active infection. Several studies have examined this approach, although better defined reagents still need to be developed (HILLYER, 1993). The few studies on the detection of circulating immune complexes for fascioliasis immunodiagnosis have tended to be disappointing (HILLYER, 1993).

The detection of circulating antigens by ELISA using antibodies against crude (AMBROISE-THOMAS, DESGEORGES & BOUTTAZ, 1980) and E/S (ESPINO, MARCET & FINLAY, 1990; ESPINO, MILLAN & FINLAY, 1992; HAMMOUDA *et al.*, 1997) antigens and by EITB using antibodies against crude antigen (MERCADO, 1989) as well as of circulating immune complexes (CIC) by ¹²⁵I-Clq binding test (SAMPALIO SILVA, SANTORO & CAPRON, 1981) can diminish serodiagnostic problems in immunosuppres-

sed subjects, enabling a more precocious indirect diagnosis. A close relationship was observed between *F. hepatica* egg output and the detection rate of CIC of *F. hepatica* (SAMPAIO SILVA, SANTORO & CAPRON, 1981).

Molecular probes and hybridomas: New techniques available in recent years open a large field for the development of useful diagnostic tools.

Several attempts have been undertaken to develop a nucleic acid probe capable of sensitive and specific detection of *F. hepatica* in lymnaeid snails (SHUBKIN *et al.*, 1992; HEUSSLER *et al.*, 1993; ROGNIE, DIMKE & KNAPP, 1994; KAPLAN *et al.*, 1995; BARGUES & MAS-COMA, 1997; BARGUES *et al.*, 1997). Several results appear to be highly promising, although studies are needed to ascertain the value and applicability of these or similar probes for diagnostic purposes in man.

An *F. hepatica* cDNA clone was isolated from an expression library by immunological screening using calf blood serum. This antigen was expressed in *Escherichia coli* as β -galactosidase fusion proteins. In ELISA this threonine-rich protein detected antibodies from calf by 4 weeks of infection (SOLEDAD MARIN *et al.*, 1992), although its specificity needs to be defined.

A fluke-myeloma hybridoma expressing a 57 kDa *F. hepatica* antigen has been described (HILLYER, 1989). This approach for the development of antigen-expressing hybrids for immunoprophylaxis and immunodiagnosis of fascioliasis needs to be explored further (HILLYER, 1993).

For monitoring post-treatment evolution

Worth mentioning are several studies on the detection of antibodies (HILLYER, BERMUDEZ & RAMIREZ DE ARELLANO, 1984; GARCIA-RODRIGUEZ, MARTIN & GARCIA, 1985; HILLYER & SOLER DE GALANES, 1991; ESPINO, MILLAN & FINLAY, 1992; APT *et al.*, 1995) and circulating antigens (HILLYER & SOLER DE GALANES, 1988; ESPINO, MILLAN & FINLAY, 1992; HAMMOUDA *et al.*, 1997) in *F. hepatica* infection after effective treatment for assessing cure in patients with fascioliasis.

It has been shown that after effective chemotherapy, anti-*F. hepatica* antibodies became undetectable. DD and IHA became negative after a longer period (1-2 years after treatment) according to GARCIA-RODRIGUEZ, MARTIN & GARCIA (1985).

HILLYER & SOLER DE GALANES (1988) found by EITB that the serum from humans with fascioliasis recognized two antigenic polypeptides of 17 and 63 kDa; this recognition lasted for at least 3 years of infection, and concretely the 17 kDa antigenic polypeptide disappeared 6 weeks post cure. This antigenic polypeptide was an excellent candidate for the definition of chemotherapeutic cure.

HILLYER & SOLER DE GALANES (1991) applied FAST-ELISA with FhE/S antigens and found that humans with fascioliasis had continually elevated antibody

levels for over 3 years. Those treated and cured had their antibody levels slowly decrease to nearly normal levels 6-12 months later.

According to APT *et al.* (1995), ELISA using a soluble extract of somatic antigen of mature *F. hepatica* was highly effective in post-treatment monitoring. Before treatment with Triclabendazole, 20 (83.3%) of 24 confirmed cases had positive test results. The test results became negative by the second month of treatment in 40% of the cured cases. This percentage increased progressively, reaching 91.3% at 12 months after therapy. In the five cases in which treatment failed, the ELISA results remained positive until the end of the follow-up period (six months). In three of these cases who accepted a second round of therapy with Triclabendazole six months after the first treatment, the ELISA results became negative in all three six months after parasitologic cure and remained negative until the end of the period.

