" WHAT ? " AND " HOW OFTEN ? " IN MEDICAL RESEARCH

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NATURE makes some people restless and inquisitive; others take life at its face value. So it is with the verb " to see ". It may be either transitive or intransitive, active or passive. In the early days of modern Japan, when it was being reopened to foreigners about 100 years ago, some visitors expressed their shock and disapproval at seeing Japanese men and women bathing together naked in the hot springs. The Japanese reply, full of Oriental wisdom, was simply " We see but we do not look ". In research, however, neither seeing nor looking alone are enough. Something is needed as well. " To perceive " is defined in some dictionaries as " to see with understanding " and this is my theme today.

Can we write a prescription for research? The recipe sounds so simple. First you make an observation, then you see how often you can repeat it. Please note that there are two steps, not one. The crux of the matter is to make the primary observation. What you see depends on how you look and at what, and it depends on your powers of perception. If you only look at your patient and try to carry all the syndrome in your mind, you will either forget or invent the details later when you require them. This is where the value comes from records written at the time they were made and before your hypothesis was framed; but if you are always too busy ever to read your records again, you will not perceive the lessons they are trying to teach you. If you are too rushed in your daily visiting, you may not even have time to look at what you see.

As each disease and the use of each new drug comes to the notice of a young doctor for the first time, he should give himself time to look at what he sees. He should write notes at the bedside or soon after. From time to time he should look back at his recent notes,

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particularly of puzzling cases, and try to frame hypotheses for testing against his subsequent experience. This is the educational value of research and, if a doctor pursues it, he will one day " see with understanding " something which others have missed. Take for example, measles. Imagine the difficulty we should all have in diagnosing measles, if there were no rash to help us. Yet, if we look for and find those spots in the mouth which Koplik " saw with understanding ", our diagnosis of measles can be made quite as certainly as if we wait for the rash to develop. If any patient's illness is considered step by step there are probably many lessons to be learnt. This is our great advantage in general practice. We can watch a case develop and visit our patient daily or twice daily if we need. Do I hear someone say that in a busy practice he has no time for research? I was taught many years ago by a wise man that time is something you make, not have.

Go back to the distinction between " what " and " how often ".

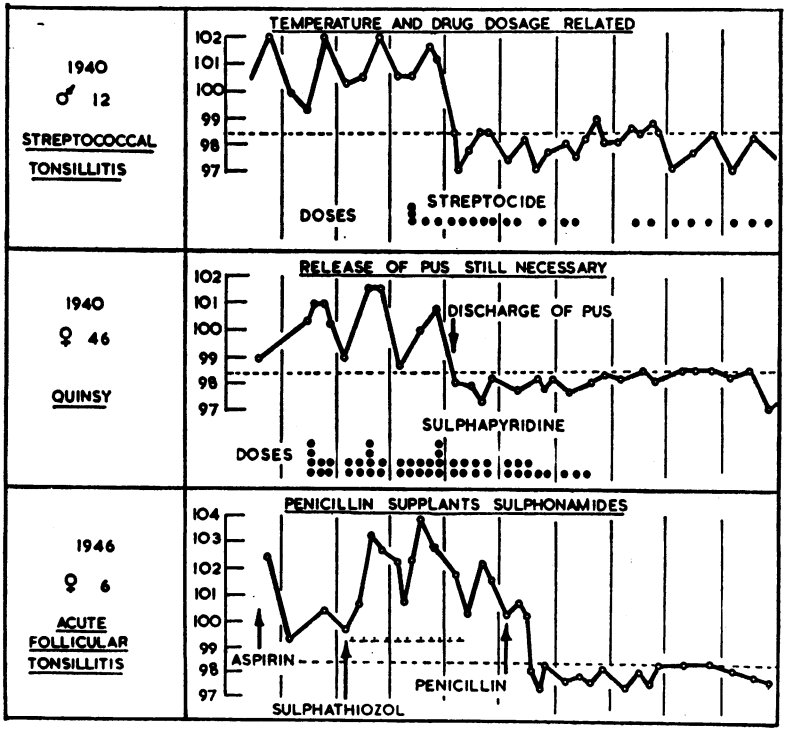

Figure 1

Sulphonamides and penicillin: some early lessons.

