but one deteriorated during the 2–8 month follow-up period, usually within two weeks.

Their stools were analyzed before and after treatment, those from four patients undergoing 27 different types of culture for comparison with previously published data from adult controls. This analysis is not yet finished, but the team has already discovered a potentially interesting absence of anaerobic cocci.

Future studies

'Seeing most of these children apparently improve significantly was very exciting', says Sandler, but he cautioned that the work needs to be repeated by others. The mechanism behind the benefit from vancomycin is not known, but it might be related to the temporary elimination of a neurotoxin-producing bacterial pathogen. Clostridial species are thought to be the most likely bacterial agents[1,5]. 'The next step is to go back to the lab and try and find out why these effects may have been observed,' says Sandler. According to Bolte, 'careful analysis of the stool specimens would provide valuable information, but this is very time consuming, and research progress has been severely hampered by a lack of financial support'.

The authors emphasize that vancomycin, chosen because it is poorly absorbed in the gut, should not be used lightly because of the public health implications of any increase in resistance to it. However, says Bolte, 'We are, cautiously, very optimistic that the gut flora approach of antimicrobial treatment and probiotic therapy will eventually provide meaningful treatment for a subset of children with autism.'

According to Dr Bernard Rimland, Director of the Autism Research Institute (San Diego, CA, USA), the study merits attention 'as it casts light on both the cause and treatment of a large subset of autism.' However, he too is concerned about the use of vancomycin. 'A preferable approach would be to use substances known to enhance the immune system, such as certain vitamins, minerals and essential fatty acids. This would, hopefully, control the autism-causing pathogens without contributing to antibiotic resistance.'

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Jo Whelan

A new role for old weed killer

A range of compounds currently used as herbicides (the s-triazines) have been found to be possible future treatments for malaria, say scientists at Biomes (Pelham, MA, USA). This research examining the possibility of using chloroplast-specific poisons as antimalarial drugs was prompted by findings that a cellular organelle in the malaria parasite – the apicoplast – was genetically very similar to the chloroplast[1]. The function of the apicoplast is unknown but, explains Miles Hacker (President, Biomes), 'We reasoned that if the parasite has maintained this organelle all this time then it must provide some benefit. We further reasoned that it could be the Achilles heel of the parasite and a parasite-specific target.' They finally focused their attention on a group of chloroplast-specific herbicides that have been in use for over 30 years, the s-triazines.

Why the s-triazines?

Hacker explains that the s-triazines were selected for a number of reasons, 'They are safe and have LD_{50} values on a par with table salt, they have been in use for decades, and there is plenty of animal toxicology and pharmacokinetic data available, so clinical development time should be significantly decreased. Furthermore, excellent synthetic pathways for large scale production have already been developed and they are amazingly inexpensive.'

The s-triazines are cyclic structures in which the ring contains alternating carbon and nitrogen atoms. They kill plants by blocking photolysis-induced electron transport in chloroplasts[2]. The addition of a chlorine group increases both antimalarial efficacy and potency. Of the chloro-s-triazines studied by Hacker's team, atrazine (Fig. 1), propazine and simazine all exhibit antimalarial activity and, he says, 'They are as effective and potent *in vitro* as chloroquine, the gold standard for antimalarial drugs.'

The researchers found that atrazine, Biomes' lead compound, was also effective against multi-drug-resistant strains of the malaria parasite, *Plasmodium falciparum*, and the parasite has so far shown no signs of developing cross-resistance. 'We feel that there is no reason to think that the parasite will not become resistant to atrazine. New antimalarial drugs have a finite period of efficacy. Nevertheless, our hope is that the new drugs will provide benefit until a safe and effective vaccine is finally developed. Better use

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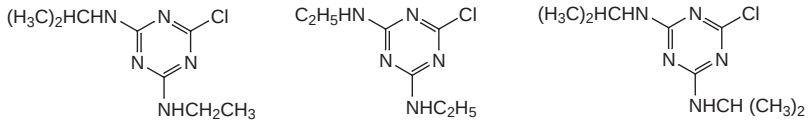

Figure 1. *Molecular structures of atrazine, simazine and propazine, chloro-s-triazine herbicides, the former currently in development as an antimalarial drug.*

of antimalarial drugs and the use of combination chemotherapy will also slow the rate of resistance development,' says Hacker.

Mechanism

The team is currently working hard to explain the mechanism of action of atrazine and related compounds against the malaria parasite. They also hope that their studies will shed light on the role of the apicoplast itself.

Antimalarial drugs with triazine nuclei, such as proguanine, are already in clinical use and they act by inhibiting parasitic dihydrofolate reductase (DHFR), thus preventing the formation of tetrahydrofolates and limiting DNA synthesis[3]. However, atrazine does not affect either mammalian or microbial DHFR *in vitro*, nor does it affect the activity of yeast transfected with malarial DHFR, which requires functional malarial DHFR to grow. 'While pyrimethamine and cycloguanil, both malarial antifolates, inhibit yeast growth in this assay, neither the triazines nor chloroquine affect growth, demonstrating that atrazine is not another triazine antifolate,' explains Hacker.

In vitro, Hacker's group has shown that atrazine also acts in synergy with chloroquine and, *in vivo*, it appears to be as effective as chloroquine against *Plasmodium berghei*. Hacker says, 'Our data clearly demonstrate the efficacy of atrazine and suggest a novel mechanism of action for the drug. The latter is extremely important as it indicates that atrazine will be useful in parasites resistant to currently used medications.'

Safety

Commenting on the safety of atrazine, Hackers says: 'We are testing other triazines to see if we can find a more effective molecule and, perhaps, a less toxic one. However, it is unlikely that we will find a safer drug than atrazine with such significant antimalarial activity.'

Future research

Hacker and his team now hope to work with other pharmaceutical companies to develop atrazine as an antimalarial drug. If they can find a suitable collaborator, they hope to begin clinical trials within two years. In the meantime, they are continuing their basic research into the mechanism of action of the triazines. 'At present, we are concentrating all our efforts on the malaria parasite, but we feel that there may well be a much larger spectrum of antiparasitic activity, given that there are a number of parasites in the apicomplexan family. This family includes several parasites of human and veterinary importance, such as *Toxoplasmodia*, *Cryptosporidia*, *Emeria* and *Babesia*,' says Hacker. 'We hope to form collaborations with other groups working with such parasites to assess the spectrum of activity of the triazines in treating apicomplexan diseases,' he concludes.

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Sharon Dorrell

News in brief

Potential for improved pig-to-human xenotransplantation success rate

Research funded by ML Laboratories PLC (London, UK) has shown that the rejection of foreign cells by a host's immune system can be prevented by donor-specific costimulatory blockade[1]. Robert Lechler and colleagues investigated mice transplanted with pig pancreatic xenografts, and reported that these mice showed a significant increase in survival time after immunization to induce an antibody blocking response. This research might consequently eliminate the current need for long-term immunosuppression following transplantation.

Robert Lechler, Head of the Immunology team at Hammersmith Hospital (London, UK), said 'Our first models using cells from the pancreas have been successful and we are now taking these findings on to further,

 1359-6446/00/$ – see front matter PII: S1359-6446(00)01588-9