HAMMOUDA *et al.* (1997) detected *Fasciola* circulating antigen by ELISA in the sera of 10 patients, before treatment with Triclabendazole, but no antigen was detected 3 months after treatment.

INTRADERMAL TESTS

Skin tests employing a crude antigen or purified fraction of *F. hepatica* (LAVIER & STEFANOPOULOU, 1944; COUDERT & TRIOZON, 1958; BIAGI, TAY & PORTILLA, 1959; PAUTRIZEL *et al.*, 1962; STORK *et al.*, 1973; MORA *et al.*, 1980; PICOAGA, LOPERA & MONTES, 1980; SMITHERS, 1982; KODAMA *et al.*, 1991; APT *et al.*, 1992, 1993; MAS-COMA *et al.*, 1995) have been used. The tests were simple and sufficiently sensitive to propose a diagnosis of the infection (CAPRON *et al.*, 1973) but not very specific (STORK *et al.*, 1973). This technique is rarely used nowadays.

STOOL ANTIGEN DETECTION TESTS

YOUSSEF, MANSOUR & AZIZ (1991) report the use of hyperimmune serum from rabbits immunized with partially purified worm antigens in CIEP for the detection of parasite antigens in saline extracts of patients' stools. All saline extracts from fascioliasis patients developed 2-5 precipitin bands. No precipitin band developed with stool extracts of patients with spurious *Fasciola* infection or other parasitic infections, or from negative controls. Although initially developed for *F. gigantica*, this assay proved to be simple, rapid, sensitive, and specific for the diagnosis of early as well as established fascioliasis infections.

A sandwich ELISA (FASCIDIG®) was developed for the detection of *F. hepatica* E/S antigens in stool specimens of infected humans (ESPINO *et al.*, 1993; ESPINO & FINLAY, 1994). None of the patients with *F. hepatica*

showed cross-reactions. Results obtained proved that FASCIDIG show a 93,8% sensitivity, 100% specificity and 100% and 89,5% to 99% predictive values for positive and negative, respectively (ESPINO *et al.*, 1993, 1997a). When patients were retested 2-3 months after treatment, all of the specimens from the parasitologically cured patients were negative by the antigen detection assay, while the specimens from the patients with persisting *F. hepatica* eggs in their stools remained positive (ESPINO & FINLAY, 1994).

Recent data of studies on the dynamics of antigenemia, coproantigens and antibody response to *F. hepatica* indicate that circulating antigens are linked to the earliest phases of the infection, whereas coproantigens are related with its more advanced phases. The disappearance of the antigenemia appeared to be linked to an increase of antibody levels and formation of circulating immune complexes (ESPINO *et al.*, 1997b).

The measurement of antigen(s) in faeces appears to be an excellent immunodiagnostic tool, especially for the early prediction of chemotherapeutic success (DIAZ *et al.*, 1997; HILLYER & APT, 1997). Data were presented that showed that nine of ten patients treated and cured were negative for coproantigens by 15 days post-treatment. A problem with this method is that storage at 4°C results in fungal overgrowth and antigen deterioration. It was recommended that a multicenter trial be implemented for the evaluation of the use of coproantigen detection for the immune diagnosis of fascioliasis and the prediction of success of chemotherapy (HILLYER & APT, 1997).

Other techniques

Non-invasive diagnostic techniques which can be used for human diagnosis are radiology, radioisotope scanning, ultrasound (US), computed tomography (CT) and magnetic resonance (MR).

RADIOLOGY

Human *F. hepatica* infection has been diagnosed by abdominal and chest X-ray examination, by oral, percutaneous and intravenous cholangiography, as well as by endoscopic retrograde cholangio-pancreatography (ERCP) (ZARAGOSI MOLINER, 1972; WOOD, STEPHENS & PORTER, 1975; BELGRAIER, 1976; DONNELLY & HEDERMAN, 1977; PERA, ASTUDILLO & FERNANDEZ-CRUZ, 1978; PIECUCH, 1979; EISENSCHER & SAUGET, 1980; MORETO & BARRON, 1980; PALACIO VELEZ *et al.*, 1983; SAPUNAR *et al.*, 1983, 1992; VITI *et al.*, 1983; ALIAGA *et al.*, 1984; BONNIAUD *et al.*, 1984; HAUSER & BYNUM, 1984; HEREDIA *et al.*, 1984; ORIVE *et al.*, 1984; CONDOMINES *et al.*, 1985; JUAREZ *et al.*, 1985; WONG *et al.*, 1985; APT & TISELJ, 1987; MAROY *et al.*, 1987; BEERS *et al.*, 1990; VEERAPPAN *et al.*, 1991; RONDE *et al.*, 1992; HAN *et al.*, 1993; LOPEZ ROSES *et*