Some of the simplest lessons about " what " can be learned from a critical study, case by case, of the benefit or failure of antibiotic treatment in patients with infection. In the early days of sulphonamides and penicillin, I soon found the value of teaching my patients to take and write down a record of their temperatures. The top chart in figure 1, and others like it, showed me the importance of keeping up the intensity of sulphonamide treatment if the initial benefit was not to be lost. You see that as the tablets were more spaced out so fever returned, only to be controlled by giving more tablets more frequently. In the second chart you see that even a high dose of antibacterial drugs alone would not cure a quinsy, once pus had formed. The release of pus was essential but antibacterial drugs, given before surgical incision, may make healing quicker and more complete. In the bottom chart you see not only the deceptive relief which aspirin provides but also the rebound of temperature when the infection breaks through once more. This was a case of staphylococcal tonsillitis, in which sulphonamides were of no benefit but penicillin gave immediate and lasting control. I will say something more in a minute about possible disadvantages of suppressing the body's febrile reaction against infection.

Figure 2 shows how easy it would be to conclude that oxytetracycline or chlortetracycline possessed some antiviral action. The course of illness in both these patients was similar. At first each had a rather featureless pyrexial stage before starting to cough, and only after that did signs of endobronchial secretion develop. This syndrome is characteristic of atypical primary or so-called " virus " pneumonia. The upper chart shows how dramatically the temperature was controlled by oxytetracycline. Eaton's agent, the cause of this condition, is now known to be not a virus but one of the pleuropneumonia-like organisms, against which the tetracyclines are known to be active.

Whatever our doubts about the value of penicillin for any particular patient, the benefits over the years have been enormous. I want now to contrast these first two examples of " what " we may learn from single cases with one that shows " how often " and " how long " something happened. How long did pneumonia last before antibacterial drugs were in regular use? How often did a doctor have to visit his pneumonia patients in the old days? Figure 3 shows that in 1940, the first winter that sulphonamides were coming into general use, daily visiting for about a week or even a fortnight was not uncommon during an illness, which often lasted a

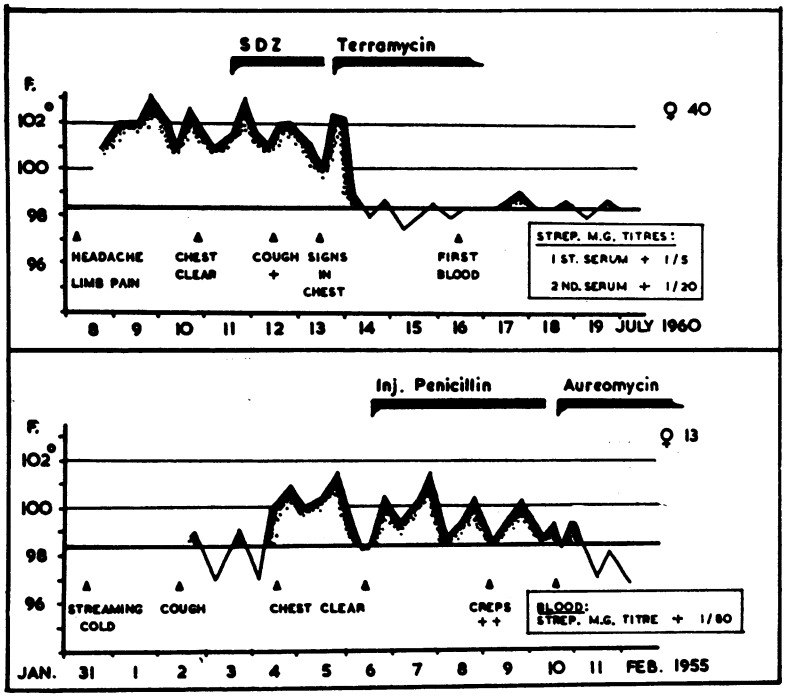

Figure 2
Atypical primary virus pneumonia: ? anti-viral action of daily lerramycin.

month or more. Note how many patients had to be sent to hospital because they were just too ill to be looked after at home. It may surprise you to see that about the same number of cases of pneumonia started in each of these months 20 years apart; antibacterial drugs have not made the disease less common, but by 1960 they had greatly shortened the illness and speeded up the patient's recovery, as well as cutting down the doctor's work and letting him do more for his patient. Even so, in each group one patient died at home: in 1940 before being sent to hospital—in 1960 after dozing overnight on aspirin but before being given penicillin, although at post mortem we found that both infections were due to pneumococci.

