

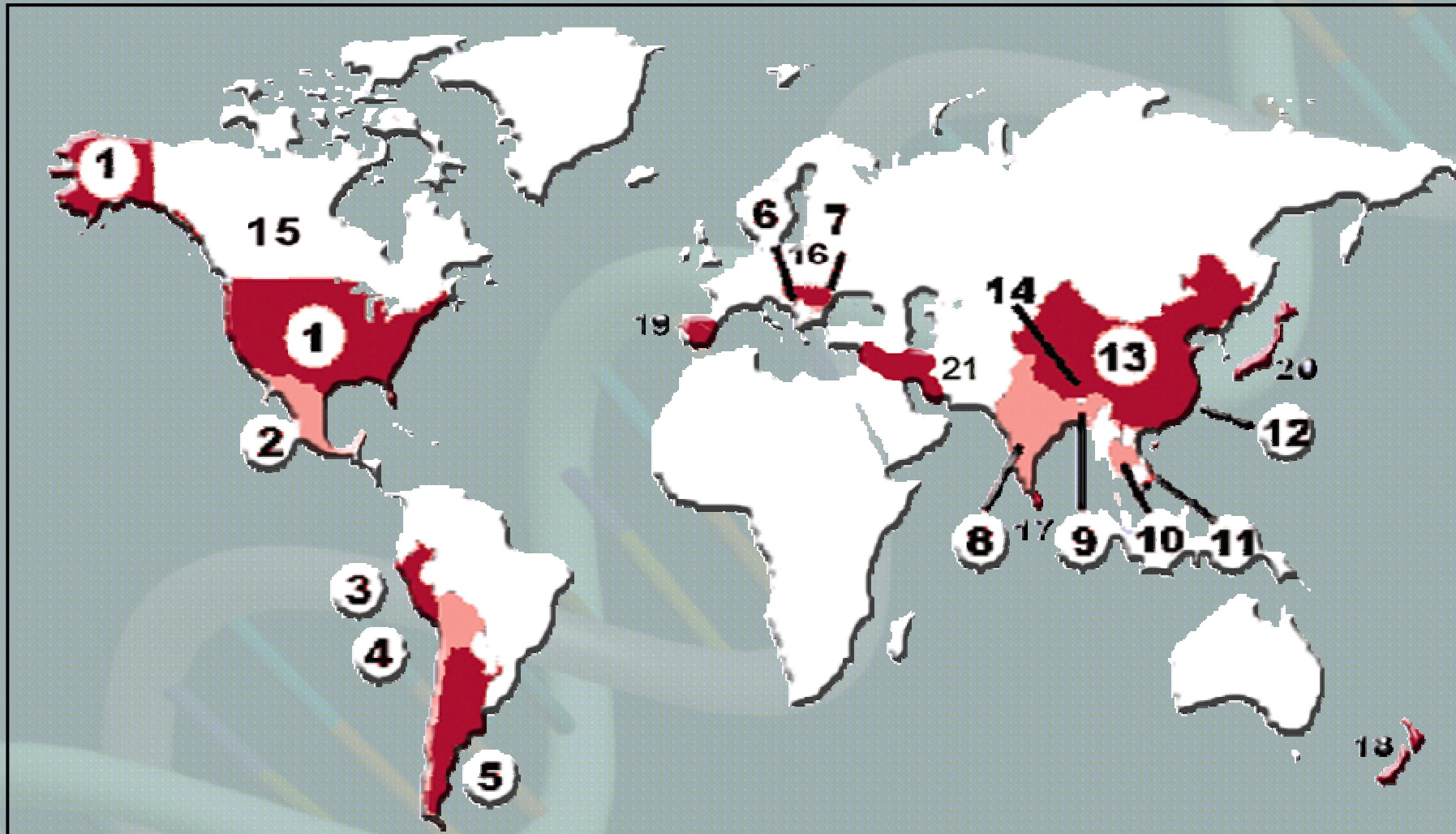
The background of the slide is a faded, light blue image showing a pair of hands holding a large puzzle. The puzzle pieces are in various colors, including yellow, blue, and red. The hands are positioned as if they are about to place a piece into the puzzle, symbolizing the process of solving a complex problem or 'unscrambling' a puzzle.

**CYTOGENETIC AND GENETIC POLYMORPHISM STUDIES FURNISH CLUES
TO UNSCRAMBLE THE PUZZLE OF ARSENIC SUSCEPTIBILITY**

Mayukh Banerjee

**School of Earth, Atmospheric and Environmental Sciences, University of Manchester
Molecular and Human Genetics Division, Indian Institute of Chemical Biology**

