On 6 July 1885 Joseph Meister, a 9 year old boy who had been severely bitten 2 days before by a rabid dog, was treated in Paris with the rabies vaccine developed in Louis Pasteur’s (1822–95) laboratory after years of brilliant scientific research and experimentation on animals. Before this, no one who had developed the symptoms of rabies had survived. Meister was at the highest risk of developing symptoms but, after 10 days of vaccinations, he was fine and lived for many years. The results of this and a second case were so dramatic compared with previous experience that, by October, speakers at the French Academy of Sciences stated that it was “necessary to organize this treatment for everyone” and “This is a memorable day in the history of medicine”. Philanthropic contributions poured in and by 1888 the Pasteur Institute was founded. By then about 1200 patients had been vaccinated with a mortality rate of 1%.

RABBIES

Transmitted to humans by animal bites, rabies has always been a rare event. A biting animal may not have rabies. Verification that an animal is rabid is not always possible if the animal cannot be caught and watched. A rabid animal that bites does not always transmit the rabies virus. If the person is infected, the incubation period is about 20–60 days before symptoms develop leading to a painful and certain death. Today there are occasional reports of survival but these are so rare as to make headlines. The rarity of rabies and the long incubation period led to Pasteur’s novel approach of not vaccinating everyone preventively. The incubation period allowed time for his 10 days of vaccination to build immunity.

Would you—having been infected by a rabid dog—be willing to participate in a randomized controlled trial (RCT) when being in the control group had a certainty of a “most awful death”? If volunteers could be found, the trial would have to be small and would therefore have low statistical power. If one wished to show that vaccination was effective for men and women—young, middle aged, and old—the sample size would have to be 264, condemning half those people to a certain death. In this example the application of statistical process control (SPC) makes more sense. SPC avoids the ethical issues, saves lives, builds on prior experience to control confounding variables, gives an answer more rapidly, and has much more statistical power.

In order to demonstrate the application of statistical process control (SPC) by the use of control charts, we have simulated pre and post 1885 rabies mortality using data from the literature. This simulation assumes a mean (SD) survival of 20 (10) days before 1885. Patients were grouped into blocks of five so that each point on the control chart represents five patients recorded sequentially over time. This would be equivalent to an average of five patients bitten in a day. The survival in days is plotted for 500 groups of five patients sequentially. Survival in days after receiving Pasteur’s treatment is simulated for a similar number of patients based on a mean survival of 45 years combined with a mortality rate of 1% from the treatment (figs 1 and 2).

The results are so dramatic that we have presented them in two formats. In fig 1 the vertical axis is measured in number of days of survival. In this presentation the variation before 1885 is so small as to be unobservable. Even the 3-sigma upper and lower control limits are too close together to be seen. The shorter survival points in the post 1885 treatment experience reflect one death in that group of five patients. In order to show more clearly the pre 1885 variation, fig 2 presents exactly the same data but with the vertical axis transformed into a logarithmic scale. The pre 1885 data show a very stable process without special cause variation. Every
one with rabies symptoms soon died. The serious scholar may
disagree with our simple approach and assumptions about
survival, but we think that the before and after differences
were so great that this simulation is plausible.

The statistical power of this evidence is overwhelming.
Based on these pre 1885 control limits, the probability of
living 4000 days is above the 894-sigma level yet the results
were even more dramatic than that. When little Joseph
Meister had lived to October (or 90 days), his survival was at
the 20-sigma level ($p = 6.4 \times 10^{-13}$) and the French academi-
cians were right in declaring Pasteur’s treatment a great
victory. Thus, SPC methods can demonstrate a dramatic
difference as a result of the outcome from one patient and the
new treatment can be started immediately, rather than
waiting for the results of a prospective controlled trial.

