"Dosage is the secret that is never taught"

(zhongyao bu chuan zhi mi zai liang shang)[1]

by Charles Buck

Do we confine ourselves to a narrower dose range than we should - one that is generally more restricted than we find in the historical literature? Does our clinical practice sometimes tell us that our dose regime might be wrong? Is it possible that some patients respond better to doses that might be considered ineffectual in modern Chinese hospitals? On the other hand do some patients not respond unless we give doses that are in excess of traditional *bencao* (materia medica) recommendations? Why do we find that patients in China often receive prescriptions containing 10g of most herbs? Most prescriptions I saw in Shanghai's famous Shu Guang TCM Hospital went something like this:

Long Dan Cao (Radix Gentianae Scabrae) 10g, Huang Qin (Radix Scutellariae Baicalensis) 10g, Sheng Di Huang (Radix Rehmanniae Glutinosae) 20g, Dang Gui Wei (Extremitas Radix Angelicae Sinensis) 10g and so on.

On some occasions I have seen small children given similar doses. Quizzing this I was told "its OK, the child won't drink it all"! Why, I wondered, does the ancient literature often suggest lower doses than are used in modern Chinese practice?

Take *Xiao Yao San* (Rambling Powder) as an example. One modern text[2] suggests the following doses:
Chai Hu (Radix Bupleuri) 10g
Bai Shao (Radix Paeoniae Lactiflorae) 15g
Dang Gui (Radix Angelicae Sinensis) 10g
Bai Zhu (Rhizoma Atractylodis Macrocephalae) 10g
Fu Ling (Sclerotium Poriae Cocos) 15g
Bo He (Herba Menthae) 2g
Zhi Gan Cao (Radix Glycyrrhizae Praeparatae) 6g
Sheng Jiang (Rhizoma Zingiberis Officinalis Recens) 3 slices

But in the source text, the *Imperial Grace Formulary of the Tai Ping Era* (Tai ping hui min he ji ju fang)[3], the doses given were:I would argue that CM DID survive because its basic convictions were
clinically so effective and correct. For 'widespread acceptance of WM' I
would translate "through the drive by the US to push Western medicine
into China by Rockefeller through the application of political will and
big money, not scientific acumen or ability" it was a market ready to be
taken advantage of, and had no more acceptance by the masses than any
other 'world view', until the 1940's when a more pragmatic and
corruptible regime took over.
Chai Hu (Radix Bupleuri) 1g
Bai Shao (Radix Paeoniae Lactiflorae) 1g
Dang Gui (Radix Angelicae Sinensis) 1g
Bai Zhu (Rhizoma Atractylodis Macrocephalae) 1g
Fu Ling (Sclerotium Poriae Cocos) 1g
Bo He (Herba Menthae) 1g
Zhi Gan Cao (Radix Glycyrrhizae Praeparatae) 1g
Sheng jiang (Rhizoma Zingiberis recens) no dose
given in source text

Admittedly, the source text suggested using the formula as a powdered draft but these doses are still much lower than those generally used today. Dr. Shen of New York used to say this was because today's herbs are not as strong as they used to be. Maybe, but my own experience has taught me that whilst some patients do not respond until we push them hard using higher doses than normal, other patients respond much better to lower doses. Often I have begun treatment using standard modern doses only to find that lowering the dose, and taking a longer-term view of the treatment plan, has produced better results.

For example, in my first few years of treating patients with obvious phlegm-damp patterns I often relied on using modern standard doses of pungent, warm, dry substances such as Ban Xia (Rhizoma Pinelliae Ternatae), Hou Po (Cortex Magnoliae Officinalis), Cang Zhu (Rhizoma Atractylodis), Chen Pi (Pericarpium Citri Reticulatae), Cang Er Zi (Fructus Xanthii Sibirici) and Bai Zhi (Radix Angelicae). Patients would sometimes

return saying things like "was it okay to wake up at night with my tongue stuck to the roof of my mouth?" Not only did I observe such side effects but, in the long run the patient often failed to get any lasting benefit. More often than I would have liked, I failed to help these and some other patients. Clearly either I was doing something wrong or some prescriptions did not do what they were supposed to. Saving the second option for later I decided to look at the question of dose, eventually realising that besides the puzzle of diagnosis and formulation of treatment principles, the problem of correct dose represented a further challenge. In a moment I will describe a few of the cases that helped confirm to me that the dose question is more complex than we might think. What I have got to say is quite simple. We need, in my view, to exercise more judgement in our dose prescribing. Of course it is a core principle of TCM that we adapt treatment according to individual circumstances; we always do this with regard to formula constituents, patient age, weight and so on, and according to traditional principles of hierarchy within prescriptions. But in textbooks and in observing practice in China's hospitals we find doses usually restricted to the upper range of normal or often above normal *bencao* and *fangji xue* (prescription text) recommendations.