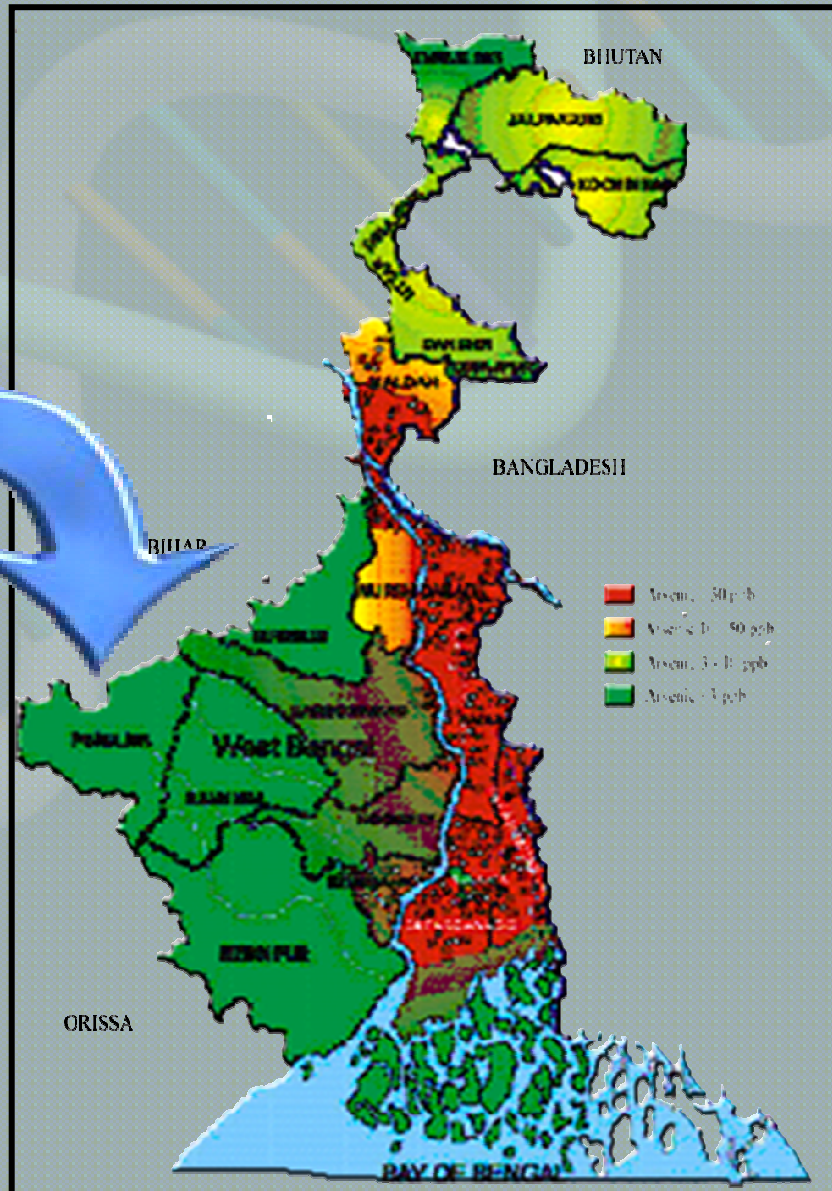
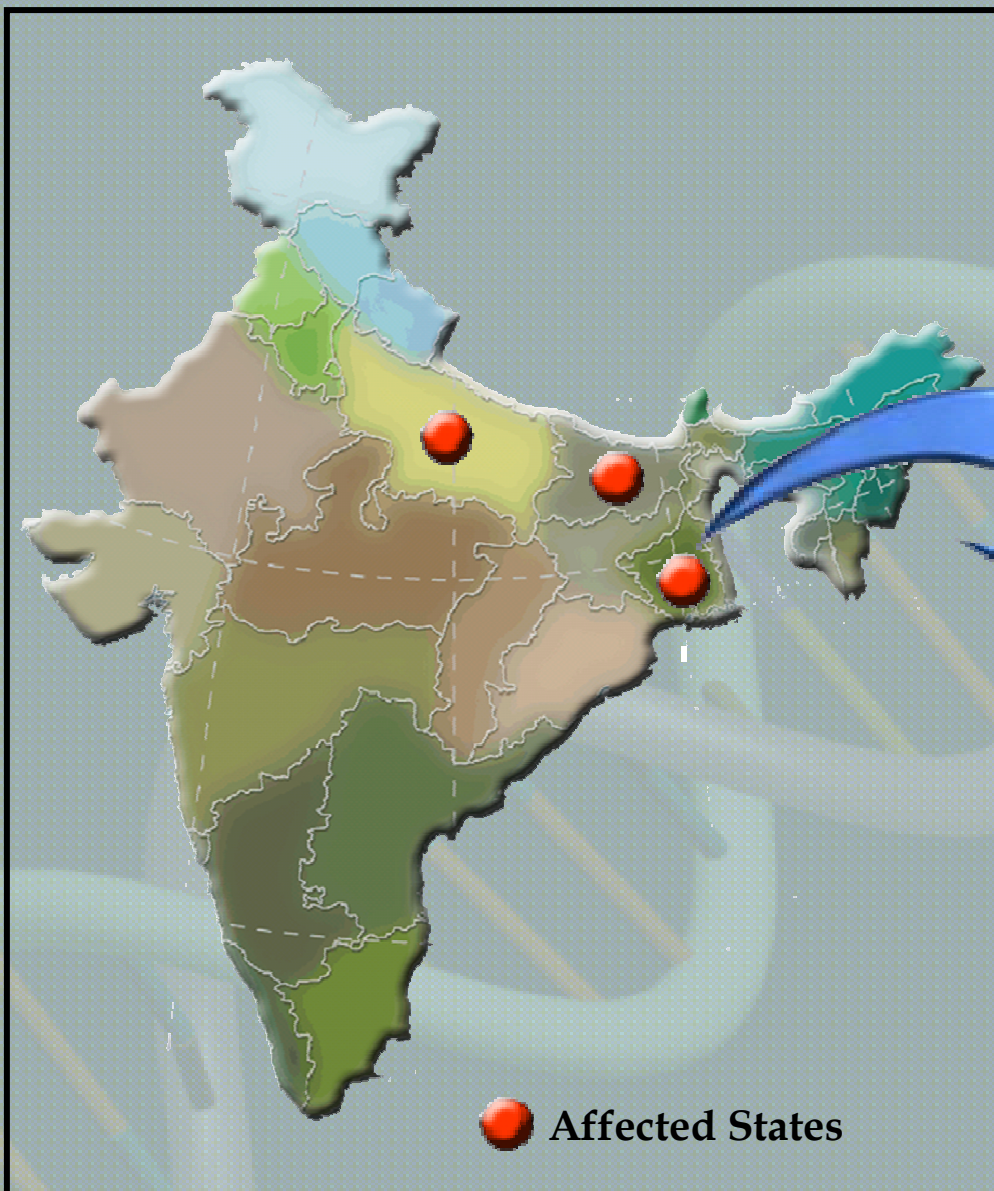
Arsenic: A Global Scourge



World map showing countries affected by arsenic contamination in groundwater

1. USA, 2. Mexico, 3. Chile, 4. Bolivia, 5. Argentina, 6. Hungary, 7. Romania, 8. India, 9. Bangladesh, 10. Thailand, 11. Vietnam, 12. Taiwan, 13. China, 14. Nepal, 15. Canada, 16. Poland, 17. Sri Lanka, 18. New Zealand, 19. Spain, 20. Japan, 21. Iran.