Can we learn any more in general practice about the action of aspirin in febrile illness? The top chart of figure 4 is of a patient with a continuing infection whose temperature was at first suppressed by aspirin but in whom, eventually, fever was rekindled. Such a break-through is to be expected in any continuing infection. The lower chart shows how, in a patient with a febrile catarrh, aspirin at first deceptively appeared to be succeeding; then came the break-

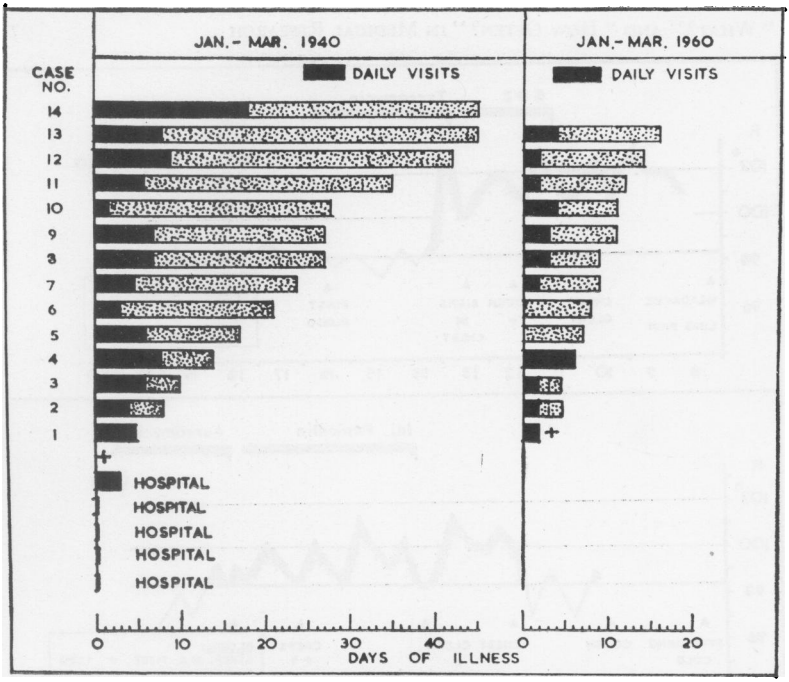

Figure 3. Pneumonia: length of illness and daily visits.

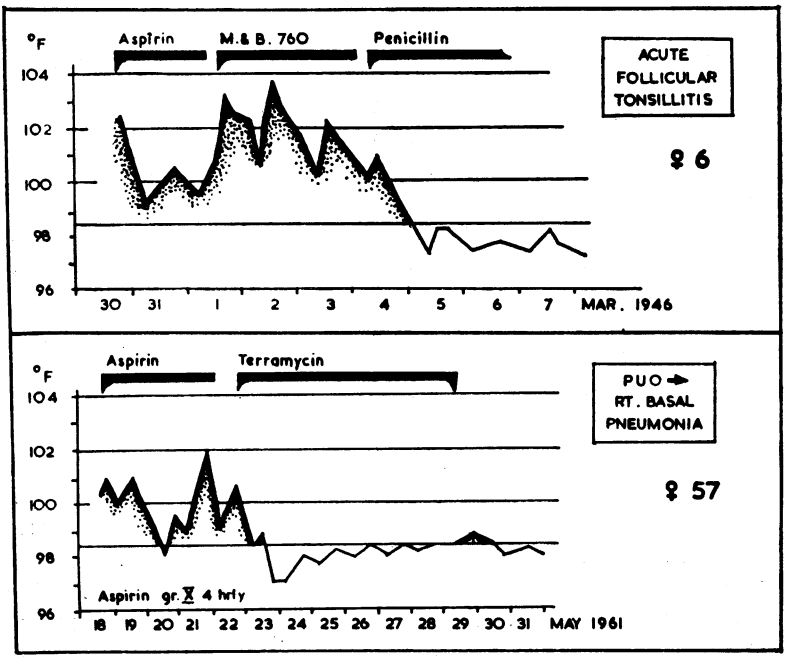

Figure 4. Aspirin suppresses fever but does not cure infection.

through. She developed pneumonia and her infection was only controlled effectively by an antibiotic. These, then, are examples of the first lesson which everyone can learn for himself; namely, that aspirin may suppress fever for a while but, if the infection is of a continuing type, since aspirin can never *cure* any disease, it will eventually fail to benefit these patients, whose temperature will subsequently rise—often to a higher level than before aspirin was given. This is true not only of bacterial infections but also, for example, in influenza. Figure 5 shows the typical biphasic response to influenza infection, uninfluenced by drugs. Note that the second spike of fever is usually lower than the first. The same pattern appears in the lower chart of figure 6. The upper chart is, however, that of a nurse who stayed on duty throughout her first bout of fever, suppressing it with tablets until they made her vomit. She was then persuaded to leave off her suppressive treatment, allow her

