infections, or against the subsequent systemic episodes). Thus, although J5 antibody did not appear to prevent gram-negative infection, it did prevent the severe manifestations of established infection which are believed to be mediated by endotoxin. Antibody to core glycolipid appears to act, therefore, by neutralising the harmful effects of LPS; whether this occurs directly in the circulation or by enhancing clearance remains uncertain.

Anti-core glycolipid antibody improves survival rate when given to patients in whom gram-negative septic shock has already developed and can prevent septic shock in high-risk surgical patients. Practical application of this therapy requires mass production of core glycolipid antibody in a convenient, safe, and standardised form. The protective power of anti-J5 immunoglobulin fractions or monoclonal antibodies is now being studied. Immunoglobulins prepared from donors with naturally occurring high titres against endotoxins appeared to be protective in a recent study,[26] but the study has been questioned because it was inadequately controlled.[27] Active immunisation of immunocompetent patients before elective surgery might substitute for passive prophylaxis, but this approach is impractical in patients undergoing emergency surgery. Regardless of the form of immunisation, prophylaxis against gram-negative shock in high-risk surgical patients promises to improve the overall outcome of surgery.

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THREE-YEAR PROSPECTIVE STUDY OF THE EVOLUTION OF MANSON'S SCHISTOSOMIASIS IN NORTH-EAST BRAZIL

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Summary A cross-sectional study of morbidity associated with *Schistosoma mansoni* infection in an area in North-East Brazil where the disease is endemic was carried out in 1974. The survey was repeated in 1977, before mass treatment with oxamniquine, providing a cohort of 210 individuals who had both examinations. The high prevalence of hepatomegaly (over 80%) and of splenomegaly (over 15%) contrasted with rates of 10% and 1%, respectively, in a non-endemic area. Over the 3-year period hepatomegaly spontaneously regressed in 13% of patients, and splenomegaly regressed in 56%, a phenomenon most common in older individuals with light infections. Those with heavy infections—ie, 500 or more eggs per g faeces, had an excess risk of splenomegaly of 19·6% and, of its persistence, of 61·5%. Thus, intensity of infection was a critical factor in liver and spleen involvement, and programmes of chemotherapy that reduce infection should mitigate the risk of schistosomal morbidity.

Introduction

THE development of safe, orally administered antischistosomal drugs and a better knowledge of the epidemiology of schistosomiasis now permit control of the disease.[1,2]

In the evaluation of disease-control programmes consideration must be given to changes in morbidity and infection that might occur in the absence of drug interventions. Cross-sectional studies in endemic areas have shown hepatomegaly and splenomegaly to be consequences of infection, but studies of the evolution of schistosomal organomegaly are few and the conclusions differ. Kloetzel,[3]

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for example, concluded that schistosomal splenomegaly develops over a period of 10–15 years and never resolves spontaneously, and Prata and Bina[4] recorded a steady increase in hepatosplenomegaly over a 3–5 year period in 20 untreated individuals. Katz and Brener[5], however, noted the disappearance of hepatosplenomegaly over a 10-year period in some untreated cases; Barbosa and Voss[6] in a 7-year study made similar observations but attributed them to observer error.

In 1974 we carried out a cross-sectional study of morbidity associated with schistosomiasis mansoni in Castro Alves, an area in North-East Brazil where the disease is endemic.[7] Infected persons were not offered treatment because available anti-schistosomal drugs were considered to be unsafe for community-based treatment. This changed when oxamniquine became available in 1977, and the population was re-examined by the same physician; egg excretion was determined by means of the same qualitative and quantitative techniques. Thereafter oxamniquine was offered to infected persons.[8] Prospective data were obtained on the course of infection in a cohort of 210 subjects. A comparable population from Riacho de Santana, a non-endemic area, was examined as a control.

Methods

We defined infection as synonymous with egg excretion and graded the intensity of infection by the faecal egg counts. Schistosomal disease (ie, morbidity) was diagnosed in individuals with a palpable liver or spleen and was classified by the size and characteristics of the palpable organs.