To experienced practitioners what I say here may seem obvious; they may already have reached similar conclusions and indeed I have met a few practitioners who routinely use a broad dose range. Other practitioners will want to stick to their existing routines because they are happy with their results. My aim in writing this however, is simply to encourage closer consideration of this question.

One other important factor that should be considered is safety, an increasingly sensitive issue in the practice of Chinese herbal medicine in the west. If we find that we can get good results by emulating the lower dose regimes often seen in the classics then there will be benefits both in terms of fewer adverse reactions as well as in terms of reduced cost to patients.

This is not just a modern concern. Xu Da-chun of the Qing dynasty wrote:

> When the ancients employed medicines they were never applied in extreme doses, but during the last 20 years doctors have followed the fashions of their own times, wrongly interpreting ancient prescriptions by heavily increasing doses. (Yi Xue Yuan Lin Lun 1757[4])

Case examples

It does seem that sometimes extremely low doses can produce a good response. Three of my case histories illustrate this.

Case 1

Mr. F 52 years

I saw Mr. F in 1990 when he had already suffered from severe sinus problems for forty years. He had complete nasal obstruction with encrusted dry phlegm in the nose, constant frontal headaches, no smell or taste, a dry mouth and throat, stubborn phlegm on the chest and mild tinnitus and fullness in the ears.

The diagnosis was: heat and phlegm stagnated in the lung channel, failure of clear qi to ascend and transform turbidity, and injury to yin due to heat and inhibition of the *qi ji* (qi mechanism).

That same week I saw three new patients with very similar problems. Previously I had generally used the textbook approach and had often been disappointed with the results. I was beginning to think that perhaps acupuncture might be a better option, but these patients had all travelled some distance to see me and were specifically requesting herbs instead. I had to try something different. For Mr F. I prescribed: Huang Qin (Radix Scutellariae Baicalensis) 12g, Tai Zi Shen (Radix Pseudostellariae Heterophyllae) 12g, Fu Ling (Sclerotium Poriae Cocos) 12g, Shan Yao (Radix Dioscoreae Oppositae) 12g, Zhi Shi (Fructus Citri seu Ponciri Immaturus) 9g, Sheng Ma (Rhizoma Cimicifugae) 3g, Tian Hua Fen (Radix Trichosanthis) 12g, Shi Chang Pu (Rhizoma Acori Graminei) 9g, Jie Geng (Radix Platycodi Grandiflori) 6g, Xing Ren (Semen Pruni Armeniacae) 12g, Bai He (Bulbus Lilii) 9g, Huang Qi (Radix Astragali) 15g, plus Xin Yi Hua (Flos Magnoliae) 6g and Huo Xiang (Herba Agastaches seu Pogostemi) 12g as a *xiabao* (late addition)

This looks like a prescription suitable for one or two days, use, but I asked Mr. F to cook one bag, freeze the brew in an ice cube container and take 1 cube in the morning and one in the evening. This way a single pack would last about two weeks, and each day he would be consuming the equivalent of under 1g of each herb. I told him that he should think in terms of three, six or even nine months before he would see a clear benefit and that I would monitor him after two weeks and then monthly after that. Frankly, for me this was an experiment. I could see that it was unlikely his 40-year condition was going to change in two weeks so I thought I would see if it would respond a tiny dose.

Modern pharmacology is most interested in acute or instantaneous effects, and to some extent so is Chinese medicine. You take a medicine and something happens almost straight away. But Chinese medicine has always included the notion that some medicines have to be taken for a prolonged period to have an effect. In the famous story, Mr. He's hair did not instantly become black when he first ingested He Shou Wu (Radix Polygoni Multiflori), the effect accrued gradually with time. But it is not always good to take high doses of herbs for prolonged periods of time. I wondered if this was the basis of the *Shen Nong Ben Cao* (Divine Framer's Materia Medica) categorisation of substances into three classes. The *shang pin* (upper class) herbs were substances that generally needed to be taken long term to exert a good effect. The words of a doctor from the Shu Guang Hospital came to mind, "treating disease is like unwinding silk".

Mr. F did better than I had anticipated. After two weeks his headache had gone, and after six week he could smell and taste things intermittently. After about four months he

was completely clear of symptoms, and during the last ten years he has reappeared a couple of times for repeat shorter courses. On each return visit just a couple of bags of herbs has been sufficient.