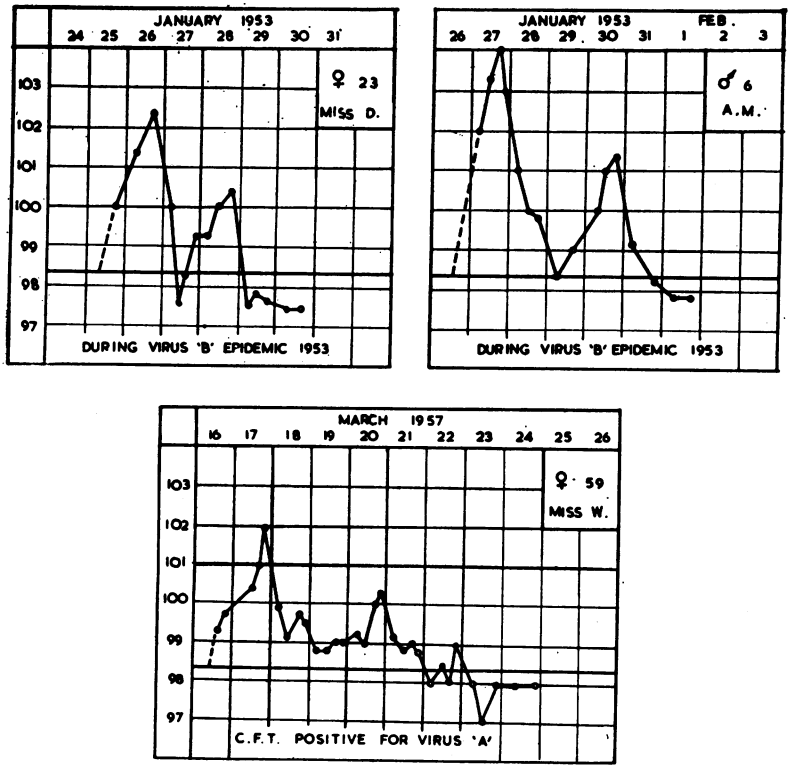

Figure 5
Temperature charts of influenza prior to the Asian epidemic.

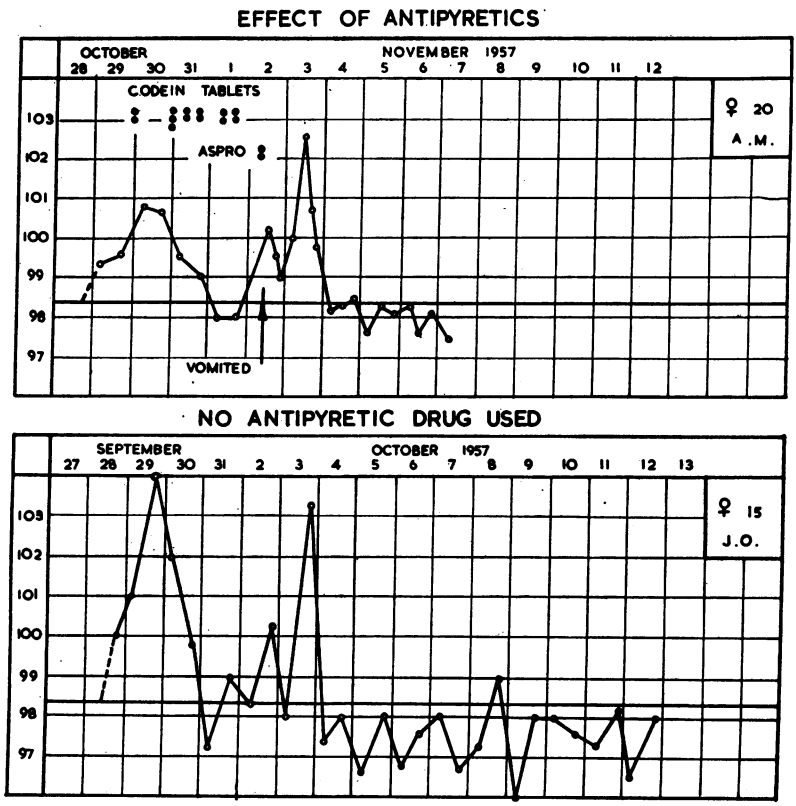

Figure 6
Illustrating the effects of antipyretics on fever.

second spike of fever to come and go as expected, after which she recovered normally.