Populations studied were defined by a census of all residents and were not subject to other diseases, such as malaria or visceral leishmaniasis, that might cause persistent organomegaly. The census data permitted assessment of the influence of non-compliance on the results.

The Riacho de Santana Population: an Area where Schistosomiasis is not Endemic

People of Riacho de Santana are subsistence farmers in a region of the state of Bahia where the cultural patterns are comparable with those of Castro Alves.[9] In connection with studies of Chagas' disease in 1979 an area was mapped, and a census identified 365 residents aged 5 years or more; of these 80% (291) had stool examinations. Physical examinations were done on 85% (309).

The Castro Alves Population: an Area of Endemic Schistosomiasis

The study population consisted of all inhabitants of 3 contiguous rural geopolitical units (Fazendas 1, 2, and 8) in the county of Castro Alves, state of Bahia.[7] After a census of the area faecal and physical examinations were done in April, 1974. There were 417 people resident in the area at this time, of whom 357 were aged 5 years or more. The census was done annually, and in April, 1977, the examinations were repeated. Between 1974 and 1977 111 people left the area, and 11 deaths were recorded. 7 of these were in individuals aged 5 years or more at the start of the study. The cultural situation was such that deaths in small children, particularly infants, were not always recorded.

295 people were resident in the area over the 3-year period. 261 of these were aged 5 years or more at the start of the study. A cohort of 262 individuals had both faecal examinations; thus the longitudinal assessment of infection as defined in terms of egg excretion included 89% (262/295) of the resident population. A subgroup provided data on organomegaly since physical examinations were done only on subjects aged 5 years or more; 210 had stool and physical examinations in 1974 and again in 1977, thus morbidity-infection data were available for 78% (210/261) of the age-eligible population.

To minimise the effect of non-compliance and of concurrent illness subjects who did not attend the examination centre were offered examination at home. The possible influence of non-compliance was also assessed by comparing the 210 persons in the morbidity-infection cohort with the 261 persons eligible to participate: there was little difference in mean age (29·4 versus 29·1 years), sex (40% versus 43% males), or schistosomal infection (initial prevalence 83% versus 85%, initial geometric mean egg counts per g faeces 87·7 versus 88·3). By these criteria the morbidity-infection cohort was representative of the study population.

TABLE I—STABILITY OF *S MANSONI* WORM BURDENS AS ASSESSED BY COMPARING EGG COUNTS IN 1974 AND 1977 FOR 262 PERSONS RESIDING IN CASTRO ALVES

—	Egg count category*	1977			
		Negative	Light	Medium	Heavy
1974	Negative	35	27	1	0
	Light	20	48	21	0
	Medium	2	18	48	12
	Heavy	0	2	11	17

*Egg counts were divided into 4 categories; negative = 0 epg, light = 1–99 epg, medium = 100–499 epg, heavy = ⩾500 epg.

Physical Examination

Subjects were examined in the supine position. Liver size was recorded as the maximum distance (cm) from the costal margin to the edge in the midsternal and midclavicular lines. Consistency (hard or soft) and surface texture (nodular or smooth) were noted. For palpable spleens the size was recorded as the maximum distance (cm) from the costal margin to the edge in the anterior axillary line, and the consistency (hard or soft) was noted. For each subject the liver size was expressed as the average of the measurements in the midclavicular and midsternal lines. For analysis of various groups the mean and standard error of the average liver size and of the spleen size was computed.

Faecal Examination

Specimens were collected as previously described.[7] Those from Castro Alves were examined in duplicate with a modification of the Bell method.[10] Specimens from Riacho de Santana were examined by means of the Kato-Katz method.[10] Results were expressed as schistosome eggs per g faeces (epg). For some analyses the counts obtained in 1974 and in 1977 were averaged.

