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# A CULTURE IN THE BALANCE

Traditional Chinese medicine and Western science face almost irreconcilable differences. Can systems biology bring them together? **Jane Qiu** reports.

Liu Wen-long's modest Beijing practice looks no different from most clinics. But he is no ordinary doctor. Liu never orders lab tests, nor does he prescribe high-tech imaging diagnostics. He relies on simple observations, checking a patient's pulse, complexion and odour, and asking about habits and medical history. At 69 years old, he has been practising traditional Chinese medicine for 43 years and he is resolute about its benefits. "People keep coming back because it cures them and improves their well-being," he says.

Indeed, patients trickle in to see Liu all morning for conditions ranging from allergies to lung cancer. Some are nervous first-timers, others are regulars, confident in what traditional Chinese medicine has to offer. Ms Huang, an accountant from the outskirts of Beijing, is delighted that her migraines, which haunted her for years, disappeared after three herbal regimens. "I used to live on painkillers and felt tired all the time," she says. "I am now a totally different person."

In a country that is fiercely embracing modernity, clinics such as Liu's, which have been operating the same way for thousands of years, seem vulnerable and out of place. Indeed, attitudes on traditional Chinese medicine have divided the country. Last year, Zhang Gong-yao, from the Central South University in Changsha, Hunan, published an article in a Chinese journal calling traditional Chinese medicine a pseudoscience that should be banished from public healthcare and research[1]. The article caused uproar in the country, and earlier this year the government announced an ambitious plan to modernize the millennia-old practice[2].

But should such a formidable gap be bridged? Modern Western medicine generally prescribes treatments for specific diseases, often on the basis of their physiological cause. Traditional Chinese medicine, however, focuses on symptoms, and uses plant and animal products, minerals, acupuncture and moxibustion — the burning of the mugwort herb (*Artemisia vulgaris*) on or near the skin. But whether these methods are effective and, if they are, how they work remain a source of some derision. The greatest divide is in the testing. In the West, researchers test a drug's safety and efficacy in randomized, controlled trials. Traditional Chinese treatments are mixtures of ingredients, concocted on the spot on the basis of a patient's symptoms and characteristics and using theories passed down through generations.

The mainstream medical community, in China and abroad, has been highly critical of the underlying theories. Traditional Chinese medicine is based on ideas such as *qi* (meridian), in which illness is caused by blocked energy channels; *yin* and *yang*, which emphasizes the balance of energy; and *wuxing* (five elements), in which people's organs and health status are categorized according to their 'elemental characteristics': fire, wood, water, earth and metal.

Pharmaceutical companies have become more interested in traditional Chinese

medicines over the past decade. But their approach has been characteristically Western: isolate the active ingredients and test them one at a time. This reductionist approach has led to the approval of drugs such as artemisinin for malaria, which is used to treat fever in traditional Chinese medicine, and arsenic trioxide, which has been carried over from Chinese medicine for treatment of acute promyelocytic leukaemia.

But identifying the active ingredients isn't easy. Most remedies in traditional Chinese medicine, as it turns out, are compound formulae — or *fufang* — that contain as many as 50 species of herbs, and thousands of chemicals therein (see 'Knowledge mining'). To tap into the deeper well of traditional Chinese treatments, researchers think they may need to look at how the mixtures of ingredients act in concert.

## Relaxed regulation

The criteria for approval of herbal mixtures as medicines are now starting to relax, at least in the United States. In June 2004, the US Food and Drug Administration (FDA) issued new guidelines that permit the approval of herbal mixtures if they can be shown to be safe and effective, even if the active constituents are not known. Last October, the FDA approved the first such botanical drug under the new rules, a proprietary mixture of green-tea extracts called Veregen developed by the German company MediGene for treating genital warts.

These new regulations have helped to renew industry's interest in the complex formulae. And a buzzing new Western field could be poised to capitalize on the deeper secrets of traditional Chinese medicine. Systems biology attempts to understand the function and behaviour of an organism by studying the interactions between its components. It has been called a more holistic approach to biology and is seen by some as a perfect match for traditional Chinese medicine.