So much for what happens in particular cases where a continuing infection is suppressed by aspirin. How often does this matter? Figure 7 shows " how often " various tablets containing aspirin had been taken by patients with proved type I polio virus infection in Belfast in 1957. These observations, stimulated by my discussion of the problem with Dr David Surrey Dane, were made by himself and Dr S. N. Donaldson, assistant medical officer of health of Belfast at the time, to both of whom I am grateful for their use. The diagram shows that proportionally more tablets of aspirin had been taken, and by more patients, among those whose paralysis was severe than among those whose illness was non-paralytic. The lesson is that aspirin suppresses the symptoms of fever, allowing an ill patient to think that he *is* as well as he *feels*, allowing a stubborn

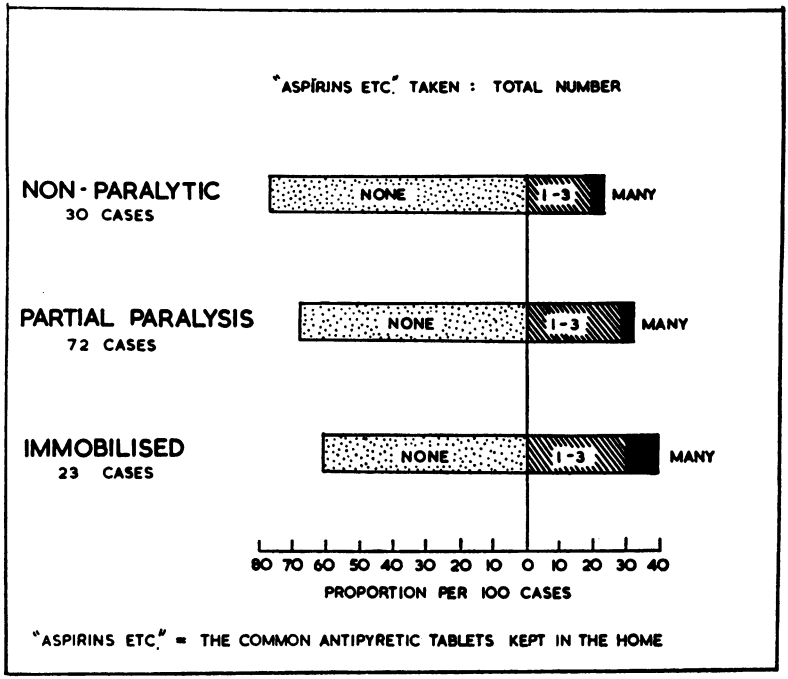

Figure 7
The effect of " aspirin etc. " on the degree of paralysis in proved type 1 polio virus infection (Belfast 1957).

patient with an infection to keep on at his job without giving in, allowing the young athlete to keep on at his games and, as is shown in figure 6, allowing a young nurse to stay up and about, probably infecting others who were already ill, instead of going to bed herself, as she eventually had to do. Antipyretics used for these purposes may do the patient and his contacts more harm than good.

Let us now go back to the difficulty of diagnosing measles before the rash appears, and watch another case develop. This is a composite story of two children who began febrile respiratory illnesses during a measles epidemic, but let us pretend that there was only one patient—a girl of six (figure 8). On the first day measles was the most likely diagnosis but, as she had a cough and signs in her chest already, she was put on oral penicillin. Next day (figure 9) her temperature was higher but she was " better in herself ", not " iller". As the chest signs persisted, her treatment was changed to oxytetracycline. You have all heard a mother say about her child incubating measles " Doctor, she's better in herself ". Have you ever thought what that really means? It means her invasion fever is over. On