al., 1993; RIEDTMANN *et al.*, 1995; DIAS *et al.*, 1996). Nevertheless, the findings are not pathognomonic of *F. hepatica* infection. Dilated and sacculated bile ducts, multiple filling defects consistent with calculi in the bile duct and/or in the gall bladder and multiple areas of alternating narrowing and fusiform dilation in the intrahepatic radicals have been shown by different types of cholangiography.

In acute fascioliasis ERCP may be normal (TAKAYAMA *et al.*, 1986). In biliary fascioliasis it may show typical pictures of *F. hepatica* parasites in the gall bladder (BONNIAUD *et al.*, 1984; HEREDIA *et al.*, 1984), dilated bile ducts with small, radiolucent, linear or crescent-like shadows, suggesting worms (SAPUNAR *et al.*, 1983; BONNIAUD *et al.*, 1984; ORIVE *et al.*, 1984; WONG *et al.*, 1985; BEERS *et al.*, 1990; VEERAPPAN *et al.*, 1991; RONDE *et al.*, 1992; HAN *et al.*, 1993; LOPEZ ROSES *et al.*, 1993; DIAS *et al.*, 1996), and with jagged, irregular margins (BEERS *et al.*, 1990; RONDE *et al.*, 1992; HAN *et al.*, 1993). Similar pictures have been described on percutaneous and perioperative cholangiography (BELGRAIER, 1976; DONNELLY & HEDERMAN, 1977; VITI *et al.*, 1983; CONDOMINES *et al.*, 1985; VEERAPPAN *et al.*, 1991). In chronic fascioliasis, ERCP pictures have been misinterpreted as primary sclerosing cholangitis (HAUSER & BYNUM, 1984).

ERCP may also be used in follow-up to evaluate the efficacy of medical therapy (DIAS *et al.*, 1996).

RADIOISOTOPE SCANNING

The diagnosis of fascioliasis may also be achieved by radioisotope liver scan (KNOELL, KIRSCH & RYGG, 1972; WOOD, STEPHENS & PORTER, 1975; GALLARDO, SAEZ & ENRIQUEZ, 1976; AGUIRRE *et al.*, 1978, 1981a; MARTINEZ L. DE LETONA *et al.*, 1982; PEÑA SANCHEZ *et al.*, 1982; RIVERA & BERMUDEZ, 1984; GARCIA-RODRIGUEZ *et al.*, 1985; ARJONA *et al.*, 1995). The patterns observed are, however, not specific. A radiocolloid demonstration of the presence of cold areas in the liver in 18 out of 23 cases with *F. hepatica* infection have been reported. Among them, 13 showed positive uptake with ⁶⁷Ga in the cold areas in a radiocolloid scan (AGUIRRE *et al.*, 1981a). *F. hepatica* infection is one of the causes of «cold areas» in traditional liver scan and positive ⁶⁷Ga uptake. Similar scintigraphic images using radiocolloid were observed in 4 persons with fascioliasis in whom the differential diagnosis had included metastatic liver cancer, hydatid disease or another parasitic infection (RIVERA & BERMUDEZ, 1984). Increased liver uptake of ⁶⁷Ga was observed and focal defects were demonstrated by Tc-99 (KNOELL, KIRSCH & RYGG, 1972; PEÑA SANCHEZ *et al.*, 1982; ARJONA *et al.*, 1995) as well as hepatomegaly (4 cases) and splenomegaly (3 cases). Filling defects in the right lobe and in the porta hepatis area on liver scan have also been observed (CHEN & MOTT, 1990).