Another of the patients who presented that week with essentially the same problem responded in a similar way to Mr. F. I felt I had learnt something that had not been taught to me, and that I had not read in the textbooks. My best explanation at the time for the frequent use of maximal doses was that perhaps patients in China come much sooner for treatment and so can be treated more acutely with higher doses.

Case 2

A few years before I saw Mr. F I treated an elderly lady with Parkinson's disease. Mary had signs of yin-blood xu with stirring of internal wind so I gave *Si Wu Tang Jia Wei* (Added Flavours Four-Substance Decoction) in standard modern doses, enough for two weeks. A few days later she phoned to say that she really could not stomach the herbs and wondered what could she do. Privately I thought that perhaps she was not suited to taking Chinese herbs but I did not want the herbs to be wasted. "Don,t worry", I said, "just freeze them and take small amounts, a melted ice cube twice per day. Get back to me when you are running out". I did not hear from her again for 9 months when she phoned to ask for a repeat prescription as she had run out of the herbs. I was a bit surprised, as by then I had forgotten I had even seen her. "Has it done you any good", I asked. "Oh yes" she said, "the tremor is less and I can move around more easily, but also my hair seems to be growing stronger and has more life, my nails are not flaking now, my skin feels younger, my eyesight has improved, I am sleeping better and I am less dizzy". At no point had I told Mary that the prescription might affect any of these things, and as far as she knew the prescription was only designed to help her Parkinson's disease symptoms. She had taken doses that might be laughed at in a Chinese hospital but had responded better than I would have expected even if she had taken the full dose (unlikely given the cost and bother of full dose Chinese herb decoctions). I estimated that she must have been taking roughly 0.2g of Shu Di Huang (Radix Rehmanniae Glutinosae Conquitae) per day in the prescription! How was it that such a tiny amount had done exactly what it is supposed to do? And yet, only yesterday I gave another patient 30g per day of the same herb.

Case 3

Stephen had Sjogrens syndrome (autoimmune dry eyes). I gave the Lanzhou (factory) pill form of *Zhi Bai Di Huang Wan* (Anemarrhena, Phellodendron and Rehmannia Pill) to support my acupuncture, but after a while he relied only on the pills. The condition improved so I said he could gradually reduce the pills to the amount needed for a continued effect. He could easily measure the effect by how often he needed to use his artificial tears each day and in a few months we got these down to virtually zero. A few months later I saw him when he needed some more pills. He reported that he was now taking 1 pill per day and that if he missed that one he would need to use the artificial tears. Eventually he could do without the pills completely. I wondered what the actual dose of each herb is in a single Lanzhou pill. Research in China into the treatment of Sjogren's syndrome advocates using doses perhaps a hundred times this size, and of course that amount may well be needed for many patients.

So, it seems that some patients to respond well to lower doses, others require standard doses, and some appear to need doses that significantly exceed the standard, although to do this you have to know the properties of the herbs very well and to have tested the dose boundaries with experience, or very occasionally, by accident.

A few years ago I treated a patient who had both Lung deficiency and an acute bronchitic retention of phlegm-heat in the Lung. I was especially worried about the deficiency aspect because I had a decade earlier treated her for chronic fatigue. I wanted to support the zheng (normal) and expel the xie (pathogen). My prescription contained both Huang Qi (Radix Astragali) 18g and Huang Qin (Radix Scutellariae Baicalensis) 9g. When she had taken it for a week with little change, I was concerned. I expected things to improve more quickly but, certain the prescription was right, I repeated it. A week later she came back saying that her chest had suddenly cleared up after just a couple of days on the "new" prescription. She also reported that it tasted more bitter than the previous prescription. She was so much better that she had brought two bags of the herbs back, as she felt she did not need them. Not having changed the prescription I could not understand why it would taste different. When she had gone I examined the bag, only to discover that my pharmacy had mistakenly swapped the doses of Huang Qi and Huang Qin. She had been taking double the intended dose of Huang Qin, rather more than I would ever use.

If some patients need low doses, others normal doses, and others high doses, how can we tell the difference? How can tiny doses of Shu Di Huang (Radix Rehmanniae Glutinosae Conquitae), for example, have a pharmacological effect? Is it always true to say the bigger the dose the bigger the response?

Reflecting on this I realised that our thinking is conditioned to a great extent by modern pharmacology which bases its view of therapeutics on the dose-response curve. A very low dose produces no response and the response increases through the therapeutic range before levelling off at a maximal dose when no further benefit is obtained. This curve accurately reflects the relationship between single receptors and a single pharmaceutical substance[5]. Minimal, sub-clinical doses are generally considered to have no effect. Modern research into Chinese herbs confirms that they can indeed act as pharmacological agents and this is considered to explain their effect.