Statistical Analysis

For statistical analysis the 95% confidence intervals were computed for means by adding and subtracting to each mean 1·96 times the standard error. When confidence intervals did not overlap the means were inferred to differ significantly at the 0·05 probability level.

Results

The Riacho de Santana Population

Eggs of *S mansoni* were found in only 2 of the 291 faecal specimens; both subjects had light infections. 4 of the 309 subjects who had a physical examination had palpable spleens, and in 31 the liver edge was palpable. Livers extended more than 2 cm below the costal margin in either the midclavicular or midsternal lines in only 6% (20/309) of the population examined.

The Castro Alves Population

Prevalence and intensity of infection with S mansoni.—After 3 years 68% (177/262) of the people were still egg positive. The intensity of chronic infections, when divided into light, medium, and heavy categories, remained fairly stable: 64% (113/177) showed no change in egg-output category (table I).

In 13% (35/262) both examinations were negative. In 19% (50/262) only 1 stool was positive and almost invariably such individuals had low egg counts in the positive specimen: 82% (18/22) of subjects with reverting infections (1974 positive, 1977 negative) and 79% (22/28) of those with incident infections (1974 negative, 1977 positive) had egg counts of only 5–25 epg in the single stool that was positive, and in only 3 instances did the count exceed 100 epg.

Hepatic and splenic enlargement.—62% (131/210) of subjects had organomegaly at both examinations (table II). Of those with no initial organomegaly hepatomegaly developed in 61% (22/36), and hepatosplenomegaly developed in 6% (2/36). Of those with a spleen initially palpable, 56% (24/43) had no detectable splenomegaly at the 2nd examination; hepatomegaly spontaneously regressed in 13% (22/174). 83% of the 210 subjects had palpable livers at the 1st examination, 84% at the 2nd examination, and 72% at both; the corresponding prevalences of palpable spleens were 20%, 16%, and 9%, respectively.

The means of the size of livers palpable at both examinations were similar ($p>0\cdot05$) ($3\cdot13\pm0\cdot03$ cm in 1974, $2\cdot95\pm0\cdot12$ cm in 1977). Livers palpable only in 1974 (mean size $1\cdot90\pm0\cdot25$ cm) were significantly smaller ($p<0\cdot05$) than those that were also palpable at the 2nd examination. Livers palpable only in 1977 had a mean size ($2\cdot76\pm0\cdot27$ cm) intermediate between those enlarged at both examinations and those palpable only in 1974.

Most palpable livers were hard (87% in 1974, 85% in 1977); 89% (134/150) of hard livers palpated in 1974 were also palpable 3 years later. Few enlarged livers had a nodular surface (19% in 1974, 14% in 1977), and only 1 of the 24 livers initially palpable in 1977 was nodular. Also, 3 of the 33 nodular livers palpated in 1974 were not palpable in 1977.

Analysis of splenic enlargement with respect to size and consistency indicated no significant difference between the mean size of spleens that were palpable at both examinations ($3\cdot36\pm0\cdot77$ cm), those palpable only in 1974 ($2\cdot29\pm0\cdot54$ cm), or those palpable only in 1977 ($3\cdot78\pm0\cdot77$ cm). The consistency of enlarged spleens was a good predictor of chronic enlargement; 89% (17/19) of spleens palpable at both examinations were hard at initial examination, whereas only 38% (9/24) of spleens palpable only in 1974 were hard. Such a difference, or one more extreme, between the consistency of spleens palpable at both examinations and those palpable at the start of the 3-year period only is highly significant. (Fisher's exact test. $p=0\cdot0006$.) Also, of spleens first palpable in 1977 only 20% (3/15) were hard.

Individuals in whom a palpable liver or spleen developed during the 3 years tended to be younger than those in whom initially palpable livers or spleens regressed. The difference is most striking when older adults (50 years or more) are compared with children (less than 15 years), and is especially noteworthy for splenic enlargement (table III).