Arsenic Poisoning in West Bengal: Greatest Arsenic Calamity



Arsenic: Leaving Permanent Marks on the Skin



Hyperpigmentation



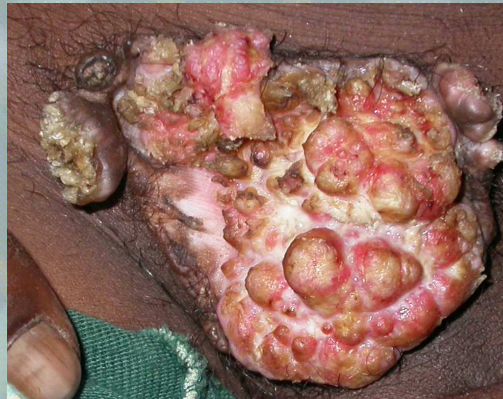
Raindrop Pigmentation



Palmar Hyperkeratosis



Planter Hyperkeratosis



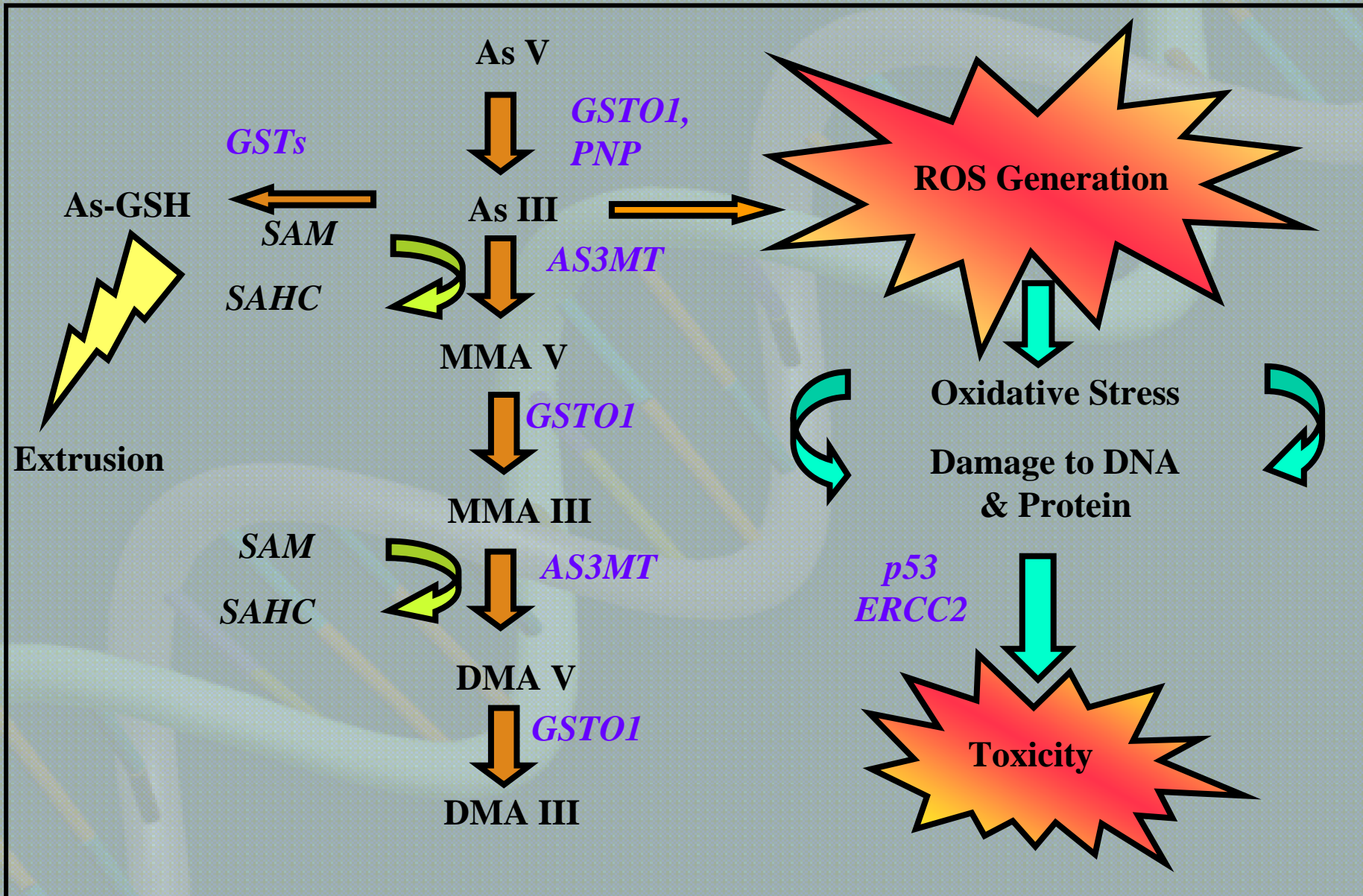
Squamous Cell Carcinoma



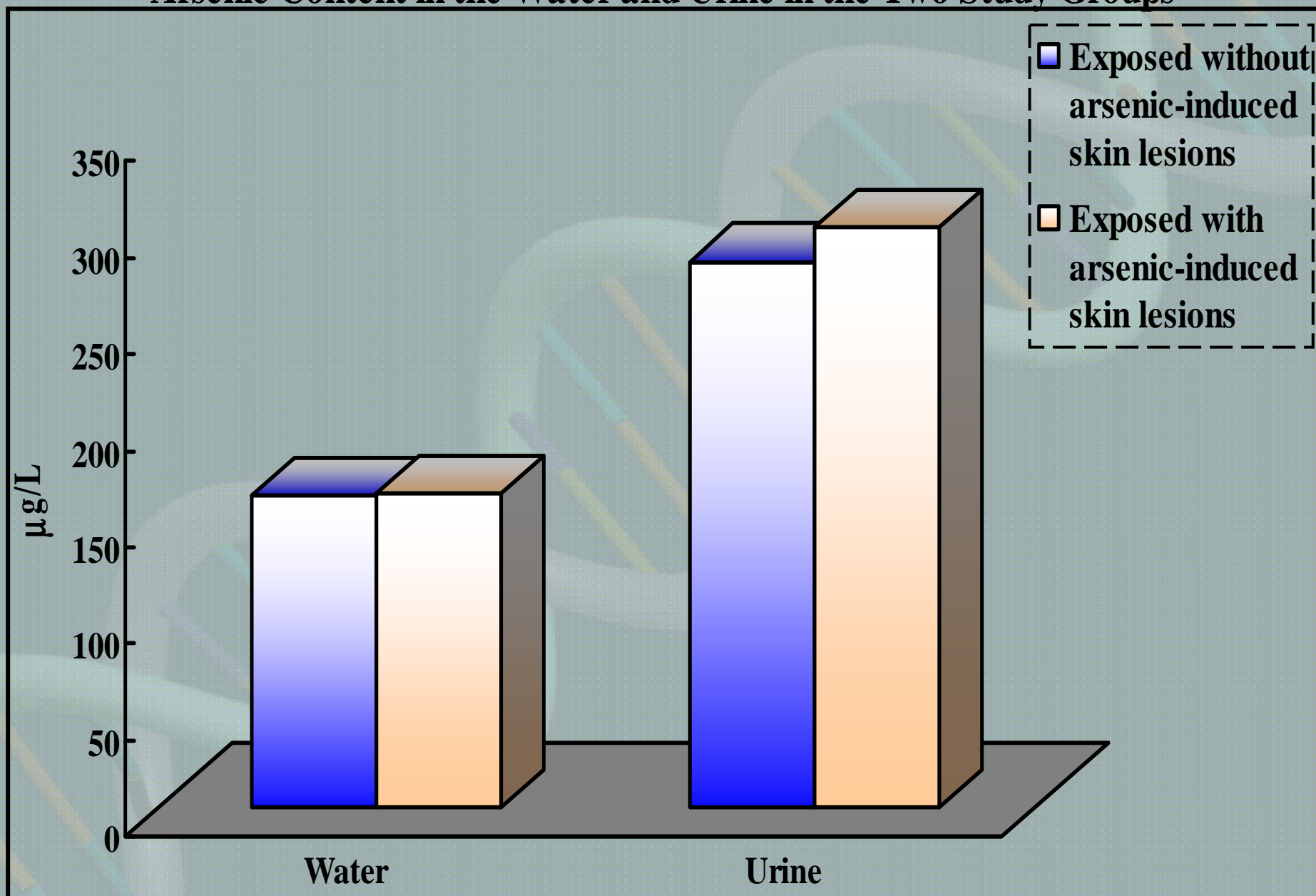
Arsenic: The True Picture

- ▶ 137 million people in more than 70 countries are probably affected by arsenic poisoning of drinking water.
- ▶ In West Bengal, India, 9 of the 18 districts have arsenic contaminated groundwater.
- ▶ 42.7 million people are exposed to this environmental toxicant in West Bengal alone.
- ▶ Studies show that only 15 - 20% of the exposed individuals ultimately develop arsenic-induced skin lesions, which are considered to be the hallmarks of arsenicosis.
- ▶ This observation led to the hypothesis that some individuals must be more prone to develop arsenic-induced skin lesions than the others.
- ▶ In order to find out what factors might be responsible for arsenic susceptibility, we employed cytogenetic and molecular genetic techniques.

Arsenic Metabolism Pathway: The Candidate Genes



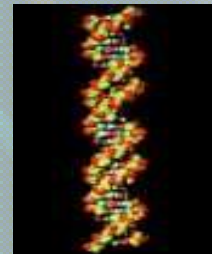
Arsenic Content in the Water and Urine in the Two Study Groups



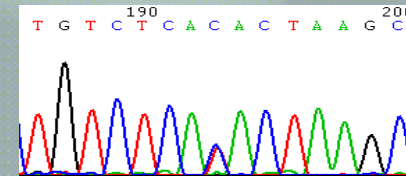
Genotyping Strategies



Blood



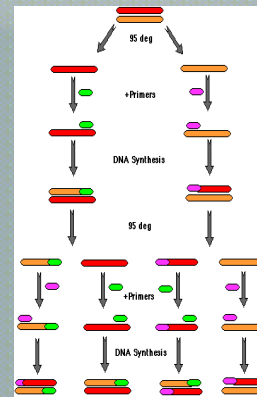
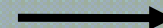
Genomic DNA