Ancient physicians did not see things entirely in these terms (indeed, modern pharmacology is now starting to think outside this box). True, they could appreciate that

sometimes we need to increase doses to get an effect - the *Shang Han Lun* (Discussion of Cold-Induced Disorders) suggests gradually increasing the dose of Gui Zhi Tang (Cinnamon Twig Decoction) until it is sufficient to cause a response[6]. However ancient Chinese medicine was not based on pharmacology as we understand it today. Rather it explained the way things exert an influence on each other by the concept of *gan ying* - perhaps best translated here as "resonance". An early observation of Chinese proto-scientists was recorded by Dong Zhong-shu in the 2nd century BCE who said:

> The kung note or the shang note struck upon one lute will be answered by the kung or shang notes from other stringed instruments. They sound by themselves … when the note kung is struck forth from a lute, other kung strings [on other instruments] reverberate of themselves in complementary [resonance]; a case of comparable things being affected according to the classes to which they belong[7].

Herbs also were felt to induce a response by this *gan ying* effect, and causality was seen as being a consequence of things having a similar nature. In other words herbs were able to change activity in the body because they had a qi quality that was related to that function in the body. This is not pharmacology and is a notion not easily sustainable in current scientific thinking . Nevertheless clinical experience suggests that Chinese herbal medicine may involve more than the simple pharmaceutical response of, say, an isolated frog heart to a single chemical.

Complex systems such as the human body do not behave in the same way as their simplest isolated components. They may not always follow the basic rules of pharmacology, especially when a complex polypharmacy stimulus is involved. Nor do body systems necessarily always react according to the dose-response curve.

By analogy, if you read a sad story it is not made sadder by making the letters bigger; the quality of a painting is not related to the amount of paint it uses. A story is made more sad by a better choice of words, a painting improved by better composition and use of colour. These qualities evoke a stronger response in the organism as a whole. So when an intervention based on the polypharmacy prescriptions of Chinese herbal medicine meets the body's complex immune and neuro-hormonal systems, the quality of the message may be more important than its quantity.

In conclusion, we can argue that it is insufficient in the practice of Chinese herbal medicine to make a diagnosis, formulate an appropriate treatment principle, select a prescription and make suitable adjustments for the individual patient. We should perhaps more carefully consider the dose range, taking into account not only the patient's age, body size, etc. but also their individual sensitivity and their likely response in the light of our experience. We might think broadly in three ranges for the typical medicinal

Low dose 0.3-3g

Standard dose 3-9g

High dose 9-20g

A low dose may be applicable if:

- the patient is known to be sensitive
- the response is likely to be slow
- the disease is relatively mild and chronic
- there is long term deficiency or chronic phlegm-damp
- the pathology is complex

Low dose methods include patent medicines, concentrated powders, frozen decoctions, powdered whole herbs, etc.

A moderate dose is applicable:

- as a first move to test response
- in relatively recent disease
- in moderate disease states
- where response is likely to show in roughly 1-16 weeks

A high dose is applicable:

- when using herbs for their pharmacologic effects, e.g. herbs with antibiotic effects, "clotbuster" herbs, etc.
- to bring serious acute disease under control, for example bleeding, fevers, etc.
- when lower doses fail to work

Why is dosage the "secret that is never taught". Not because of a conspiracy to maintain secrets but, as Clavey has pointed out[1], because it cannot easily be taught. If we never think carefully about doses, and never experiment a little, we might never learn this secret.

Notes

1 This saying is taken from Stephen Clavey's *Fluid Physiology and Pathology in TCM*, Churchill-Livingstone, 1st Edition 1996 p223.

2 Ou Ming (1989) *Chinese-English Manual of Common-Used Prescriptions in Traditional Chinese Medicine,* Joint Publishing (HK) Co Ltd & Guandong Science & Technology Press.

3 In Bensky & Barolet (1990) *Formulas and Strategies,* Eastland Press.

4 In Unschuld (translator) *Forgotten Traditions of Ancient Chinese Medicine,* Paradigm Press.

5 Most pharmaceuticals exert their effect by binding to receptors on cell walls and altering the cell response either by stimulating a greater response or making the cell do less of what it is supposed to do by blocking the receptor.

6 Zhang Zhong-jing's Shang Han Lun, Trans. Mitchel, Ye & Wiseman, *Shang Han Lun: on cold damage*, Paradigm Press 1999.

7 In Joseph Needham *Science & Civilisation in China*, Cambridge University Press Vol II; p 281-2

8 There are, however, increasing numbers of mechanisms by which we can understand the actions of substances working outside the traditional dose-response rules of pharmacology.

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