ULTRASOUND

US has proved useful in the diagnosis of the pathological lesions secondary to *F. hepatica* infection in the liver, biliary tract and gall bladder (EISENSCHER & SAUGET, 1980; VIVES *et al.*, 1982; BONNIAUD *et al.*, 1984; KARABINIS *et al.*, 1985; CAUQUIL *et al.*, 1986; BASSILY *et al.*, 1989; HODLER & MEIER, 1989; BEERS *et al.*, 1990; AGOTE *et al.*, 1991; PANDOLFO *et al.*, 1991; PULPEIRO *et al.*, 1991; RUIZ REBOLLO *et al.*, 1991; FAWZY, SALEM & OSMAN, 1992; HAMAMOTO *et al.*, 1992; GUÇLU, DIK & AGAOGLU, 1995; NARAIN *et al.*, 1997). In chronic fascioliasis, abdominal US may either be normal (BASSILY *et al.*, 1989) or show mobile vermiform structures without acoustic shadowing within the gall bladder (EISENSCHER & SAUGET, 1980; BONNIAUD *et al.*, 1984; BASSILY *et al.*, 1989; BEERS *et al.*, 1990; PANDOLFO *et al.*, 1991; PULPEIRO *et al.*, 1991; RUIZ REBOLLO *et al.*, 1991; FAWZY, SALEM & OSMAN, 1992) and in the bile ducts (BASSILY *et al.*, 1989; BONNIAUD *et al.*, 1984), representing worms, that may be confused with stones (HEREDIA *et al.*, 1984). Duct dilation may also be seen (HEREDIA *et al.*, 1984; BASSILY *et al.*, 1989; BEERS *et al.*, 1990).

Among the lesions that have been reported are: a) an echogenic defect which corresponded with a defect on radiocolloid scan (RIVERA & BERMUDEZ, 1984); b) cyst in the left lobe with patchy focal echogenicity in the liver parenchyma (similar to the image observed by ERCP) (HAUSER & BYNUM, 1984); c) liver abscess with regression after specific treatment (HAN *et al.*, 1993; KARABINIS *et al.*, 1985; STURCHLER *et al.*, 1981); d) intrahepatic hyper- and hypo-echogenic nodule with extension to a thickened liver capsule (MESSNER *et al.*, 1983; CAUQUIL *et al.*, 1986; MORA *et al.*, 1992); e) echodense mass in the gall bladder (HOURLY, YOUNES & HUGUIER, 1983; PANDOLFO *et al.*, 1991; ARJONA *et al.*, 1995); f) heterogeneous echogenic subcapsular lesion diagnosed as a subcapsular haematoma confirmed by computed tomography and arteriography (PIQUET *et al.*, 1986; SAPUNAR *et al.*, 1992).

US may also be used in follow-up to evaluate the efficacy of medical therapy (BEERS *et al.*, 1990; PULPEIRO *et al.*, 1991; RUIZ REBOLLO *et al.*, 1991).

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CT has a high level of resolution for auxiliary and pathological diagnosis of *F. hepatica* infection (PEÑA SANCHEZ *et al.*, 1982; DE MIGUEL *et al.*, 1984a; TAKEYAMA *et al.*, 1986; ZAPATERO *et al.*, 1986; CAMARA, CICERO & SAHEL, 1987; PAGOLA SERRANO *et al.*, 1987; CABANILLAS *et al.*, 1989; HODLER & MEIER, 1989; KODAMA *et al.*, 1991; HAMAMOTO *et al.*, 1992; PARTIDARIO *et al.*, 1992; HAN *et al.*, 1993; ARJONA *et al.*, 1995; KIM *et al.*, 1995; DIAS *et al.*, 1996; TCHIRIKHTCHIAN *et al.*, 1997). The abnormalities found initially were small

areas of decreased attenuation in the periphery of the liver which sometimes could not be detected by ultrasound (DE MIGUEL *et al.*, 1984a; BEERS *et al.*, 1990; AGOTE *et al.*, 1991; NARANJO *et al.*, 1991; HAN *et al.*, 1993; JIMENEZ *et al.*, 1995).

Two types of lesions may be found. One is an abscess-like lesion, with single, or more commonly multiple, hypodense nodular areas (PEÑA SANCHEZ *et al.*, 1982; DE MIGUEL *et al.*, 1984a; GOEBEL, MARKWALDER & SIEGENTHALER, 1984; TAKEYAMA *et al.*, 1986; HAMAMOTO *et al.*, 1992; PARTIDARIO *et al.*, 1992; HAN *et al.*, 1993; ARJONA *et al.*, 1995; JIMENEZ *et al.*, 1995; TCHIRIKHTCHIAN *et al.*, 1997). The second type lesion is highly suggestive of fascioliasis in an appropriate clinical setting and consists of tunnel-like branching hypodense areas, which are better delineated after contrast injection (DE MIGUEL *et al.*, 1984a; PAGOLA SERRANO *et al.*, 1987; ARJONA *et al.*, 1995). They result from the migration of the parasite through the liver and therefore CT scan can be a useful tool for the diagnosis of the disease, fundamentally of invasive fascioliasis (HAN *et al.*, 1993; ARJONA *et al.*, 1995; JIMENEZ *et al.*, 1995).