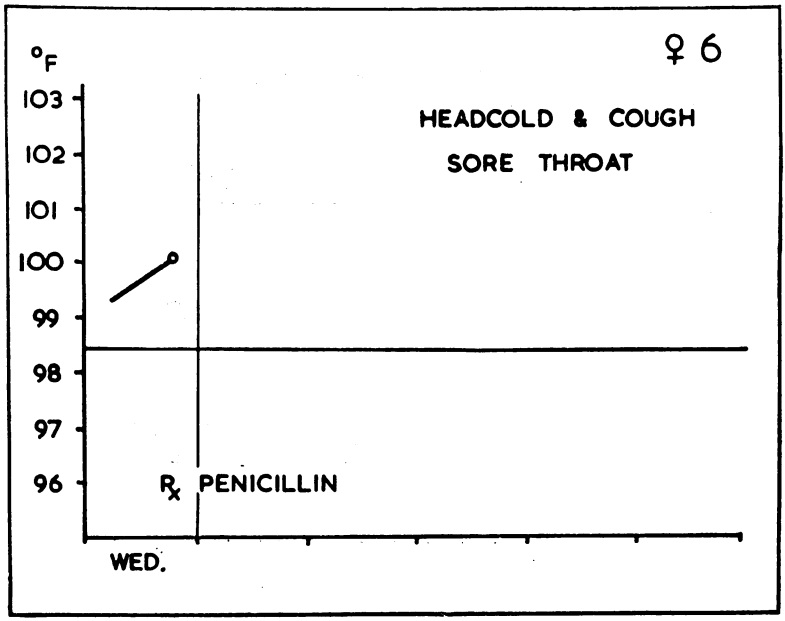

Figure 8
An exercise in diagnosis: P.U.O. chest during a measles epidemic: first day

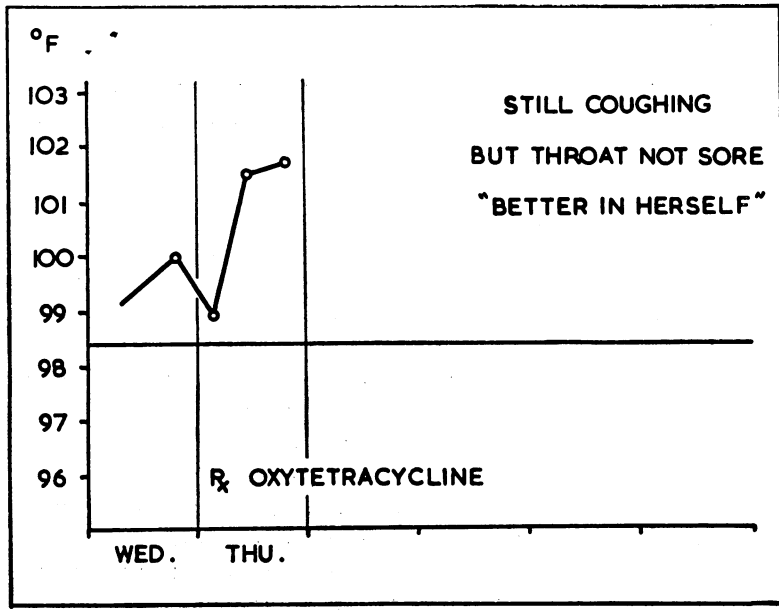

Figure 9
An exercise in diagnosis: second day.

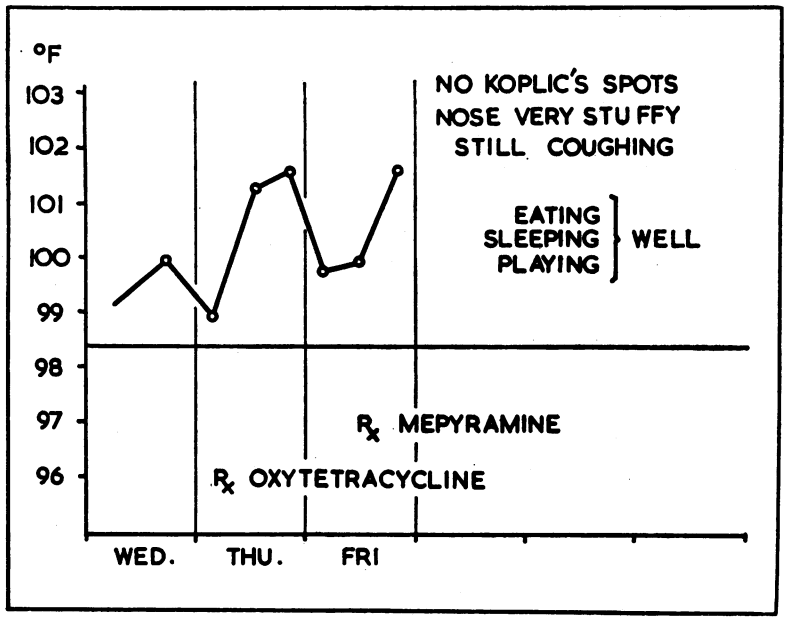

Figure 10
An exercise in diagnosis: third day.

