the parameters of null equations, assuming that the first concentration–state curve fits a logistic equation, is closely related to methods originally developed by Waud[4,5] but has wider application. Finally the principles set out in Eqns 1 to 4, enable the generalized version of ALLFIT to be used to estimate parameters of null equations even from concentration–state data which can only be fitted satisfactorily by some function that is not logistic.

Acknowledgement
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This and that: clots, creamers and canals

ONE OF THE more complex biological processes is that of blood coagulation. Here, as with so many of the phenomena inherent with life, functionality is a metastable state. The circulation exists on a rheological see-saw between rust-choked blood vessels and hemophilia.

Coagulation is achieved by the triggering of an extraordinary cascade of events, each of which amplifies the succeeding step, until the final step of fibrinogenesis arrests bleeding. The difficult task of keeping the see-saw balanced is achieved by the presence of a matching set of inhibitors for each step.

An imbalance in the process, a tilt of the see-saw, leads to a thrombosis. In common parlance, you are in trouble if your blood is either too thick or too thin. The profligacy of the process is man's opportunity, in that it allows so many sites for potential pharmacological intervention.

The pharmacology, however, is conditioned by the physiology of the circulation as much as by the biochemistry of coagulation (Fig. 1). Blood is ejected from the left ventricle into the arteries at high speed (25–40 cm sec^{-1} in a resting adult; five times greater during exercise). Thus, despite the length of arteries, up to about a meter to the lower leg, blood spends a comparatively short fraction of the circulation time in them. Hitting the arterioles and capillaries, however, is rather like coming down the M1 into London. The long stretches of unimpeded high-speed linear flow end in a violent deceleration into the winding streets of the metropolis. The difference between arterial and capillary flow reminds me of the old joke of the Texan who boasted that in his state you could get into your car, drive all day, and still be in Texas. A Londoner sourly replied that you could do the equivalent in London. Venous flow is gentler than arterial, and less pulsatile – more akin to punting on the Cambridge backs.

Thrombi can form as an expression of normal physiological activity: the slower blood flows, the greater its predisposition to clotting. However, this intrinsic process, leading to fibrin production, is slow, taking up to a minute or more to occur. Thrombosis as a result of stasis, therefore, occurs in the venous circulation; typically in the legs where, due to the vertical distance from the heart, venous return is slowest. In fact, many thousands of small thrombi are formed each day in the lower body. These pass via the vena cava into the lungs where thrombolysis occurs, this being a normal metabolic function of the organ.

Arterial thrombi, leading to myocardial or cerebral infarcts, occur by a different mechanism. Here, previous sclerotic damage to the vessel wall predisposes to platelet aggregation, an extrinsic process occurring within a few seconds. Then, with blood flow reduced by a loose platelet thrombus, fibrinogenesis occurs to consolidate the thrombus.

These differing mechanisms in the two sides of the circulation are reflected in the differing pharmacologies employed in their prophylaxis. In neither case is there a defect in coagulation *per se*. The venous abnormality is impaired return for whatever reason; the arterial abnormality is damage to the vessel wall, which interferes with the normal non-thrombogenic surface. The drugs employed prophylactically (i.e. to prevent thromboses occurring where there is a predisposition) act by modifying a functionally normal response, and the risks of increased bleeding associated with such prophylaxis derive from this.

On the arterial side, antiplatelet drugs, such as aspirin, or inhibitors of thromboxane synthase (thromboxane A_2 is a stimulator of aggregation), such as dazoxiben, are used. Their effectiveness is controversial. One can predict that evolution of effective antiplatelet drugs will be one of the achievements of our discipline before the dawning of the next century.

The two staples for venous prophylaxis are warfarin and heparin. The latter is a high molecular mass (4000–20 000 Da), polysulfonated glycosaminoglycan which is almost ubiquitous in the animal kingdom[1]. The sulfonate groups with which it is richly endowed make heparin one of the strongest organic acids present in mammalian tissues. It is particularly rich in mast cells underlying vascular endothelium, and is also found immobilized in the walls of blood vessels where it appears to be involved in maintaining the nonthrombogenicity of the surface. Its anticoagulant effect is due to a potentiation of the action of antithrombin III, an inhibitor of the terminal proteolytic steps in coagulation. A major source of heparin is intestinal mucosa. A crisis for researchers and hospitals developed in the mid-1970s when the hot dog manufacturers of