Relation between intensity of infection and hepatosplenomegaly.—At all levels of infection the prevalence of hepatomegaly was much higher than the corresponding prevalence of splenomegaly. However, for both organs there was a direct association between development or persistence of organomegaly and the intensity of infection (table IV). Development and persistence of a palpable spleen was much more likely in those with heavy infections (500 or more epg) (table V). In this group the excess risk of persistent splenomegaly was 61·5%.

TABLE II—COMPARISON OF 1974 AND 1977 FINDINGS ON ABDOMINAL EXAMINATION OF 210 RESIDENTS OF CASTRO ALVES, BAHIA, BRAZIL

—	Class*	1977		
		I	II	III
1974	I	12	22	2
	II	18	100	13
	III	4	20	19

*Class I: neither spleen nor liver palpable, class II: liver palpable, spleen impalpable (includes 2 instances when spleen data were not recorded), class III: liver palpable, spleen palpable (includes 3 instances when liver data were not recorded).

TABLE III—DEVELOPMENT OR DISAPPEARANCE OF HEPATIC AND SPLENIC ENLARGEMENT IN YOUNG AND IN OLD RESIDENTS OF CASTRO ALVES OVER A 3-YEAR PERIOD

Development or regression of organomegaly* 1974–1977		Children (<15 yr)† %	Ratio developed /regressed	Adults (≥50 yr)† %	Ratio developed /regressed
Liver	Developed	75 (6/8)‡		64 (7/11)	
	Regressed	6 (4/62)‡	1·50	26 (8/31)	0·88
Spleens	Developed	12 (7/57)‡		6 (2/35)	
	Regressed	45 (5/11)‡	1·40	88 (7/8)	0·29

*For 3 individuals either liver or spleen data were not recorded on 1 examination. This produced a slight difference in cohort sizes for liver and spleen observations. †Based on age at the start of the study. ‡No of people in whom organ palpability changed divided by the number of people in whom that change could have occurred.

TABLE IV—RELATION BETWEEN THE INTENSITY OF SCHISTOSOMAL INFECTION AND THE DEVELOPMENT OR PERSISTENCE OF HEPATIC AND SPLENIC ENLARGEMENT

Development or persistence of organomegaly		Intensity of *S mansoni* infection (average of 1974 and 1977 epg)			
		0	1–99	100–499	≥500
% Development	Livers	40 (2/5)*	65 (13/20)	83 (10/12)	..(0/0)‡
	Spleens	0 (0/16)*	6 (4/72)	10 (6/60)	26 (5/19)
% Persistence	Livers	77 (10/13)†	80 (63/79)	91 (53/58)	100 (23/23)
	Spleens	0 (0/2)†	41 (11/27)	40 (4/10)	100 (4/4)

*No in whom palpable organs developed between 1974 and 1977/no without palpable organ in 1974. †No with organs palpable in both 1974 and 1977/no with an organ palpable in 1974. ‡All of cohort had palpable livers initially, therefore % in whom hepatomegaly developed could not be calculated.

TABLE V—THE RELATIVE AND ATTRIBUTABLE RISK THAT HEAVY *S MANSONI* INFECTION WILL PRODUCE OR SUSTAIN SPLENOMEGALY OVER A 3-YEAR PERIOD IN CASTRO ALVES

Disease category	Persons in category/ no at risk		Risk associated with heavy infection (≥500 epg)	
	<500 epg* a	≥500 epg* b	Relative risk b/a	Attributable risk (b–a) 100
Splenomegaly developing between 1974 and 1977	10/148	5/19	3·9	19·6
Splenomegaly persisting from 1974 to 1977	15/39	4/4	2·6	61·5

*The egg counts of 1974 and 1977 were averaged for each individual.