CT may also be used in follow-up to evaluate the efficacy of medical therapy (DE MIGUEL *et al.*, 1984a; TAKEYAMA *et al.*, 1986; PAGOLA SERRANO *et al.*, 1987;). Several months after treatment, a marked improvement in the CT images has been shown by different investigators. The multiple hypodense areas in the liver were reduced significantly in number and size (DE MIGUEL *et al.*, 1984a; GOEBEL, MARKWALDER & SIEGENTHALER, 1984; TAKEYAMA *et al.*, 1986; PAGOLA SERRANO *et al.*, 1987; JIMENEZ *et al.*, 1995).

MAGNETIC RESONANCE

MR may also be used for the diagnosis (HAN *et al.*, 1996; TCHIRIKHTCHIAN *et al.*, 1997). According to HAN *et al.* (1996), hepatic fascioliasis produces three types of lesions in MR images arranged in tract-like fashion. The outermost area presents as an iso-signal area in T1W1, with slightly higher signal intensity in T2W1 and diffuse enhancement after i.v. contrast. The second type presents as a well-defined low signal area in T1W1, not enhanced, and also shows low signal intensity in T2W1. The third type has low signal intensity in T1W1, is not enhanced, and has high signal intensity in T2W1, which is similar to fluid-containing inflammatory lesions such as pyogenic abscess. These findings of MR imaging suggest various changes associated with traumatic hepatitis caused by the migration of the worm in the liver, and this diverse signal intensity can be a suggestive finding of fascioliasis.

Clinical orientative diagnosis

The clinical presentation may be helpful for the diagnosis, although only parasitological findings can confirm

the diagnosis of the infection and a positive serological test permits a presumptive diagnosis. Fascioliasis is frequently considered among the differential diagnoses in a well-known endemic area. However, in areas where the disease is rarely reported or absent, physicians may not consider this diagnostic possibility. History of ingestion of raw wild or cultivated watercress or other vegetables, or other contaminated food or water may be suggestive of the infection (CHEN & MOTT, 1990).

According to ARJONA *et al.* (1995), the clinical situations in which the diagnosis of *F. hepatica* infection should be considered are: history of watercress ingestion, eosinophilia, fever of unknown origin, atypical abdominal pain, focal intrahepatic lesions, granulomatous hepatitis, serositis and meningitis with peripheral or fluid eosinophilia, family history of fascioliasis, biliary colic or cholangitis, and normal ultrasonography. Eosinophilia has also been successfully used for a first selection in general surveys (GIL-BENITO *et al.*, 1991; GIL-BENITO, 1994).

In the acute phase the clinical presentation includes fever, pain in the right hypochondrium, prominent eosinophilia with leucocytosis, anaemia and a moderately to significantly high ESR. Increase in AKP, GPT, GOT and γ -globulin may or may not be present. In this phase, CT-scan and/or a positive serological reaction against *F. hepatica* antigen are most suggestive of the diagnosis (CHEN & MOTT, 1990).

In the chronic (latent and obstructive) phase the clinical picture is attenuated and easily confused with other diseases. The classic pattern includes: vague gastrointestinal complaints, pain in the right hypochondrium or epigastrium, cholecystitis, cholangitis and bile duct or gall bladder stones. The liver is usually enlarged with or without pain on palpation. Ascites may appear in advanced cases. Radiology, radioisotope, US, CT and MR are of value in confirming the diagnosis. Definitive diagnosis can be made by finding eggs in the stool or biliary drainage, or by finding egg granulomas or sections of the fluke in the liver tissue sections, adult worms in the bile ducts or eggs in the bile through exploratory laparotomy (CHEN & MOTT, 1990).

In both the acute and chronic infections, ectopic localization of the parasite may cause a confusing clinical presentation.

In the differential diagnosis, febrile diseases such as typhoid, brucellosis, acute schistosomiasis, hepatitis and hepatic abscess should be ruled out. Other parasitic infections causing eosinophilia, such as schistosomiasis, clonorchiasis, trichinellosis, hydatid disease, visceral larva migration and Loeffler's syndrome, as well as eosinophilic leukaemia, must be excluded (FACEY & MARSDEN, 1960; HARDMAN, JONES & DAVIES, 1970; WEI, 1984).