PARACHUTE JUMPING AND OTHER EXAMPLES
Gordon Smith and Jill Pell wrote a fine satirical article in
2003 pointing out that the use of parachutes has never been
subject to a randomized controlled trial. A careful literature
review found rare examples of people falling from great
heights and living. Olympic ski jumpers survive their falls.
The authors report that parachutes can fail to open resulting
in death. We all learn at an early age the unvarying power of
gravity and do not need to be convinced that falling from a
great height is likely to be fatal. SPC evaluation using past
experience which we applied to rabies vaccination may be
relevant here. Even more dramatic control charts could be
simulated, particularly if ski jumpers are excluded.

There are other examples. The progress made in the
treatment of acute lymphoblastic leukemia (ALL) of
childhood is one of the true success stories of modern
medicine. Incremental advances over 50 years mean that
ALL has gone from a uniformly fatal disease to one with an
overall cure rate of more than 75%.

Another example was the dramatic introduction of ether as
an anaesthetic during surgery. In this case the outcome
measure would be pain rather than mortality.

RCT VERSUS SPC
For the four dramatic improvements described here, we
propose that information from prior experience using SPC is
to be preferred to RCTs for six reasons (table 1). In these
circumstances SPC has greater statistical power to exclude
chance as an explanation. The RCT is designed to control for
unknown confounding variables. Perhaps the treatment only
works for young boys and not for older women. In the case of
symptomatic rabies before 1885, men and women (young
and old) all died without variation. If there were any
unknown confounding variables they would appear as special
cause variation in a long series of prior observations.

SPC can give a very rapid answer in these circumstances.
There needs to be a plausible process (treatment) change
associated with the astonishing outcome that is replicable for

<table>
<thead>
<tr>
<th>Evaluation characteristics</th>
<th>RCT</th>
<th>SPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Show treatment effect not due to chance (statistical power, tests of significance)</td>
<td>Large sample size</td>
<td>Much greater statistical power to exclude chance as an explanation in the sequential context</td>
</tr>
<tr>
<td>To control for confounding factors</td>
<td>Randomization</td>
<td>Prior experience (everyone died regardless)</td>
</tr>
<tr>
<td>Causation</td>
<td>Experimental change is causal</td>
<td>Plausible process change which can be replicated with similar results</td>
</tr>
<tr>
<td>Speed of answer</td>
<td>Typically in years for a large trial</td>
<td>For a large change the results can be demonstrated for one patient</td>
</tr>
<tr>
<td>Ethics</td>
<td>Would you volunteer for such a trial</td>
<td>No one foregoes the new treatment</td>
</tr>
<tr>
<td>Use of knowledge from prior experience of outcome</td>
<td>Not used</td>
<td>Uses knowledge of prior experience</td>
</tr>
</tbody>
</table>
the next patients. Without this scientifically based replicable treatment, Joseph Meister’s survival could be declared a miracle and his cure associated with the intervention of a saint—the statistical analysis of miracles. One test of an ethical randomized trial is whether you yourself and others would volunteer for random assignment to control or experimental groups.

When the expected differences are small, when unknown confounding variables are likely to overwhelm the treatment effect, where the casual model is weak, where prior information is thin, when there is a single intervention and single end point, and results are not urgent—then RCTs are more useful.

Appendix: Technical Note

This section describes the simulation we performed to demonstrate the applicability of control charts to detect extraordinary causes in the rabies case study.

We generated two samples to represent the survival of two populations of individuals after onset of rabies symptoms. They are before and after July 1885, the date in which Pasteur incidentally initiated the test of the rabies vaccine in humans. We modeled each population’s survival assuming that the survival time presents a Weibull distribution, a common probability distribution used to model time-to-an-event variables. This distribution allows for a dependence of the hazard on time. In this case, this would represent a potential change in the risk of death with time since presentation of the disease.

We performed all the computations for the simulation in SAS for Windows Version 9.1.

Table 1 Parameter values used to generate samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>λ</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1</td>
<td>0.044</td>
<td>2.5</td>
</tr>
<tr>
<td>Sample 2</td>
<td>7.4×10^{-5}</td>
<td>13</td>
</tr>
</tbody>
</table>

After we generated the two samples and joined them together to represent our rabies cohort, we proceeded to apply the concepts of control chart to assess the significance of extending the survival time after the injection with rabies vaccine.

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