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Dehydrated Elephants and Other Matters*

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The title that I have chosen may seem very strange. It comes from a cartoon in Hein's book[1] where two academic powder technologists are studying a little heap of powder, and remarking: 'Of course, nobody really wanted a dehydrated elephant, but it's nice to see what we can do'. I am more concerned with the second part of this statement than with the first. I am going to talk on the methods that exist for achieving progress in science, show some applications of these in pharmacy and drug research, and try to identify areas where the application of the scientific method has been poor or non-existent. I am also interested in scientific prediction.

The lay public is ill-informed about how discoveries are made, mainly because the mass media are baffled by, or uncaring in their attitude to, the process of discovery, and over-react to the nature of the discovery itself. People would be better able to assess the significance of a discovery, if they knew more of the method by which it had been made. One common delusion is that discoveries like explosions, happen. Nothing happens at all if the environment is not right.

To begin with there has to be access to information. This is supposed to take the form of facts. Our so-called facts are not facts, but the experimental results available to us. Some of these may be wrong, but while acknowledging this we have no reason at this time to believe they are wrong.

Data also depend on the way the experiments were done. A good illustration of this is given in Walker's 'Diagnosis of Man'[2] where different people are examining an elephant, which none of them had seen before, in the dark. One touched the trunk and thought an elephant was like a water pipe, another touched an ear and thought an elephant was like a fan. Each gave an account of the elephant according to his own experience.

Since the data are only true to varying degrees, there is no reason why they should escape bias in their collection. Popper[3] has made the point that science is a collection of data made according to the collector's interests and viewpoints. The common delusion that scientists are impartial is not really true; they are biased in that they wish to test their own viewpoint. Where they must be impartial is in accepting the situation if their viewpoint turns out to be incorrect.

Having assembled the facts according to preconceived ideas, a hypothesis is developed which is a tentative statement arising from them. As a simple example, a man studying neuromuscular blockade by quaternary ammonium compounds might make a hypothesis that two quaternary ammonium groups were needed for activity. This would be fair enough as far as it went. However, if he did a lot more experiments, and found that the decamethonium compound was the most active, he might theorise that maximum neuromuscular blocking activity occurs when the distance between the two nitrogen atoms is about 9·5 Å [4]. This is a much more precise statement and deserves to be called a theory, not a hypothesis.

How does the theory emerge from the data? There is no simple answer to this question. Davies[5] states it arises from a leap of the imagination, from inspiration, from creativity. There is an intuitive leap from what

* A shortened version of the text of Professor Elworthy's Science Chairman's Address to the British Pharmaceutical Conference in 1971 in Glasgow reprinted, with permission, from the Pharmaceutical Journal 1971 207: 265-269.

Einstein called 'a sympathetic understanding of experience'. James Watt has left us an illustration of this leap. He is describing a walk on Glasgow Green: 'I was thinking on the engine, and gone as far as the Herd's house, when the idea came into my mind that as steam was an elastic body it would rush into a vacuum, and if a communication was made between the cylinder and an exhausted vessel, it would rush into it and might be there condensed without cooling the cylinder.... I had not walked further than the Golf House when the whole thing was arranged in my mind'. Kekulé said, 'Let us learn to dream, and then perhaps we shall learn the truth. Let us beware of publishing our dreams before they have been put to the proof by the waking understanding.'

Having given birth to the theory, there are two things to be done with it. It must be published and tested. The desirable thing is to test first and publish after, as Kekulé said. Before speaking of the testing of theories it is worth stating the necessity for eventual publication. This is to enable other minds to be critical. The proud parent wants to show his brainchild to the world, and there are quite a few other brainchildren being exhibited by equally proud parents. Thus there is the possibility of conflict amongst the parents. This is part of the cruel method of science, in that conflict is invited. It is part of the testing process for the theory. Publication also enables others to judge if the initial facts on which the theory was based were well chosen or too biased.