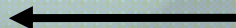
Chromatogram



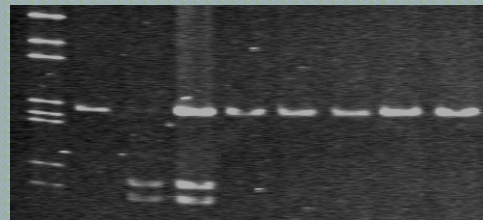
Sequencing



PCR



RFLP



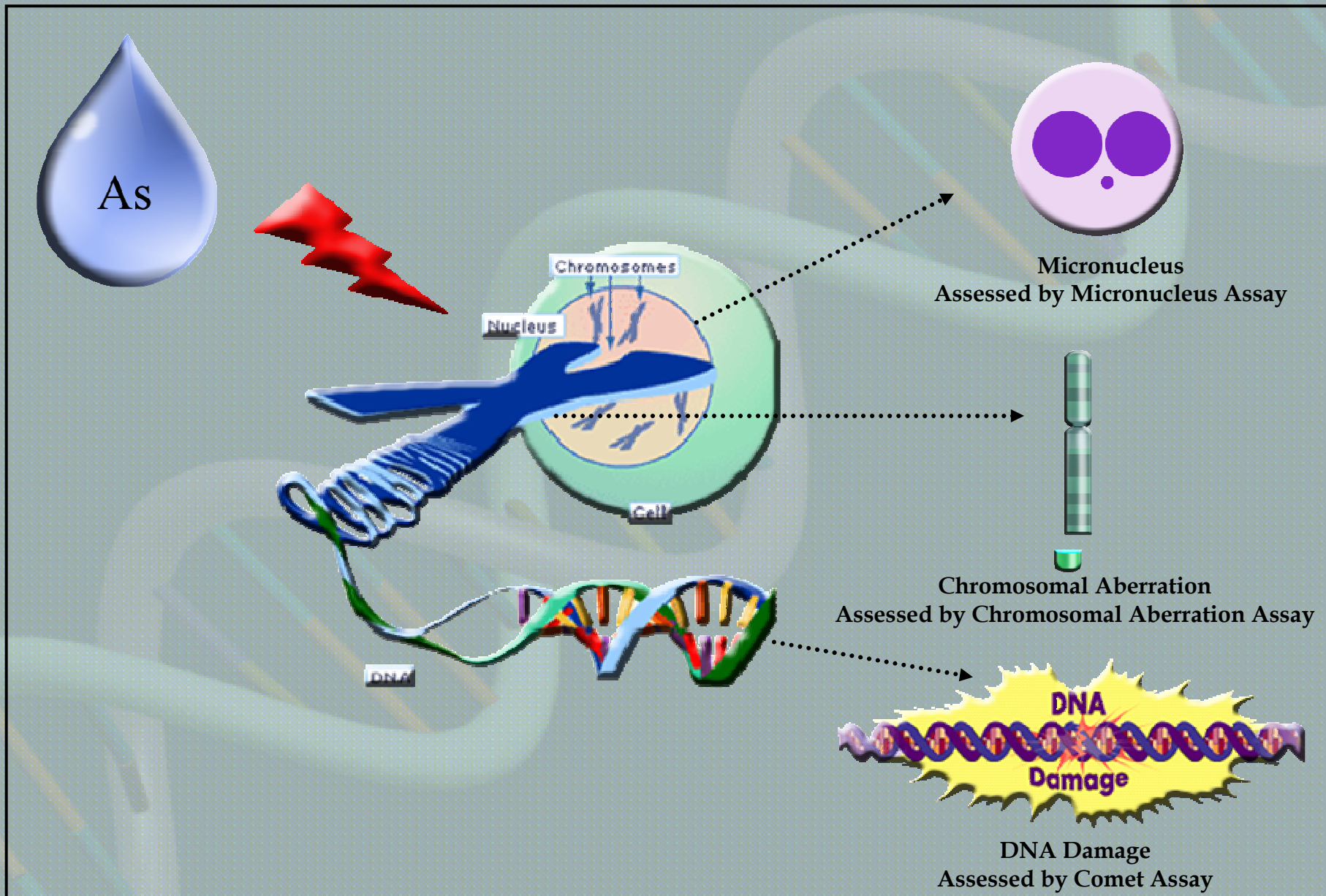
Gel Electrophoresis



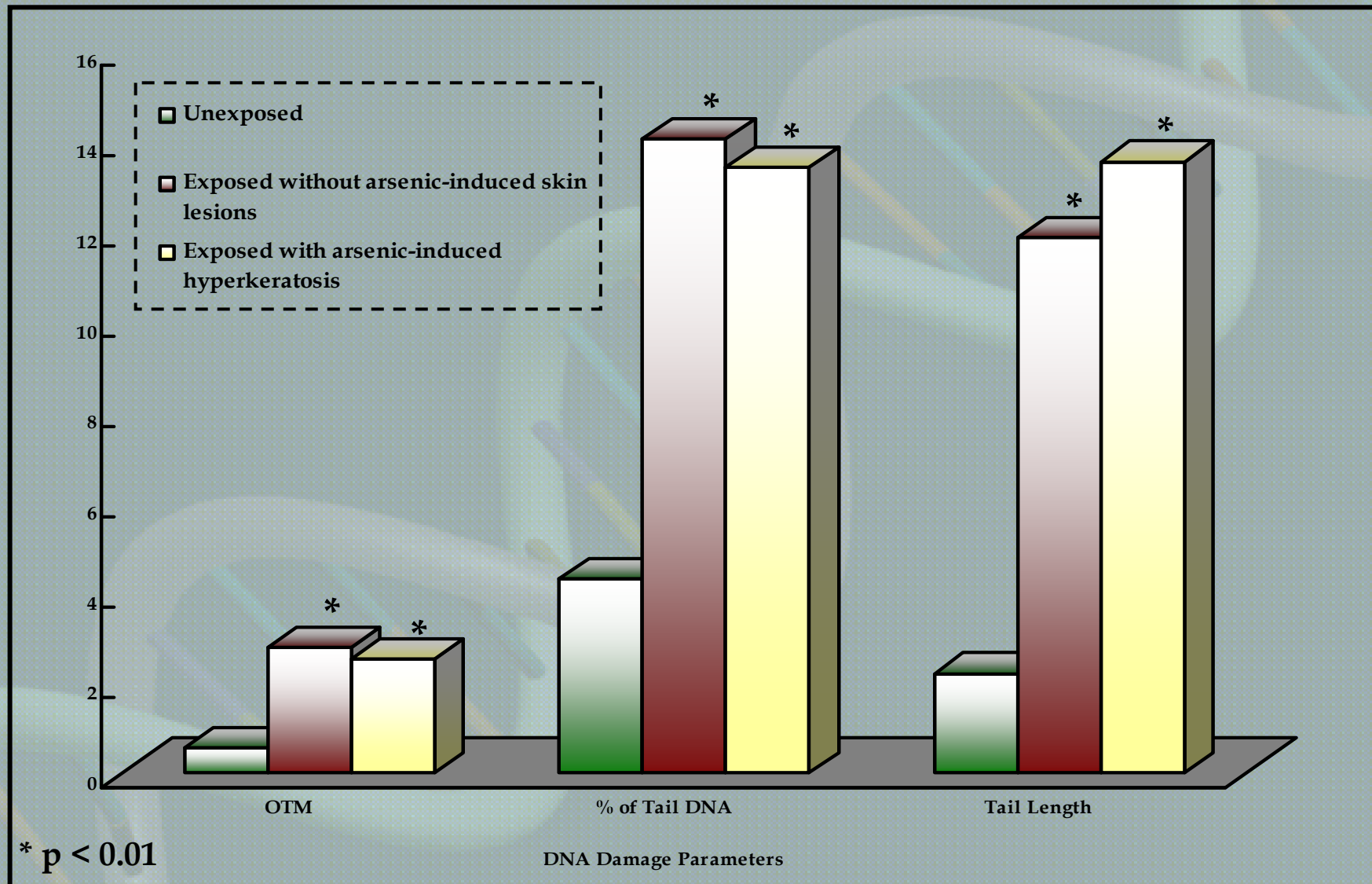
Results

Gene	Variant	Risk Genotype	OR (95% CI)