Care must be taken to know which human parasites exist in the area. As pointed out by ESTEBAN *et al.* (1997a), the coexistence of *F. hepatica* infection and different recognized symptoms-inducing and/or pathogenic

parasites clearly suggests the inappropriateness of the clinical-symptomatological picture for the diagnosis of fascioliasis. From the diagnostic perspective as well, the coexistence of *F. hepatica* and several helminths is also of interest, due to the possible induction of cross reactions in serological tests.

TREATMENT

There was no consensus about the therapy of choice for human fascioliasis until very recently when, after proving that appropriately dosified Triclabendazole is 100% curative in humans, Ciba (now Novartis Pharma) came to an agreement with WHO to make this drug available for human use. At any rate, there are many other drugs today available for human use that are also effective against *F. hepatica*.

Many drugs were used in the past that have now been abandoned, including gentian violet, antimony salts and quinine. Moreover, bithionol is apparently no longer being manufactured, despite being one of the most used drugs for human treatment and even having been considered the drug of choice for years, despite its long treatment course.

No new drugs have been developed during the last 15 years for fascioliasis treatment, and drug resistance in *F. hepatica* has already been reported to affect the efficacy of the drugs against immature stages in animals. Fortunately, recently-tested drug combinations have shown their synergistic action increasing efficacy against immature flukes and removing resistant flukes, which may reduce the development of resistance (BORAY, 1994).

Although the cure is possible in some cases without specific therapy, asymptomatic patients should also be treated to avoid the risk of future complications (ARJONA *et al.*, 1995).

Emetine derivatives

Emetine derivatives, the classic drugs, were used widely and continue to be used today, given intramuscularly or subcutaneously; emetine at doses of 1-10 mg/kg a day for 10 days (PADILLA ANTONI, SALEME & JORRATT, 1972; COURAUD *et al.*, 1975; PICOAGA, LOPERA & MONTES, 1980; APT & TISELI, 1987; SICILIANO *et al.*, 1989; BORIE *et al.*, 1990; CHEN & MOTT, 1990); dehydroemetine, at a usual dose of 1 mg/kg daily for 10-14 days, was even considered the therapy of choice a few decades ago (PAUTRIZEL *et al.*, 1964; GIRAUDET, 1968; FARID, KAMAL & WOODY, 1988; FARID *et al.*, 1990; CHEN & MOTT, 1990; AYADI, MAKNI, BEN SAID, 1997) and has sometimes shown to be more effective than bithionol (ALVAREZ-CHACON *et al.*, 1992).

Emetine derivative therapeutic effects in eliminating the infection as well as in improving the symptoms are well known, but they cause a variety of toxic manifestations involving the heart, liver and digestive tract. Fre-

quent changes are seen in the electrocardiogram. Hypotension sometimes occurs during treatment. Dehydroemetine has a shorter tissue half life and disappears more rapidly from the heart and liver as compared with emetine (GOODMAN, HENDERSON & CULLITY, 1973). No deaths have been reported due to emetine derivative treatment of *F. hepatica* infections (CHEN & MOTT, 1990).

Aminoquinoline derivatives

Chloroquine has been used to treat *F. hepatica* infection, although no cidal effects on the flukes have been shown. However, in the acute phase, chloroquine treatment improved the symptoms dramatically. With the disappearance of fever, the patients' general condition improved, and hepatomegaly, eosinophilia and erythrocyte sedimentation rate were reduced. Cure of the infection has not been documented (FACEY & MARSDEN, 1960; HARDMAN, JONES & DAVIES, 1970; SUTER *et al.*, 1979; PICOAGA, LOPERA & MONTES, 1980).

Xylol derivatives

Hexachloro-para-xylol has been effectively used at a dose of 100-150 mg/kg body-weight in 4 doses at 15 min intervals in Romania (BABADZHANOV *et al.*, 1974), at a dose of 60 mg/kg daily for 5 days in the former Soviet Union (KHASHIMOV & KAMARDINOV, 1975; RAKHMANOV, 1987), and at a dose of 50-80 mg/kg body weight daily divided into 3 doses given orally for 7 consecutive days in China (WANG *et al.*, 1981; SUN, CHAI & CHENG, 1984). The side effects include gastrointestinal complaints and dizziness.