Therefore, we set out to test the theory. One method is to receive criticism from others. Another is to do experiments. These must be relevant and be planned with the purpose of strengthening the theory or ruining it. In drug research, experiments are nearly always possible, rather than in the situation that exists for astronomers, who can observe the light or radio-emissions from a distant galaxy, but not change conditions to alter these manifestations.

As human beings we are limited in our range of perception. We are limited in the range, precision, and rapidity of response of our senses, and therefore we need instruments to measure things for us and to work out the results. Before attempting experiments we must know about the precision of our instruments.

In doing an experiment, a choice of apparatus is involved, and that choice depends on several things. It may be that we need a very high degree of precision – say that our theory is confirmed if the answer to an experiment is 608·1 but ruined if it is 608·2. If the apparatus is only capable of a precision of 1 in 100, giving an answer to 608 ± 6, then we are wasting our time. If it were good to 1 in 10,000, i.e., $608 \pm 0{\cdot}06$, we still wouldn't have much chance. If the precision is 1 in 100,000, i.e. $608 \pm 0{\cdot}006$ then we have a chance of proving the theory. The point about this type of experiment is that costs rise enormously as the measurements become more precise, and we may not have the resources to do the experiment, a common cause of frustration. This puts us in the position of trying to guess the economic consequences of the result before we've done the experiment, in order that we can try and persuade somebody to give us the money. Scientists may not be everybody's image of salesmen, but sooner or later they have to try and purvey that most difficult commodity, ideas.

As an example of experimental proof, it is worth citing the theory of relativity[6]. According to the theory, light is attracted by a heavy body like the sun. Light from a remote star passing close to the sun is bent, according to Einstein's theory of gravitation. Einstein's theoretical prediction was a bending of 1·745 minutes. Experimental values of $1{\cdot}61 \pm 0{\cdot}30$ minutes and $1{\cdot}98 \pm 0{\cdot}12$ minutes were found in 1919. Precision was important.

I have been speaking about testing theories by using precise physical measurements. This is valid in some parts of drug research, but not in others. We cannot measure an animal's response to a drug to one part in 100,000 and will be lucky to get to one part in five. Therefore, the experimental design takes account of the precision by using many animals, and making sure that the design gives a statistically significant answer. We have to test the evidence, and good fortune is not on our side or against us. To quote Weatherall[7], 'for instance, two patients, suffering from a usually fatal disease, are treated with a new drug and both recover, while two not treated die, the difference is not statistically significant but it is exceedingly important'. Unless one has the

leisured life and approach of Humphrey Hastings, it is no good doing experiments whose results are uninformative. Experimentation will never become redundant, because no theory is true.

No theory is true

The statement that no theory is true may seem surprising. Yet this viewpoint is generally accepted. It might be better phrased by saying there is a theory that no theory is true. I must be careful here, or head for semantic destruction. No theory is absolutely proven; it is just not disproven. In testing a theory we work to knock a hole in it. This is a second example of the cruelty of the scientific method, in that the brainchildren are under constant threat of extinction, and that this continuing attempt at destruction is a conscious process. The ability to discard old beliefs and adopt new ones is a valuable ability, but it is sometimes difficult for those with a non-scientific training to adapt in this way.

Good theories are often simple. They have unified a number of previously disconnected experimental observations. The greater the unification, the more fundamental the theory is likely to be. It may be that the theory has stood up to testing so well, and has not been broken under test, that it is called a law. Examples are Newton's laws, and, the first two laws of thermodynamics. Even so-called laws are subject to some adjustment at times. The first law of thermodynamics states that energy can be transformed from one kind to another, but not created or destroyed; alternatively, it can be stated as: the energy in an insolated system is constant. This is a well-founded precise theory, a cornerstone on which a great edifice of chemical thermodynamics has been built. Not very long ago, nuclear reactions were realised to be significant producers of energy. However, in relativity theory there is the recognition of a relationship between mass and energy. When energy is produced in a nuclear reaction, mass decreases. The so-called law is therefore broadened and strengthened by these developments. It now is wider in that mass and energy are involved in it, and not just energy. It becomes evident that the law of observation of energy and law of conservation of mass are really the same. The first law of thermodynamics was strong enough to stand up to this new experimental data: its main thesis was unchanged. It has become a stronger theory because is now unifies more concepts, and this comes back to the basic point that nothing in science is sacred.