p53	Pro72Arg (G>C)	Arg/Arg	2.02 (1.28 – 3.15)
ERCC2	Lys751Gln (A>C)	Lys/Lys	4.77 (2.75 – 8.23)
PNP	His20His (C>T)	C/T + T/T	1.69 (1.08 – 2.66)
	Gly51Ser (G>A)	Gly/Ser + Ser/Ser	1.66 (1.04 – 2.64)
	Pro57Pro (C>T)	C/T + T/T	1.67 (1.05 – 2.66)
GST M1	Positive or Null	Positive	1.73 (1.24 – 2.22)

Biomarkers to Detect Arsenic Induced Genetic Damage

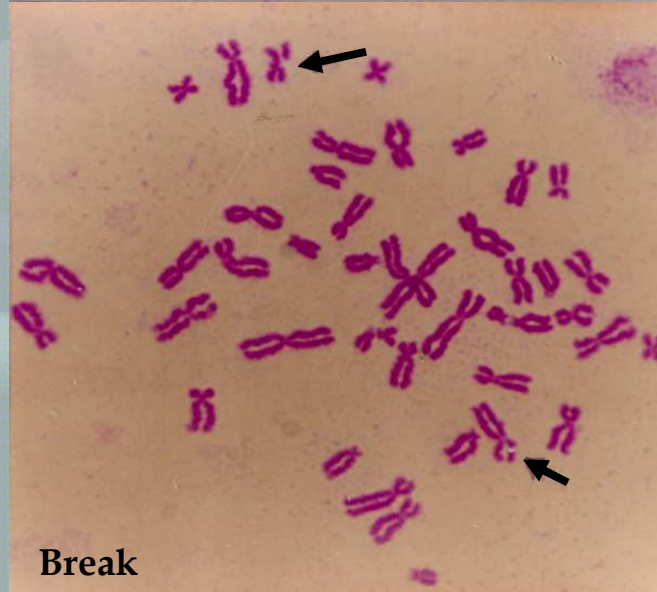


Comet Assay Measures DNA Damage at Single Cell Level

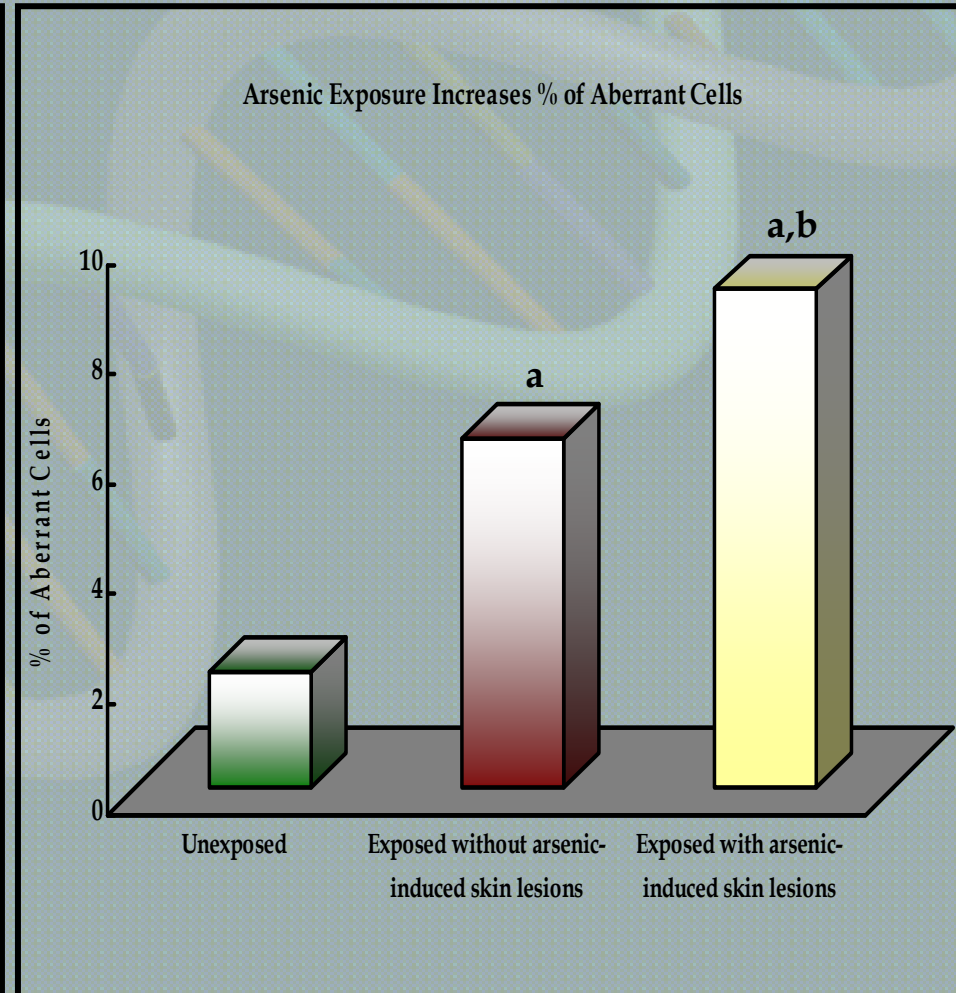
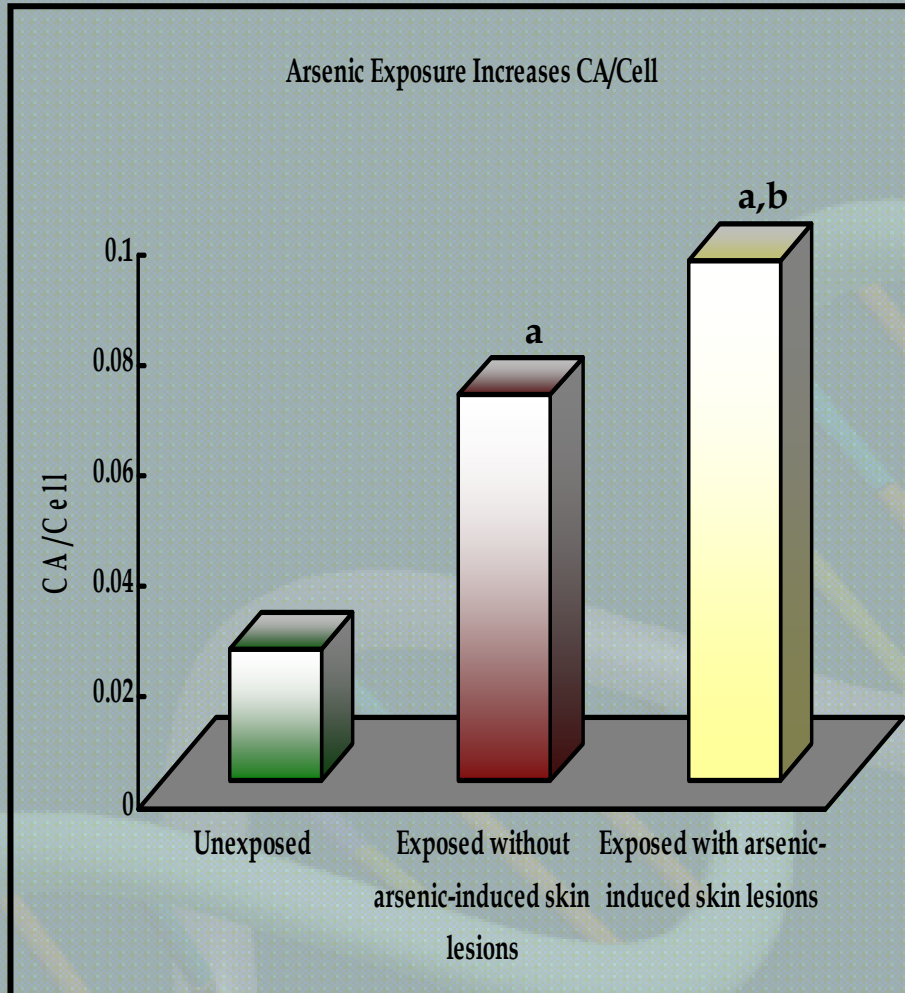