Discussion

Individual worm burdens in this area of endemic schistosomiasis appear to change slowly, since in most individuals the number of eggs excreted remained stable over the 3-year period. Even in those in whom infections were apparently acquired or spontaneously cured relative stability

of worm burdens was evident because most had low egg counts. Many of the single stool-negative examinations probably resulted from failure to detect eggs in light infections.[10] However, comparison of the age distribution of those who were stool-positive in 1974 only with the age distribution of those stool-positive in 1977 only indicated that an additional factor was operative. Incident infections were characteristic of adolescents (mean age 14·4 years, SEM 4·0, n=28), and spontaneous cures were more common in older individuals (mean age 37·7 years, SEM 5·4, n=22), a significant difference ($p<0·05$).

The control observations in Riacho de Santana indicate that hepatomegaly and splenomegaly are uncommon in the absence of endemic schistosomiasis. In Castro Alves, however, hepatomegaly and splenomegaly were frequently observed, and the rates at which palpable livers and spleens appeared and regressed counterbalanced; consequently the point prevalence of schistosomal hepatomegaly and splenomegaly remained stable. Enlargement of both organs typically followed infection in childhood or adolescence and then regressed in later life, as the intensity of infection fell. The intensity of infection was a key determinant in the evolution, persistence, and regression of hepatic and splenic enlargement. Heavy infection predisposed individuals to chronic hepatosplenomegaly and presumably to the risk of irreversible hepatosplenic schistosomal disease.

In the Castro Alves area we found that community-based treatment of infected individuals with oxamniquine reduced egg excretion considerably for at least 3 years.[8] From that study and from the data presented here the abolition of heavy infections of 500 or more epg by means of chemotherapy would be expected to prevent the development or persistence of splenomegaly over a 3-year period in 3% of the population (6/210). Thus, in Brazil, where some 10–20 million people are infected, if an equivalent intensity of transmission is assumed the national treatment programme should prevent the onset or progression of overt disease in 300 000–600 000 people within 3 years after its completion. Such an estimation is useful because it emphasises that mass chemotherapy should abruptly reduce the substantial number of people at risk of irreversible disease.

The longitudinal, population-based observations reported here reflect 782 person-years of exposure to infection and the consequences of 630 person-years of the evolution of associated morbidity. Our study is important because the advent of safe and effective schistosomicidal drugs will preclude comparable community-based studies in the future.

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PLASMA ATRIAL NATRIURETIC PEPTIDE IN CARDIAC DISEASE AND DURING INFUSION IN HEALTHY VOLUNTEERS

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Summary Plasma concentrations of immunoreactive atrial natriuretic peptide (ANP) were low or undetectable in 8 healthy subjects and 9 control patients without cardiac disease, and raised in 17 patients with congestive heart failure (CHF). Highest concentrations were measured in patients with severe CHF. High plasma ANP levels were also found in 2 patients with paroxysmal supraventricular tachycardia and associated transient polyuria. Infusion of synthetic human α-ANP, 110–125 μg over 30 min, to 3 healthy males resulted in a 2·3-fold increase in natriuresis and diuresis but had no effect on kaliuresis. Plasma levels of renin activity, aldosterone, and antidiuretic hormone did not change significantly. ANP infusion gave plasma ANP levels of the same magnitude as those found in severe CHF; levels returned to baseline within 15 min of stopping the infusion. Thus ANP appears to be a circulating hormone in man, at least in severe CHF and supraventricular tachycardia.

Introduction

MAMMALIAN atria contain peptides with potent diuretic, natriuretic, and vasorelaxing properties.[1–3] These peptides also inhibit the action of various endogenous vasoconstrictors[4] and reduce aldosterone synthesis.[5,6] Such effects suggest a potential hormonal role for atrial natriuretic peptides in the regulation of sodium and volume homoeostasis, and possibly a role in the pathogenesis of heart failure and hypertension.

Several rat and human atrial natriuretic peptides have been purified, sequenced, and synthesised,[1,3,7] and atrial natriuretic factor-like immunoreactive material has been shown to be released into the circulation in response to volume load in the rat.[8] Synthetic human alpha atrial natriuretic peptide (α-ANP) causes natriuresis and diuresis, and decreases blood pressure when injected into healthy volunteers[9] but it is not known whether ANP is released into

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