So far I have traced the path of development of the theory in which a number of facts or experimental results have been assembled according to the whim of the assembler; an intuitive leap has provided a theory, which is tested by further experiments designed to improve or upset it. The theory may be modified or strengthened as a result of this testing. The process is one of successive approximation, involving experiment and thought, and repeating these two steps.

The question must be in your minds: why go through this intellectually demanding and possibly expensive operation to get this theory, especially as we are likely to try and disprove it when we've got it? This is a fair question. What use is the theory? The simplest answer is that it provides its creator with intellectual satisfaction. In universities we have an inalienable right to think, provided we do it quietly and that the experiments on which we think do not cost too much. This is rather a selfish answer to the question. The more important answer is to have a theory so that it can be used as a tool. This is the real power of the theory: its formation is not an end in itself; it enables predictions to be made. The predictions carry the seed of a new discovery, which can flower or die, and are the forward step in scientific progress. I shall deal with some selected predictions shortly, but first I want to explain the general method.

One of the most intelligible explanations of the use of the theory is Davies'[8] extension of Popper's searchlight analogy. The analogy is that the theory is a lightbeam which makes things visible. Whether an

aircraft becomes visible in the beam depends on the properties of the beam, and also whether the aircraft is significant enough to reflect light.

Studying a theory and making a prediction from it is analogous to pointing the searchlight at one part of the sky and turning it on. Successfully finding the 'plane in the beam is analogous to making a successful prediction from the theory. If we made the prediction very wide, which is the case in which the beam illuminates the whole sky, then the beam is diffuse, it lacks power, and it does not show up the plane. This wide prediction does not case much light on the subject, and we do not learn anything from the process. We use therefore a narrow beam of light, making the prediction more precise, and giving a better test of the theory. In this stricter way, we may achieve success, by locating the plane. Alternatively we may fail by not doing so. If we have failed we must re-examine the theory; this is analogous to re-examining the setting of the searchlight, and the width of the beam. We cannot see a flaw in the theory, but there must be something else wrong. Its experimental foundation must be checked and it must be remade. This would be like scrapping the searchlight and making a different one.

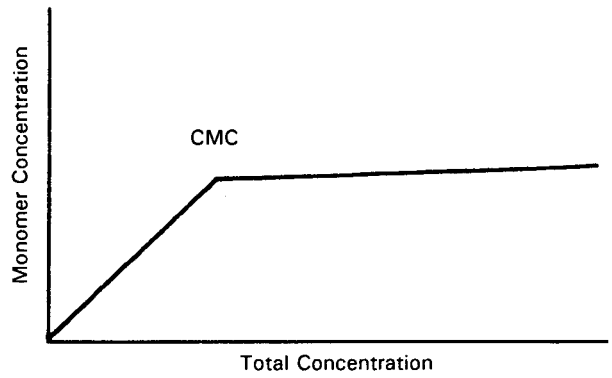
Before coming to theorisation and prediction in drug research, I shall use a simple example as illustration of the testing of theories, drawn from an area of interest to me. In 1935, Hartley and Murray[9] attempted to explain the changes which occurred when surfactant molecules came together to form a micelle. In simple terms they wrote down a chemical reaction:

$$n(\text{molecules}) = \text{micelle}$$

and for concentration C_1 and C_2 of the single molecules and micelles respectively wrote:

$$K = C_2 / C_1^n$$

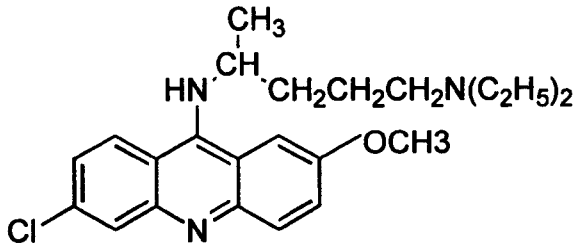
where K was the equilibrium constant. When the concentration of a single molecule is calculated, and plotted against total concentration, the graph shows that starting from zero, the added surfactant forms single molecules in solution, then at the critical micelle concentration (CMC) the micelles form. However, there is a slight increase in the single molecule concentration above the CMC. Hartley's ideas seem reasonable, and worked out well in representing the behaviour of surfactant solutions.



There was only one major discrepancy. As the change in surface tension is proportional to the change in concentration of single molecules above the critical micelle concentration, it should decrease with increased concentration. A number of experiments had appeared which showed a constant surface tension, which is in disagreement with the theory. There were two broad alternatives. Either the theory was wrong, and it was difficult to see why, or the experimental determination of the surface tension concentration curve was not correct.

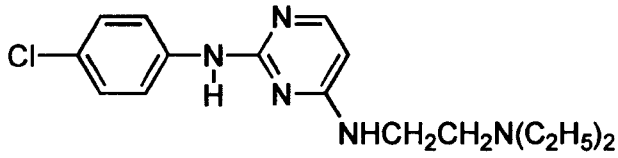
An experimental approach

This was an obvious case for an experimental approach[10], and as the expected change in surface tension was only one or two dynes per centimetre over the concentration range studied, it was necessary to have a precise experimental method. One was developed to be precise to ± 0.02 dyn/cm, (mNm^{-1}) so that the experimental effect could be observed. The second consideration was that the effect might be confused by impurities. Hence the experiment was conducted in a closed system, with purification of the surfactant by foaming, so that impurities were swept away before the measurements were carried out. When this was done, the surface tension was now found to decrease above the CMC. The prediction of the theory was thus confirmed. This does not mean that the theory is correct, but simply that it has been reprieved for another day. This is a small example of the use of the scientific method. A larger one[11], which I shall examine briefly, is from medicinal chemistry. The screening of compounds for antimalarial activity had shown that sulphadiazine had a feeble activity, as did sulphidimidine, and both contained a pyrimidine ring whereas compounds without this ring were inactive, giving a hypothesis that this ring gave activity. Simple pyrimidine compounds were inactive, destroying the hypothesis. However, it was known that the active antimalarials mepacrine and pamaquin



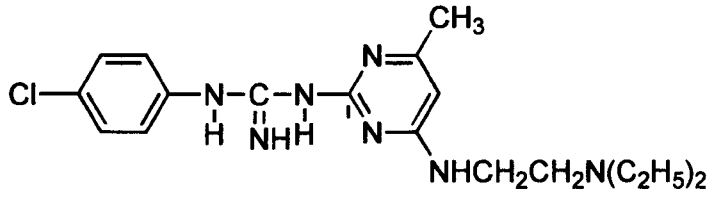
Mepacrine

both contained a diethylaminoalkyl side chain. This led to a second hypothesis of using this side chain with a pyrimidine ring, and gave an active compound I.



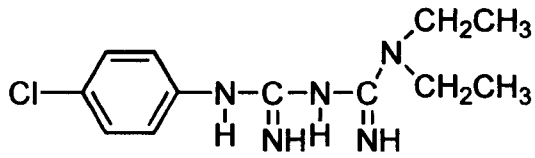
Compound I

The next step is the introduction of new data in that if the inter-ring imino link is missing, so is the activity. This gives a new working hypothesis that for activity there must be association of a pyrimidine nucleus, a basic alkyl amino group, and also an aryl group. These considerations led to the synthesis of another active compound,



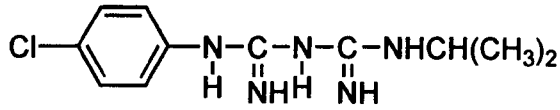
Compound II

II, and also to the idea the antimalarial activity is associated with alternating carbon and nitrogen atoms. Opening of the pyrimidine ring led to compound III (by a different route)



Compound III

which was active. Finally, by altering the alkyl substituents at the end of the chain proguanil was produced.