Int. J. Cancer (2008) 123:283-287.

Chromosomal Aberrations (CA) in the Lymphocytes



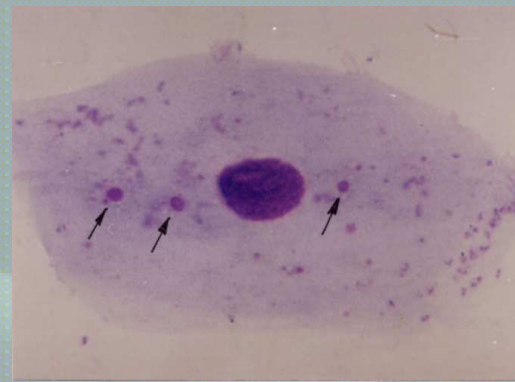
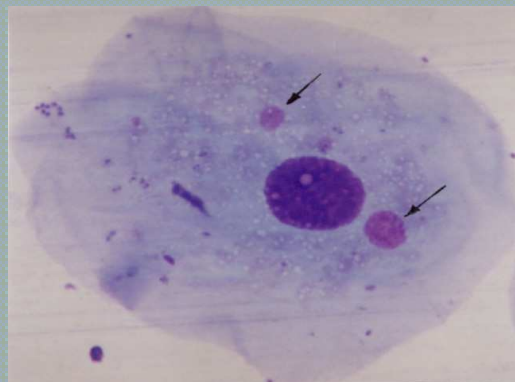
CA is a Good Biomarker for Evaluating Arsenic-Induced Genetic Damage



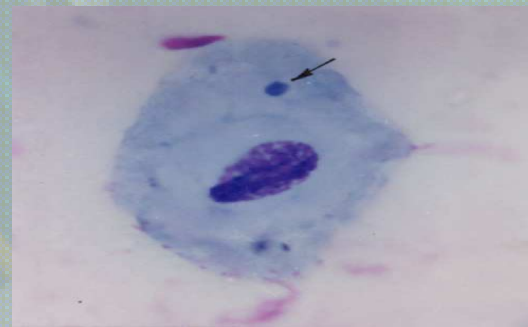
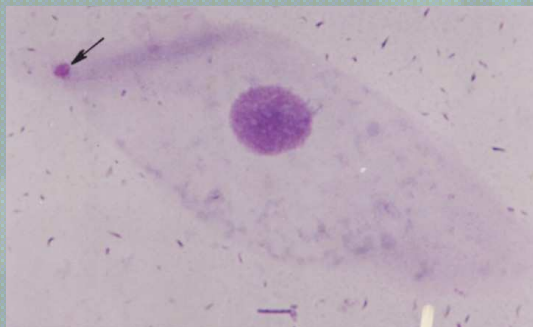
^a $p < 0.01$, when compared to unexposed group

^b $p < 0.01$, when compared to exposed group without arsenic-induced skin lesion