the third day (figure 10), in spite of oxytetracycline, this girl's temperature was higher still. What should we deduce from this one finding, namely, a rising temperature in spite of oxytetracycline and in spite of her feeling better? First, that her illness was probably viral, not bacterial, in origin and secondly, that it was probably not due to measles because, as a rule, in measles the temperature drops before it rises to the second peak with the appearance of a rash. Measles was also improbable when no Koplik's spots could be found after three days of rising fever. Three days and more of rising fever may be seen in early atypical primary pneumonia, but here chest signs are often uncertain on the first day of fever, increasing later; whereas this child's signs were evident on the first day of illness but became less troublesome. While her chest signs were no worse by the third day, the child's nose was more blocked and she was mouth-breathing all the time, but she was not off her food and she was sleeping and playing happily. On all these symptoms and signs a presumptive diagnosis of adenovirus fever was made and a prognosis was given of full recovery from fever by the evening of the fifth day. A faecal specimen was sent off to the laboratory and the top left chart in figure 11 shows her completed temperature chart.

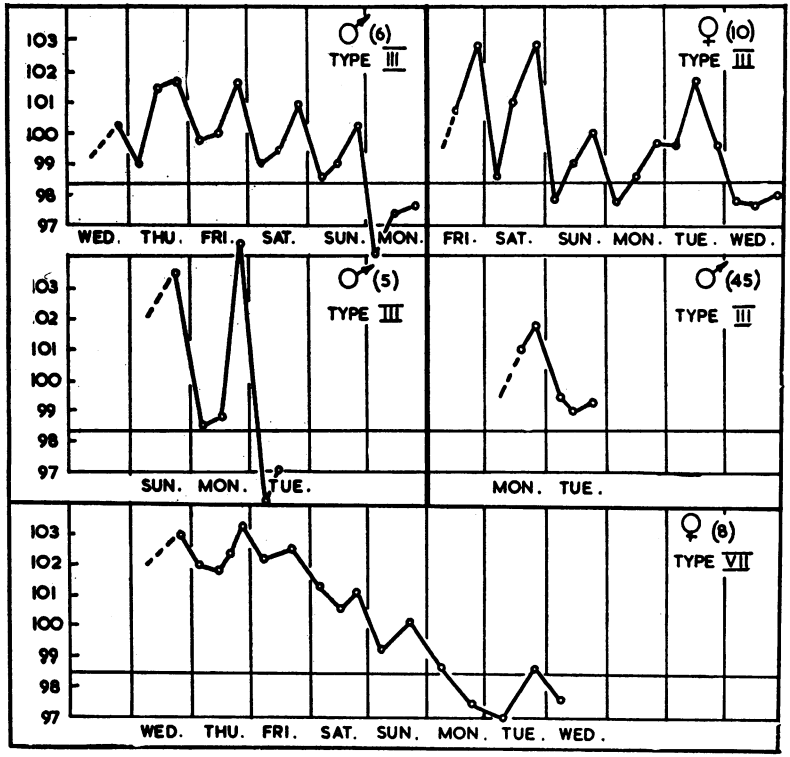

Figure 11
Temperature charts of patients suffering from adenovirus types iii and vii infections.

From her chart and those of other patients with adenovirus infection it can be seen that the peak of fever is often not reached until the second or even the third day of illness. This clue may help to raise your suspicion about the cause of a child's respiratory illness, particularly if the patient appears disproportionately well compared with the height of fever.

The next few figures show "how often" such virus infections can be identified. Figure 12 shows how often a positive viral diagnosis could be made in 120 cases of non-bacterial illness seen in a 12-month period. In each column the proved cases are shown in brackets and the other figure gives the total number of presumed or contact cases seen each month. Under "adenovirus" you see that laboratory confirmation was obtained in nearly half the cases diagnosed, whereas—two columns farther to the right—from cases of WP/60 (the code name given to an outbreak of acute biphasic febrile