Proguanil

It is interesting to note the ruthlessness of this development. The idea of sulphonamides, then pyrimidine rings, then diethylalkylamino side chains giving activity are all examined, tested experimentally, and all are discarded by the time the structure of proguanil is reached. Nevertheless, each hypothesis in turn has led to a new development, each is therefore predictive, which is one of the main reasons for going to the trouble of generating hypotheses at all.

For a further example I will look at the initial discovery of a cure for diphtheria, which again consists of a chain of hypotheses and experiments.

In terms of available facts and experimental data, Klebs had discovered *Corynebacterium diphtheria* in 1883, Leoffner had confirmed this discovery, and Koch had isolated the same organism from the throats of people with the disease. Experimental methods were sufficiently developed for great advances to be made in bacteriology at this time.

Koch made the hypothesis that *Corynebacterium* was the causative organism. He tested this hypothesis by injecting the organism into animals, and found the characteristic membranes and symptoms of diphtheria were produced. This confirmed his hypothesis, and he made a prediction from time that death was caused by the bacteria producing an exotoxin. He was led to this prediction by the retention of the bacteria close to the site of the injection. The prediction was tested by Roux and Youssin, who filtered the bacteria off from a culture, injected it into animals causing diphtheria, which confirmed Koch's hypothesis.

There is a similar chain of events leading to the theory that antibodies confer immunity. Preliminary experiments by Fraenkel indicated that if animals survived a dose of toxin, they could withstand an injection of living diphtheria bacilli. The theory proposed was that sublethal doses of toxin affected the serum of an animal, and changed it so that it could prevent the harmful effects of the bacilli or the toxin. Behring and Kitasato confirmed this experimentally in guinea-pigs.

These discoveries were made according to the local process of the scientific method. Each begins with an assessment of the existing facts, then the formation of a theory, an experimental test of that theory, and finally predictions are made from it.

In some cases we are not capable of predicting what significance a discovery may have. This comes at a much later point in time. Hence the scorn poured on some dehydrated elephants when they first appear is unfair; nevertheless, scientific scorn is part of the scientific method.

DEHYDRATED ELEPHANTS

I am going to digress briefly to remind you of a feeling of helplessness. Parish[12] calls diphtheria the most devastating disease of children of the 19th century. He quotes the village of Elcour, with 40 households, losing 42 children in one winter. We have largely forgotten the great scourges, of which diphtheria was just one. Talking about statistics does not give a human, understandable picture of how one felt about a child contracting diphtheria in the 1890s. It meant death. I quote from Sherrington's[13] account of one of the first patients to be treated in England in 1894, from the doctor's point of view, to bring home the feelings of the times. Sherrington and Ruffer had been building up immunity in a horse in order to produce serum.

"Ruffer and I had been injecting the horse — our first horse — only a short time. We were badly in the dark as to the dosage to employ and how quickly to repeat the increasing injections. We had from it serum partly effective in guinea pigs. Then on a Saturday evening, about seven o'clock, came a bolt from the blue. A wire from my brother-in-law in Sussex. 'George has diphtheria. Can you come? George, a boy of seven, was the only child. There was no train that night. I did not at first give thought to the horse, and, when I did, regretfully supposed that it could not yet be right for use. However, I took a cab to find Ruffler. I pursued him and got a word with him. He said, 'By all means you can use the horse, but it's not yet right for trial.' Then by lantern light I bled the horse into a two-litre flask duly sterilised and plugged with sterile wool. I left the blood in ice for it to settle. After sterilising smaller flasks and pipettes and some needles and syringes I drove home, to return at midnight and decant the serum.

