Sterilisation[3] of *T. cruzi* infections in mice

Drug	Dose[b] mg kg^{-1} day^{-1}	Proportion of mice sterilized with stocks of *T. cruzi*[a]				
		BG	Peru	Ml	Y	Total of all stocks (%)
353C	20	n.d.	n.d.	12/12	9/10	21/22 (95)
	10	24/40	7/11	10/12	11/11	52/64 (81)
	5	n.d.	n.d.	5/11	4/9	9/20 (45)
Nifurtimox	120[c]	1/6	7/11	0/0	4/4	12/21 (57)
	60	n.d.	0/12	n.d.	5/11	5/23 (22)
	30	n.d.	n.d.	2/12	3/10	5/22 (23)
Benznidazole	120	15/16	8/10	11/12	9/12	43/50 (86)
	30	2/16	0/12	1/12	1/11	4/51 (8)

[a] BG, old laboratory strain; Peru, Peruvian human strain; Ml, Argentinian strain; Y, Brazilian human strain. [b] Drug administered for 30 days; sterilization evaluated by haemoculture 30 days after the last dose; control mice all died before the end of the treatment period. [c] Drug related toxicity caused deaths in experiments with stock BG 6/14, Peru 1/12, Ml 12/12 and Y 6/10. n.d., not done.

Drug metabolism studies showed that 353C tartrate was well absorbed after oral administration, and that the primary metabolic step appeared to be demethylation to the corresponding secondary amine; trace amounts of the primary amine were also detected. In mice, significant accumulation of parent drug and metabolites occurred within 5 days when 353C tartrate was administered at 3 or 23 mg kg^{-1} day^{-1} although no cumulation could be demonstrated after 3 once-weekly doses of 50 mg kg^{-1}. Similar results were obtained with daily dosing in rats, dogs, and *Erythrocebus patas* monkeys, indicating that 353C had a relatively long half-life in each of these species. Plasma and whole blood levels were always much lower than tissue levels.

In toxicity studies in rats and beagle dogs, oral doses of 3 or 10 mg kg^{-1} day^{-1} for 30 days produced no haematological, biochemical or histopathological effect, although all the dosed dogs did suffer some loss in weight.

Further studies are in hand to evaluate the full potential of this novel trypanocide which, in contrast to most drugs possessing activity against *T. cruzi*, is not a nitro-heterocyclic derivative.

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Sequence organization in the DNA of three Selachians

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Summary. The DNA interspersion pattern in 3 Selachians *(R. asterias, T. marmorata* and *S. stellaris)* has been studied through the reassociation kinetics of short (0.3 Kb) and long (2.5 Kb) DNA fragments. Preliminary results show that most of the DNA (approximately 80%) of these organisms is arranged according to a short-period interspersion pattern. A notable resemblance to the pattern previously described in the teleostean *Salmo trutta* has been observed.

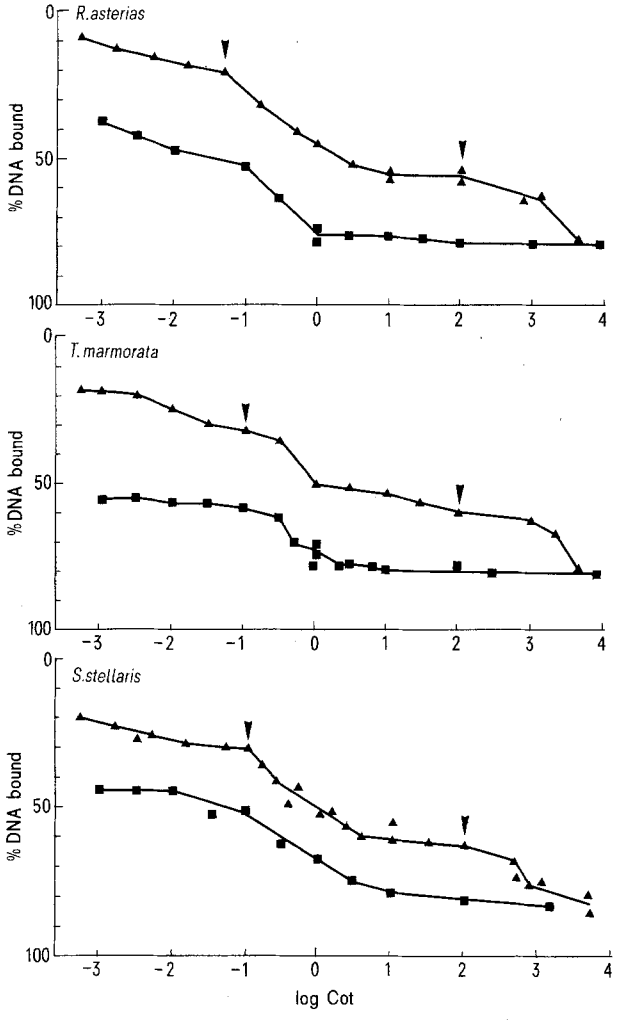
It has been observed that the 'original' vertebrate DNA interspersion pattern is Xenopus-like. In fact, a similar pattern has been found also in Amphioxus and, though sometimes with some variations, in almost all the classes of vertebrates as well[1] except the birds[2,3]. As for the fishes, thus far only the genome organization of a teleostean, *Salmo trutta*[4], has been studied. Therefore, we have deemed it interesting to undertake a study on the DNA interspersion pattern of the Selachians, which are among the most primitive vertebrates. Their DNA values are much higher than those of trout and are among the highest so far found in the subphylum[5,6]. This study will give further information on the evolutionary trend followed by the genome organization in vertebrates and, in particular, in fish.