Halogenated phenol derivatives

In recent literature, bithionol is proposed as the drug of choice for the treatment of *F. hepatica* infection (KNODELL, KIRSCH & RYGG, 1972; PEÑA SANCHEZ *et al.*, 1982; ANTON ARANDA, CIA LECUMBERRI & RIVERO PUENTE, 1985; AREJOLA *et al.*, 1985; FUJITA *et al.*, 1985; FARID, KAMAL & WOODY, 1988; GARCIA-RODRIGUEZ *et al.*, 1989; CHEN & MOTT, 1990; RAHMAN, FADALI & ABOU BASHA, 1990; BACQ *et al.*, 1991; BASSIOUNY *et al.*, 1991; KODAMA *et al.*, 1991; ANONYMOUS, 1993; ARJONA *et al.*, 1995; ABREU *et al.*, 1996). It is usually applied at a dose of 30-50 mg/kg daily, divided into 3 oral doses on alternate days for 20-30 days (ANONYMOUS, 1993), although other dosages have been used (PEÑA SANCHEZ *et al.*, 1982; FARID, KAMAL & WOODY, 1988; FARID *et al.*, 1990; BASSIOUNY *et al.*, 1991; KODAMA *et al.*, 1991). In cases of fascioliasis resistant to emetine and praziquantel treatment, bithionol achieved cure in dosages of 50 mg/kg daily for 10 alternate days (GRADOS & BERROCAL, 1977) or 40 mg/kg daily for 14-15 alternate days (BHATTACHARYYA, 1985; ABREU *et al.*, 1996). Occasionally, the patients required a second course to obtain a complete cure. The side ef-

fects, including diarrhoea, anorexia, nausea, vomiting, pruritus, urticaria and abdominal pain, are usually mild, and drug withdrawal is not necessary.

Niclofolan is widely and successfully used for veterinary purposes in China (CHEN & MOTT, 1990). Nevertheless, two oral doses of niclofolan at 2 mg/kg body weight for 3 days apart (ECKHARDT & HECKERS, 1981) and 0.5 mg/kg twice a day for 3 days (RESHEF, LOK & SHERLOCK, 1982) has been applied for human treatment. The side effects include sweating, palpitation, nausea, diffuse upper abdominal pain, itching and jaundice with dark urine. The niclofolan shows such a toxicity that clinical use cannot be recommended (CHEN & MOTT, 1990).

Imidazole derivatives

Daily oral doses of 1.5 g of Metronidazole for 13 and 28 days showed to be effective, but a smaller total dose of 4 g was reported to have failed to cure a chronic infection (NIK-AKHITAR & TABIBI, 1977; ECKHARDT & HECKERS, 1981; ARAFA & LASHEN, 1993).

Albendazole, which is efficient against animal fascioliasis, has a high rate of failure in human infections (APT *et al.*, 1991).

Triclabendazole is effectively used in animals against both adult and immature *F. hepatica*. It has also been reported as a very effective drug against both the acute and the chronic forms of fascioliasis in humans (ROBINSON, 1985; WESSELY, REISCHIG & HEINERMANN, 1987; MARKWALDER *et al.*, 1988; WESSELY *et al.*, 1988; LE BRAS *et al.*, 1989; LOUTAN *et al.*, 1989; RIPERT, 1990; BECHTEL *et al.*, 1992; LAIRD & BORAY, 1992; PICOT *et al.*, 1992; RONDE *et al.*, 1992; APT *et al.*, 1995; HAMMOUDA *et al.*, 1995, 1997; OSMAN, HELMY & MEGEHED, 1995; DIAZ *et al.*, 1997; TCHIRIKHTCHIAN *et al.*, 1997). The recommended dose is two separate regimens of 10 mg/kg of body weight. Clinical tolerability is excellent, although a transient febrile episode with reversible liver function alteration has been observed (WESSELY, REISCHIG & HEINERMANN, 1987; WESSELY *et al.*, 1988; MARKWALDER *et al.*, 1988).

According to APT *et al.* (1995), 24 asymptomatic individuals with chronic hepatic fascioliasis were treated with Triclabendazole at a single oral dose (10 mg/kg of body weight) after an overnight fast. Nineteen (79.2%) of the 24 patients were egg-negative two months after treatment. Three of five cases with eggs in faeces after the first treatment were retreated and the parasitologic cure was achieved. The satisfactory results obtained with Triclabendazole, a cure rate of 79.2% when first used and 100% after a second round of therapy, the ease of a single oral dose, its tolerability, and the absence of side effects, allowed us to consider it as a possible drug of choice for treatment of chronic fascioliasis (HILLYER & APT, 1997). According to the pharmacokinetics of Triclabendazole and its principal metabolite, the sulfoxide radical, it seems that more of the drug is adsorbed if it is

administered after meals; when two courses of Triclabendazole of 10 mg/kg each were administered after meals on the same day, cure rates of 100% were obtained (APT *et al.*, 1995).