By measuring many genes, proteins and metabolites at the same time, systems biology may provide a measure of the entire body's response to a complex mixture of herbs. "If there is any technology that could lead to a breakthrough in traditional Chinese medicine, it will be systems biology," says Robert Verpoorte, head of the pharmacognosy department at the University of Leiden in the Netherlands. But not everyone agrees that the new technology is equipped to test old ideas.

Jia Wei, a pharmacologist at the Shanghai Centre for Systems Biomedicine at Jiao Tong University, and Tang Hui-ru at the Wuhan Institute of Physics and Mathematics, part of the Chinese Academy of Sciences, want to understand more fully how herbal extracts affect the whole body. They are collaborating with Jeremy Nicholson, head of the department of biomolecular medicine at Imperial College London, and using technologies such as nuclear magnetic resonance spectroscopy and mass spectrometry to profile the metabolites in a person's urine or blood — a discipline they call metabonomics.

Jia and his colleagues found that rats given the compound 1,2-dimethylhydrazine to induce tumours in their colons had different metabolic profiles in their urine from those in the control group. And by feeding the rats a combination of two herbal extracts — *Coptidis rhizoma* and *Evodia rutaecarpa*, which are widely used in traditional Chinese medicine to treat gastric conditions — the researchers were able to reverse these changes in metabolism.

## Knowledge mining

The key to Chinese herbal medicine is to choose a combination of plant species based on the particular symptoms and characteristics of the patient and guided by the various theories of traditional Chinese medicine. There are many schools of thought on the causes of disease and the best way to formulate herbal medicines to tackle them.

One of the most influential theories is the principle of *jun-chen-zuo-shi*. The *jun* (emperor) herbs treat the main cause or primary symptoms of a disease. The *chen* (minister) herbs serve to augment or broaden the effects of *jun*, and relieve secondary symptoms. The *zuo* (assistant) herbs are used to modulate the effects of *jun* and *chen*, and to counteract the toxic or side effects of these herbs. The *shi* (courier) herbs are included in many formulae to ensure that all components in the prescription are well absorbed, and to help deliver or guide them to the target organs.

For researchers trying to develop clinically tested drugs from Chinese herbal medicine, one of the most challenging steps is scouring the extensive ancient and contemporary literature to produce a short list of compound formulae that might be promising for the disease under study. More than 11,000 plant species used in more than 100,000 compound formulae have been recorded in China, and the same plant species can have distinct roles in different formulae. Thus, *jun* and *chen* herbs in one formula may serve as *zuo* and *shi* herbs in another.

It can also be difficult to translate ancient interpretations of disease into those used in modern medicine. For example, many herbs are said to have the function of *qingre* (to clear heat). What this really means is that they may have antibacterial, antiviral or anti-inflammatory effects. Similarly, a guiding principle of traditional medicine practice is *fuzheng quxie* (to help the righteous and combat the evil), which, in the language of Western medicine, is to boost the immune system and evade viruses. "It's all about local knowledge," says Robert Miller, chief executive of Phynova in Oxford, UK, a pharmaceutical company that develops Western-styke drugs from medicines identified from China. "Having in-depth understanding of traditional Chinese medicine is absolutely essential." **J.Q.**

***SALVIA MILTIORRHIZA***
**aka: *Danshen***
**With their blood-thinning qualities, remedies containing roots from this plant are traditionally used to treat cardiac and vascular disorders. Some animal studies suggest uses in liver and kidney disease.**

***PANAX GINSENG***
**aka: Asian ginseng**
**Used to improve mental acuity, and to treat senile dementia. Often combined with with ginkgo biloba. Some evidence suggests blood-sugar lowering effects for type 2 diabetes.**

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Mix and match: traditional Chinese medicine uses a variety of products to treat people's symptoms.

Their results have not yet been published, but the researchers say that by looking at the changes in metabolites in detail, they have pinpointed the metabolic pathways that the herbs affect.

## Culture shift

Jan van der Greef from SU Biomedicine in Zeist, the Netherlands, and his colleague Wang Mei are using a similar approach. In a mouse model of metabolic syndrome — a cluster of conditions such as insulin resistance and high blood pressure that often occur together — they and their team looked at the effect of an undisclosed formula used in traditional Chinese medicine on lipid profiles. When these mice are fed a high-fat diet, they become more resistant to insulin. The lipid profiles of these mice were clearly distinguishable from those of mice fed a normal diet, and they shifted towards the healthy state when the mice were given traditional Chinese medicine[3].