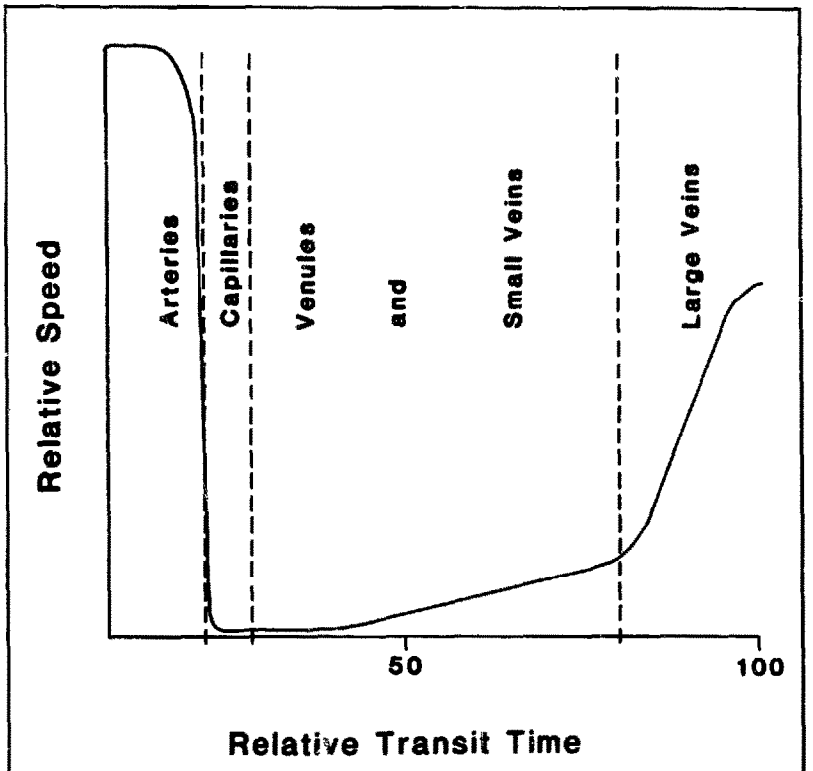

Fig. 1. Circulatory dynamics in a resting adult. Relative speed of blood flow is plotted against relative transit time for the components of the circulation between the left ventricle and the right atrium. Blood is moving at high speed and spends a short time in the arterial circulation. It moves slower and spends correspondingly more time in the post-capillary and venous portions of the circulation.

America switched their casings from pig intestines to a plastic prepared from petrochemicals. Heparin, which had been obtained as a cheap by-product of hot dog manufacture, softly and silently vanished from the market, to reappear later at much higher prices (currently $40 a gram). My butcher tells me you can determine if your hot dog is dressed in plastic or pig by applying a lit match to a portion of the casing. If plastic it will burn, but if pig it will shrivel and blacken but not burn.

Heparin, of course, has to be given by injection and has an immediate onset of action. Warfarin is prototypical of the oral anticoagulants. It is a synthetic analog of the dicumarol present in sweet clover that is responsible for outbreaks of hemorrhagic disorders in sheep and cows. In the unitary way of science, what was initially an agricultural problem led to the development of warfarin as a highly successful rat poison, and later to its use as a therapeutic anticoagulant. Would that granting agencies and the general public were more alive to the interconnected nature of scientific activity, and the need for both broad vision and frequent interdisciplinary contacts in the successful prosecution of the scientific enterprise. Warfarin has to be given for several days before its anticoagulant action develops.

Although the consequences of treatment with heparin and warfarin are the same, the mechanisms of action differ. Certain of the factors involved in the coagulation cascade (Factors II, VII, IX and X) are synthesized in the liver and then undergo postribosomal modifications before release. These modifications involve vitamin K-catalysed γ-carboxylation of glutamate residues on the factors, thereby increasing affinity for calcium, and allowing crossbinding to acidic phospholipids released onto the cytoplasmic aspect of platelets following activation. The action of vitamin K involves a reversible oxidation to its 2,3-epoxide, and warfarin acts by inhibiting this conversion. The result is that immunologically detectable clotting proteins are released from the liver, but they lack biological activity.

THE CHURCH of San Giorgio was greenly mirrored in the mellow waters of the Grand Canal in Venice (Fig. 2). I was waiting for a vaporetto, one of those infernally noisy boats which serve as public transportation in La Serenissima, when there was a tap on my shoulder.