"By the Sunday morning train I reached Lewes. Dr Fawcett of Lewes was waiting in a dogcart at the station. I joined him carrying my awkward package of flasks, etc. He said nothing as I packed them in, but, when I climbed up beside him, he looked down, and said, 'You can do what you like with the boy. He will not be alive at tea-time'. We drove out to the old house; a bright frosty morning. Tragedy was over the place, the servants scared and silent. The boy was very weak; breathing with difficulty; he did not seem to know me. Fawcett and I injected the serum. The syringes were small and we emptied them time and time again. The doctor left. I sat with the boy. Early in the afternoon the boy seemed to be clearly better. At three o'clock I sent a messenger to the doctor to say so. Thenceforward progress was uninterrupted."

Even after the discovery was 50 years old, in 1940 there were 45,000 notifications and 1800 deaths[14]. The national scheme for immunisation has cut down the disease to a very small number of cases, leading to 25 notifications and no deaths in 1965. Yet in Manchester in 1971 there was an outbreak amongst children whose parents had not had them immunised. In Holland in 1971, 27 children contracted poliomyelitis and two died, and to quote the Daily Telegraph "The Dutch government and provincial authority fought the extreme Calvinist dogma opposing vaccination". Events like this lead to the thought that people are not to be trusted, or not to be allowed to forget to have a child immunised, or, as a different matter, are not to be allowed to refuse children immunisation. And for other drugs that the administration should be removed from the patient's hands. I shall return to this concept shortly.

Prediction

One of the most important matters that has arisen in the first part of my talk is the powerfulness of the scientific method in making predictions. I mentioned the searchlight analogy in making them, and gave an example of Einstein's prediction of the amount of bending of light by the sun. We have looked at the series of small predictive steps lying behind two discoveries of medicine. There are many well-known examples, for instance, the astronomer Leverrier's study of the orbit of the planet Uranus. The perturbations of its path were such that they could not be explained by the current theory, and Leverrier predicted that an undiscovered planet was responsible. Thus Neptune was discovered by examination of the predicted part of the sky[15].

Yet there is also great danger in prediction. Any extrapolation rests on the assumption that the factors affecting the data in the past will not alter in the future. Davies[16] cites a very good example in which the predicted birth rate in England and Wales became zero in 1970. New factors, like war, prosperity and perhaps even effective new drugs, became operative in the 1930s, and affected the prediction severely.

Let us look briefly at dosage forms in a predictive sense. In the past formulation has probably been the least scientific area in pharmacy. The papers discussing the progress from sulphonamides to proguanil were published in 1945. At that time formulation was highly empirical. For example, lubricants were added to tablet granules to make them flow more easily, the over-riding situation being ease of production. Nowadays we ask what the additive does in cutting down dissolution and decreasing bioavailability.

It is probably fair to say that formulation has been unscientific, but has changed rapidly in the last 15 years. Before that time, it consisted of looking at the effects of experimental variations without having reasonable hypothesis to help progress. There is more theory now. For instance, we are engaged in testing the hypothesis that the pore structure of a tablet governs its performance, because we think that this pore structure regulates how water enters the tablet to begin the process of disintegration and dissolution. Essentially, we are beginning to test the theory that the drug has got to be in the right place in the patient in the correct concentration.

It is interesting to note one or two dehydrated elephants, which have taken on a new look, and have become useful in formulation. Who would have thought that Arrhenius's treatment of reaction rates, which was interesting to physical chemists, but not to many other people, would become of every day use to the formulator in accelerated stability testing? Or that Stoke's law, derived initially to explain the motion of a pendulum swinging in a liquid, would come into use for determining the particle size of drugs?