Material and methods. DNA renaturation kinetics of short (0.3 Kb) and long (2.5 Kb) DNA fragments has been studied in 3 Selachians: *Raja asterias, Torpedo marmorata* (Batoidea) and *Scyliorhinus stellaris* (Galeomorphii). The specimens were kindly supplied to us by the Zoological Station of Naples.

DNA was extracted from blood, liver and testis cells of 1 or 2 samples per species using Marmur's technique[7] partially modified by the addition of several enzymatic digestions and phenol deproteinization[8]. DNA was fragmented by sonication with a Branson sonifier B 12 cell-disruptor. Fragment lengths were examined by agarose gel electrophoresis according to Elsevier et al.[9], using as standard lambda DNA digested with ECO R_1 and HIND III[10].

The reassociation kinetics of 0.3 Kb DNA fragments was carried out by the optical method for Cot-values from 0.5×10^{-3} to 3×10^{-1} and by hydroxyapatite chromatography for Cot-values from 1×10^{-1} to 1×10^{4}. The reassociation kinetics of 2.5 Kb fragments was performed by HAP chromatography. Reassociation kinetics by the optical method was performed by Britten et al.[11]. HAP chromatography was performed according to the batch method[12]. *E. coli* DNA, used as reference, had a $Cot_{0.5}$ value of 5.75 msec and a rate of 0.174 M^{-1} sec^{-1}. For further technical details see also Olmo et al.[13].

Results and discussion. The reassociation curves of short (0.3 Kb) and long (2.5 Kb) DNA fragments of the 3 species assayed are represented in the figure.



DNA reassociation of 3 selachian species on short (upper curves, triangles) and long (lower curves, squares) fragments. Abscissa: Log Cot; Ordinate: percent of DNA bound to hydroxyapatite. Arrows mark the segments of the curves that have been taken to compute the values given in the table.

Relative amounts (percent of total DNA) of the various DNA fractions as a result of the reassociation of short and long DNA fragments of the species assayed

Species	DNA fraction	Fragment lengths 0.3 Kb	2.5 Kb
R. asterias	Highly rep.	20	50
	Middle rep.	34.5	26
	Slow comp.	45.5	24
T. marmorata	Highly rep.	31	59
	Middle rep.	27.5	19.5
	Slow comp.	41.5	21.5
S. stellaris	Highly rep.	29.5	52
	Middle rep.	32	27
	Slow comp.	38.5	21

The reassociation kinetics of short fragments shows that the DNA of the 3 Selachians consists of a highly repetitive fraction, part of which renatures faster than Cot 0.5×10^{-3} and probably contains palindromic sequences; a middle repetitive fraction, and a slowly reassociating one. These fractions are present approximately in the same percentage in the 3 species, though *T. marmorata* and *S. stellaris* have a genome size double that of *R. asterias*. This suggests that the genome of *T. marmorata* and *S. stellaris* is polyploid if compared with that of the ray (for a more detailed study on the subject see Olmo et al.[14]).

The reassociation kinetics of long fragments shows a remarkable increase (approximately 30%) in the highly repetitive and foldback sequences; a decrease ranging from 5 to 8% in the middle repetitive fraction and 20% in the slow one.

The results show that in the Selachians examined DNA is arranged, at least by 80%, according to a short-period interspersion pattern. The marked increase in the highly repetitive fraction and the corresponding decrease in the other 2 fractions suggest that most of both single-copy (at least 50%) and middle repetitive sequences are interspersed with short sequences of highly repetitive and foldback DNA. Anyhow, one cannot exclude the possibility that single-copy sequences are interspersed with the middle repetitive ones, which, in their turn, would be interspersed with the highly repetitive and foldback ones; or that 2 different patterns coexist.

For the comparative standpoint it is interesting to note that the results obtained in Selachians are similar to those obtained by Serra and Mandarino[4] in trout. In fact, in this teleost too, with increasing DNA fragment lenghts a remarkable increase in more highly repetitive fractions and a decrease in middle repetitive and single-copy DNAs are observed. On the contrary, in other groups of vertebrates the most remarkable increase is observed in the middle repetitive DNA, whereas the highly repetitive and foldback ones do not vary, or increase slightly[3,13,15–17]. From this one can speculate that, though there are great differences in the DNA content, fish have preserved a common interspersion pattern, which would have undergone few variations in the course of evolution. This pattern is similar, except for some variants, to the Xenopus-like one found so far in most vertebrates.

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