At present, a formulation appropriate for human use is jointly being developed by Novartis Pharma and the World Health Organization. A series of several clinical trials, including about 350 patients, have been completed in Egypt, Cuba, Bolivia, Peru, Chile and Iran. Trials were carried out under a single core protocol. A number of different dosing regimens were employed to provide information about the most appropriate dosing schedule. Pharmacokinetic studies indicated that the peak plasma concentrations, which occurred within 3 hours, were some three-fold higher following post-prandial dosage. The primary efficacy parameter was the clearance of parasite eggs from faeces. A single oral dose of 10 mg/kg has cured at least 85% of cases of chronic fascioliasis when taken after a meal. At this effective dose, the Triclabendazole was well tolerated. Results of renal function and haemathological tests remained essentially normal throughout treatment. Minimal, transient increases in serum concentrations of liver enzymes, returning to normal by day 30, were reported in some patients. Clinical adverse experiences most frequently encountered were related to the gastrointestinal tract, epigastric, abdominal or right hypochondrial pain and biliary colic (70% of the patients), nausea and vomiting (15%). This is likely to be due to expulsion of dead or damaged worms from the hepatobiliary system rather than to the drug itself. Treatment with antispasmodic was shown to reduce pain and to minimise the risk of jaundice (LABURTE *et al.*, 1997).

Isoquinoline-pyrazine derivatives

Praziquantel is today the drug of choice for human trematode infections and it is even effective against a broad range of helminths (PEARSON & GUERRANT, 1983; HARNET, 1988). Worth mentioning is that *Fasciola* may be the only genus of trematode that has practically no response to praziquantel. There are no randomized trials in human fascioliasis and the results in uncontrolled studies are controversial. Whereas some authors mentioned cases of successful treatment (ALCOBA *et al.*, 1988; CHEN & MOTT, 1990; MARTI & GARCIA, 1990; ATALAY *et al.*, 1993; MOREAU *et al.*, 1995; AYADI, MAKNI & BEN SAID, 1997; QUENEAU *et al.*, 1997), others have reported praziquantel failures (BHATTACHARYYA, 1985; ESPINOS, REÑE & CONDOMINES, 1985; KNOBLOCH, 1985; KNOBLOCH *et al.*, 1985; FARAG *et al.*, 1986; FARID *et al.*, 1986; WESSELY, REISCHIG & HEINERMANN, 1987; ATA *et al.*, 1988; FARID, KAMAL & WOODY, 1988; FARID, KAMAL & MANSOUR, 1989; WESSELY *et al.*, 1988; GARCIA-RODRIGUEZ *et al.*, 1989; CHEN & MOTT, 1990; RIPPERT, 1990; YADEGARY, FORGHANPARAST & ASSMAR, 1992; ARJONA *et al.*, 1995; ABREU *et al.*, 1996), even at high doses: 75 mg/kg daily for 1-3 days (YADEGARY,

FORGHANPARAST & ASSMAR, 1992; ARJONA *et al.*, 1995); 75 mg/kg daily for 5-7 days (WAHN & MEHLHORN, 1984; FARID *et al.*, 1986; WESSELY *et al.*, 1988; FARID, KAMAL & MANSOUR, 1989; MOREAU *et al.*, 1995); 75 mg/kg body weight divided into 3 doses over a 1-10-day period (SCHIAPPACASSE, MOHAMMADI & CHRISTIE, 1985; FARID, KAMAL & WOODY, 1988). The ideal duration of therapy is not known, although a treatment for 1-7 days has been recommended. Praziquantel is well tolerated; side effects like pruritus, abdominal discomfort, and nausea have been reported, but it was not necessary to withdraw the medication.

Other drugs

Mebendazole, in a daily dose of 4 g for 3 weeks, was reported to have cured an *F. hepatica* infection diagnosed clinically and serologically in the invasive phase (DUGERNIER *et al.*, 1986).

Rafoxanide, or pentachlorosalicylanilide, a salicylanilide derivative, was used in the treatment of a child with fascioliasis (YURDAKOK, 1985).

Prednisone at 5-10 mg by day has been advocated as an adjunct therapy before the administration of fasciolicidal drugs in acutely ill children or those who appear toxic (FARID, KAMAL & WOODY, 1988).

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