I turned to see the smiling face of Dr Setsuro Ebashi. 'You are also a pharmacologist, like me,' he said. How was this Holmesian deduction made? Are the lines of grant-chiseled worry in the brow diagnostic? Do we pharmacologists, like Cassius, circle the world with lean and hungry looks? Elementary, my dear Dr Max, he said, not in so many words. He had bagged me with his first shot, as the sportman boasted.

I had *the* bag slung over my shoulder, replete on this occasion with sandwiches, guide book, camera and bottle of wine: the Ebashi bag, status symbol of pharmacology, given to all participants at the 8th IUPHAR meeting held in Tokyo in 1981.

Dr Ebashi had been one of those responsible for this durable and utilitarian object, so much more functional than the polyvinyl puerilities normally disbursed at such gatherings. For such an act, he deserves to be 'solemnized in odes, celebrated in epigrams, and fed with the milk of soft dedication' (if anyone can identify that quote, by the way, there will be an honorable mention in this column). In the years since Tokyo, my bag has hiked moor and desert. It has jetted the Pacific and the Atlantic. It has seen the tundras of Siberia and the stones of Rome; it has been tanned by the January skies of Waikiki and mildewed by a Swedish summer. It has been my security blanket, a haven for slides, reprints,

Photograph by Vicki Rushworth

Fig. 2. The church at San Giorgio: where Ebashi bags meet.

sandwiches, field samples, plants and assorted camping gear. It is stained with the stains of a dozen misadventures.

The bags wander the world. At any gathering of pharmacologists, they can be seen, serviceable yet carrying a mystic aura of the elect, a campaign medal identifying the wearer as a participant in that most memorable of IUPHAR meetings, which opened with a feast of baccanalian pleasures, satisfying gourmets and gourmands alike, and closed to a serenade of a thousand violinaceous five year olds. What could better symbolize our discipline than these useful objects, macroreceptors slung on pharmacological shoulders around the world. I propose that IUPHAR adopt the Ebashi bag as its official symbol. The Heralds would have fun describing it: 'Bag rampant on field vert, voided and gorged with Goodman and Gilman piled . . .'

AMERICANS, WE ARE told, drink 33 million gallons of coffee a day. There has been a brisk, but inconclusive, debate as to whether the habit of imbibing coffee is associated with detrimental consequences to one's health. But what about the ingredients we add to the coffee? Ask for cream for your coffee in America, and you will be given a small container on which appears to be printed a microfilmed page from a chemical catalog. Inside is an ingenious concoction, a whitish powder known as creamer.

Creamers typically contain vegetable oils. Of 25 creamers analysed, 22 contained coconut oil, which has a high proportion of saturated fat[2]. The authors estimate that a teaspoon of such creamers yields 10 kcal of saturated fat. Several cups a day, with a spoonful or two of creamer in each, can add substantially to one's intake of these currently undesirable fatty acids. These, it has been established, lead to an increase in total circulating cholesterol, and to an undesirable shift in the HDL/LDL ratio.

B. MAX

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LETTERS

A plea for more gravity in reporting muscle research

May the force be with you

I read, and occasionally referee, papers reporting findings from experiments on muscle; all kinds of muscle. I have been dismayed by an abuse of units common in this field. The pharmacological fraternity in particular seems enamoured of the view that its scraps of blood vessel and digestive system generate *grams* when suitably provoked with adrenaline, potassium, electricity and the like. Now grams, like kilograms and milligrams, are units of *mass*. (If the butchering trade ever discovers that one apparently need only apply stimulating electrodes to best beef to increase its *mass*, the economy could take an interesting turn.)

In my well meaning attempts to disabuse colleagues of this error, I encounter a mixture of resistance, ignorance and complacency that one might expect in a faculty meeting rather than in Science. I believe that my plea for a general insistence upon calibrating force (tension) records in appropriate units is justified on these clear grounds: (1) it is misleading to you, me and others to confuse mass and force; (2) those of us involved in teaching as well as research have our task made harder when indefensible examples are set in the professional literature; and (3) imparting a clear grasp of the distinction between mass and force is a useful didactic tool in teaching 'muscle'.

I had thought to apologize for the small lesson in junior level physics which follows, but experience assures me that for some, at least, no apology is necessary! Measurements of mass are notoriously difficult, though approximations are easy by the balance principle. We all slip easily into equating objects of identical *weight* with equal *mass*. Numerical errors thus created are generally small, though by no means always insignificant.