The researchers noticed that the profile shift resembled that caused by the Western obesity drug Rimonabant, which acts on proteins called CB-1 endocannabinoid receptors. And their unpublished work with cell culture suggests that herbal extracts can affect lipid metabolism through the same receptor, says van der Greef. The team is now testing the formula in clinical trials.

Although one active ingredient may act as the Western drug, the uncertain role of additional ingredients and the variability of active ingredients confounds Western sensibilities. "Variations worry people," Nicholson says. The same plant species grown in different regions and harvested in different seasons could have distinct chemical compositions. This has always been a vexing issue for herbal-medicine researchers.

While at Nicholson's lab, Tang and his colleagues analysed the molecular components in chamomile plants from Egypt, Slovakia, and Hungary, and could classify them easily[4]. Using similar approaches, the team from the Wuhan Institute of Physics and Mathematics found significant variations in the same herbal medicines produced by different companies and even between different batches produced by the same company. "This is an issue China must tackle for its herbal medicines to raise their game in the world market," says Tang.

To many self-purported systems biologists, several approaches are needed to build a complete picture of a living organism and to understand the effect of traditional Chinese medicine. Nevertheless, systems biology has been a conspicuously hard field to define. Many have used the term loosely, and pioneers in the field contend that the technologies haven't been honed to the point that they could be used for these approaches.

> **"Whether from the East or the West, we share the same goal of improving human health."**
> — Liu Wen-long

"It's conceivable that systems biology could find applications in trying to sort out components in Chinese herbal medicine, but it's very early days," says Leroy Hood, president of the Institute for Systems Biology in Seattle, Washington, and regarded as the field's founding father. "It would be an enormous challenge at this point and time."

Systems biology has been successful in model organisms, according to Hood, but is much less so in human studies. Many hurdles need to be overcome before researchers could even begin to contemplate how to deal with subjects as complex as traditional Chinese medicine. For example, better detection systems are needed to measure metabolites, especially proteins, accurately in the blood, and more powerful computational and statistical tools are crucial for dealing with large and complex data sets. "Those technologies are at early stages of maturation," Hood says.

There are also broader concerns about the modernization of traditional Chinese medicine, from both advocates and sceptics of the practice. Some are uncomfortable with separating the study and development of Chinese herbal medicines from the theories that underlie its normal practice. "Traditional Chinese medicine is not just a medical system, but a branch of philosophy and healing art that is an important part of Chinese culture," says Fu Jing-hua, a retired researcher at the Chinese Academy of Chinese Medicine Sciences in Beijing and president of the Chinese Ancient Books Publishing House in Beijing. "Devoid of that cultural context, it would become a tree without roots."

## Lofty ideals

But Zhang and Fang Shi-min, a US-trained biochemist who now runs a society called New Threads that is known for fighting pseudoscience and research misconduct in China say that it is exactly those traditional Chinese medicine theories that should be abolished. Conceits such as *yin* and *yang*, *wuxing* and *qi* "are inaccurate descriptions of the human body that verge on imagination", he says.

Inevitably, cultural factors may be the biggest obstacle in bridging the East–West gap. "The field of traditional Chinese medicine is notorious for being averse to criticism," says Yuan Zhong, a philosopher of medicine at the Chinese Academy of Medical Sciences. "If people are not allowed to disagree or voice their opinions, there would be no hope of progress for any discipline."

But although heated exchanges are boiling over in debates on the future of traditional Chinese medicine, it's business as usual in Liu's practice. He is sanguine about the convergence between traditional Chinese medicine and Western medicine, but has a pragmatic attitude towards it. "Whether from the East or the West, we share the same goal of improving human health. As long as it works, anything goes," he remarks. But Liu says that he is yet to see any real progress in the merging of the two philosophies and, until then, his intuition and experience — as well as traditional Chinese medicine's seemingly arcane theory and practice — will serve him and his patients just fine. ■

**Jane Qiu writes for *Nature* from Beijing.**

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