Where we must further have innovation is in the nature of the dosage form itself. In 1650, the dosage forms available were syrups, oils, lozenges, ointments, plasters and pills[17]. In 320 years, tablets, capsules, suppositories, aerosols and injections have been added to the list. Aerosols and injections are the only real innovations, because aerosols rest on knowing how to compress and handle gases, and how to make valves with fine tolerances; injections rest on microbiology as well as engineering. Thus information and techniques from fields outside pharmacy have helped in the development of new dosage forms. It may be that even more use could be made of techniques from other fields in the future. Advances in electronics and engineering have been enormous.

Bear in mind the current problems of the abuse of soft drugs when they have left the pharmacist's control, which none of the social or legislative remedies has so far affected, and which is a growing problem. Combine all this with the idea that a more effective and controlled release of drugs from preparations is needed, and also that there are many reasons why we would like to remove the act of drug taking from the hands of individual patients. Should there not be research directed to the making of dosage forms containing mechanisms to release the drug on receipt of signals from outside the body, the receiver in the dosage form having been preset to a special code for the particular patient? This gives controlled release, specific to each patient. Provided the capsule is indestructible, or fitted with destruct mechanisms reacting to tampering, much of the abuse problem disappears. These ideas are crude, but worth putting forward in a speculative way. The system sounds cumbersome. The first thermionic valves were cumbersome, but scientific progresss has made its present day equivalent hard to see with the naked eye.

The scientific process of thought

All through this lecture I have developed the idea of the usefulness of the scientific process of thought. A theory unifies previously disconnected concepts. It produces a powerful intellectual satisfaction at having acted

creatively, which is also transient, because of the threat that undiscovered knowledge poses to the new theory, and therefore somewhat sad. Equally important, it produces a prediction. It is our best attempt so far at a crystal ball, and it is an age-old desire to have a crystal ball. A good theory has implications, which is the test of good research. We may not find that the implications of inspired research are good for us, and there are many instances, from thalidomide to having too much lead in the atmosphere, where this is the case. There have also been marvellous implications like diphtheria antitoxin and nylon. Science on the whole has had a tremendous return on its intellectual investments: it has had incredible success from its relatively simple but demanding method. Some of these discoveries were initially dehydrated elephants; they often have become useful.

Conclusion

There is no conclusion; there never can be when speaking of a continuing line of scientific research.

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References

1. Hein, W. H., "Die Pharmazie in der Karikatier", C. H. Boehringer: Ingelheim am Rhein, 1964, 209
2. Walker, K. M., "Diagnosis of Man", Jonathan Cape: London, 1942, p13
3. Popper, K. R., "The Open Society and its Enemies", 4th Edition, Routledge: London 1962, 213 and 259
4. Elworthy, P. H., *Journal of Pharmacy and Pharmacology*, 1963, 15, 137T
5. Davies, J. T., "The Scientific Approach", Academic Press: London 1969, p11 et seq.
6. Ricke, R. H. in "Relativity, Groups and Topology", Gordon and Breach: London 1964, p191
7. Weatherall, M., "Scientific Method", English Universities Press: London 1968, 125
8. Davies, J. T., "The Scientific Approach", Academic Press, London, 1969, p32
9. Hartley, G. and Murray, F., *Transactions of the Faraday Society* 1935, 31, 183
10. Elworthy, P. H. and Mysels, K. J., *Journal of Colloid and Interface Science* 1966, 21, 331
11. Curd, F. H. S., Davy, D. G. and Rose, F. L., *Annals of Tropical Medicine* 1945, 39, 157; 208
12. Parish, H. J.," A History of Immunisation" E & S Livingstone: London, 1965, p118 et seq.

13. Sherrington, C. S., *Nature*, 1948, 161, 266

14. Dawson, M. and Milne, G. R., "Immunological and Blood Products", Heinemann Medical: London 1967, p94

15. Doig, P. "A Concise History of Astronomy". Chapman & Hall: London 1950, p134

16. Davies, J. T., "The Scientific Approach", Academic Press: London, 1969, p71

17. Culpepper, N., "The English Physician", Enlarged, 1974, p366