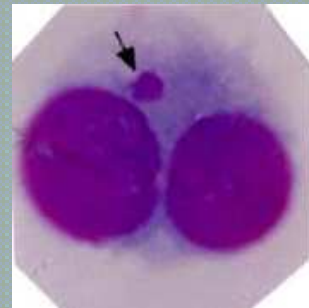
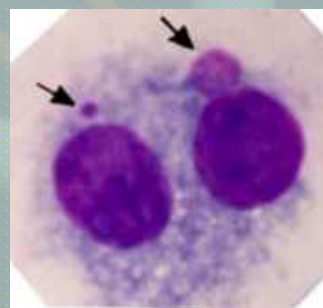
Micronuclei in the Three Cell Types Studied



Micronuclei in Oral Mucosa Cells

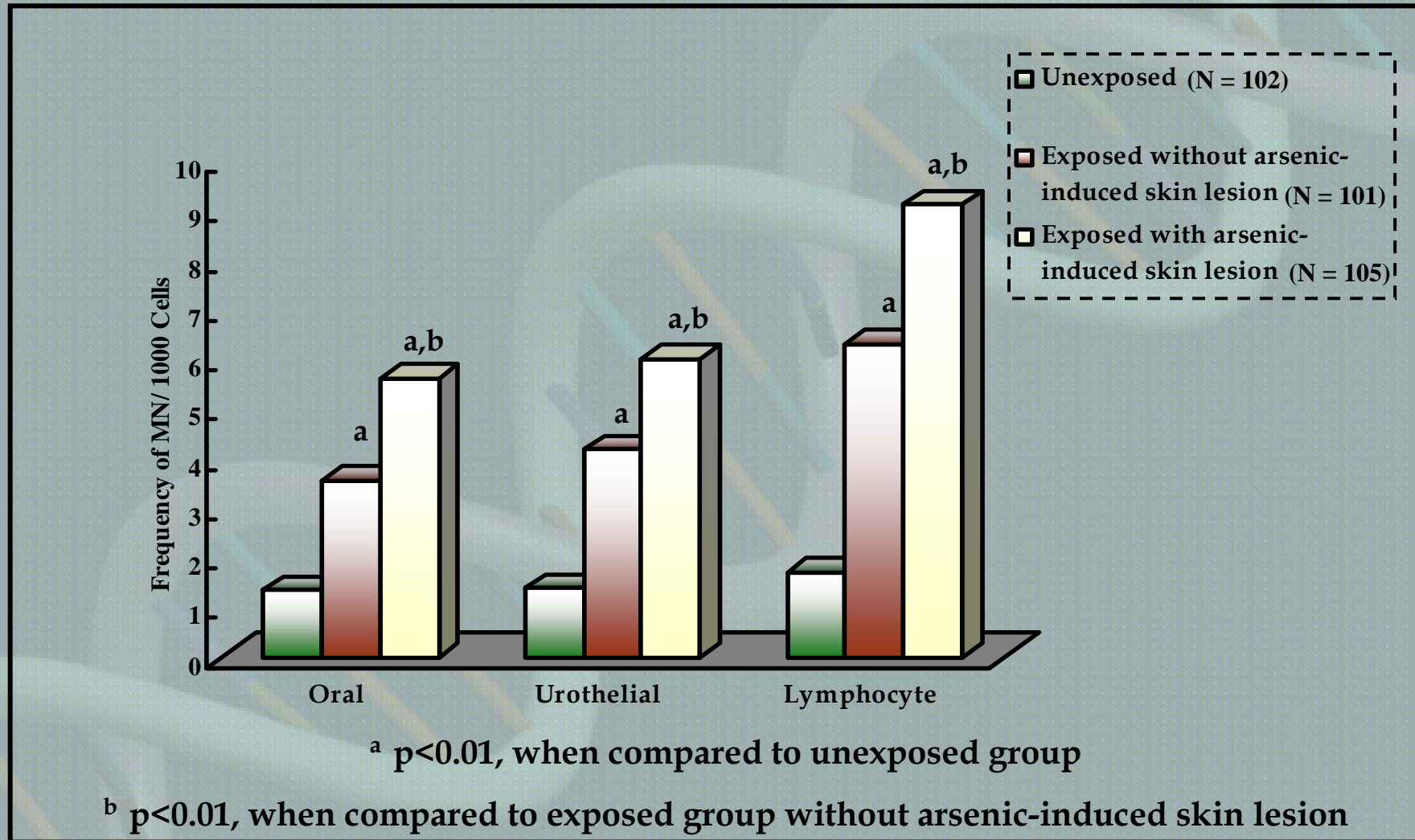


Micronuclei in Urothelial Cells



Micronuclei in Lymphocytes

Arsenic-Induced Genetic Damage can be Quantified by Micronucleus Assay



Conclusions

- Genetic polymorphisms emerge as one of the prime factors for rendering a person susceptible to develop arsenic-induced skin lesions.
- Several other polymorphisms might also be implicated in this process.
- The future lies in finding out how exactly these polymorphisms bring about arsenic susceptibility at the mechanistic level.
- Comet Assay shows that arsenic induces considerable amount of DNA damage in the exposed individuals and the basal level of DNA damage caused by arsenic is similar in the exposed population irrespective of the presence of skin lesions.
- Cytogenetic data taken together imply that arsenic exposed individuals without skin lesions are not safe, but are at considerable risk, contrary to the common belief.



PRAMA: The Future

Probabilistic Risk Assessment Modelling for Mitigation of Arsenic in Groundwaters in West Bengal (PRAMA) is a two year project co-funded by The British Council and is coordinated by the University of Manchester with the Indian Institute of Chemical Biology, Kolkata, India. The main aims of this project are:

- To review data on dose-response relationships for arsenic-attributable health outcomes. The genetic polymorphism studies reported here may contribute significantly to better defining dose-response control relationships.
- To find out the relative contribution of different routes of arsenic exposure towards the total arsenic burden in exposed individuals.
- To develop a probabilistic risk assessment model for human health outcomes arising from exposure – via whatever route – to groundwater arsenic.
- The ultimate goal is to identify at-risk groups and to inform those responsible for implementing a range of mitigation policies.

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THANK YOU