MONTH	"SHERE FEVER" COXSACKIE 'A'	P.U.O. + RASH	POLIO VIRUS	ADENO-VIRUS	COXSACKIE 'B'	WP/60	STREP M.G. PNEUMONIA	?	TOTALS
1959 AUG.	4	2	-	-	1 (1)	-	-	-	7 (1)
SEPT.	1	3	2 (2)	1 (1)	-	-	-	-	7 (3)
OCT.	-	-	1 (1)	2 (1)	1 (1)	-	-	5	9 (3)
NOV.	-	-	-	10 (3)	-	-	-	2	12 (3)
DEC.	-	-	1 (1)	4 (1)	-	-	-	-	5 (2)
1960 JAN.	-	1	-	13 (8)	-	-	-	-	14 (8)
FEB.	-	-	-	3 (1)	-	21	-	2	26 (1)
MAR.	-	-	-	3	-	4	-	-	7
APR.	-	-	-	-	-	-	-	3	3
MAY.	-	-	-	3 (2)	2	-	-	2	7 (2)
JUN.	-	-	-	-	3 (1)	-	-	2	5 (1)
JULY	8 (2)	1	-	5 (4)	1 (1)	-	2 (1)	1	18 (8)
TOTALS CONFIRMED	13 (2)	7	4 (4)	44 (21)	8 (4)	25	2 (1)	17	120 (32)

Figure 12

The laboratory diagnosis in 120 cases of P.U.O. in 1959-60 (Figures in brackets =number confirmed by laboratory).

pneumonitis) no viral or bacterial agent could be identified. Even including these, however, the type of virus was identified in about one-quarter of the cases seen during 1959-60.

By the end of 1962 more than 120 positive virus isolations had been made by Dr Cook and his staff at the P.H.L.S. laboratory in Guildford from specimens collected in our practice (table 1). There were 25 different types of virus, 11 of which had caused outbreaks involving more than one family. Indeed, the lesson of this work has been to show (figure 13) that the " new " viruses vary in prevalence just like measles or mumps, and may cause either sporadic cases or quite big epidemics. I have shown you this afternoon a number of slides which I hope will underline this distinction between " what " and " how often ", to show that each contributes in its own way to a better understanding of medical problems.

TABLE I

TYPES OF VIRUS IDENTIFIED IN GENERAL PRACTICE
120 isolations: 1959-1962—Tillingbourne Valley

Virus group	*Types*	*Outbreaks by types*
Coxsackie "A"	2, 4, 6, 10	6, 10
Coxsackie "B"	1, 2, 3*, 4, 5	2, 4, 5
Adenovirus	1, 2, 3,	3
Poliovirus	1, 3	1
Echo	6, 9, 11	—
Influenza	A_2*, B	A_2, B
Para-influenza	1, 2, 3	1, 2
Respiratory syncytial ..	+	—
Rhinovirus	H	—

*Isolated *before* 1959

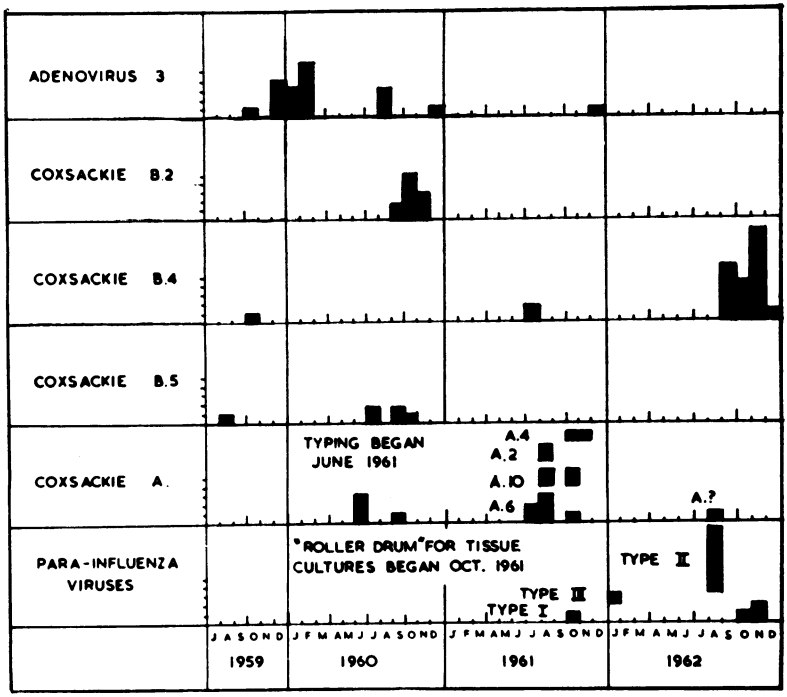

Figure 13
Showing how the "new" viruses vary in prevalence like measles or mumps causing sporadic cases and epidemics.

My plea can be summed up in a few words. Family doctors have a continuing responsibility to observe and record and think about many unexpected events during their daily contact with healthy and sick people. If they look at what they see, and make time to go back over their old records occasionally, then sooner or later they will perceive some new meaning which has lain hidden among their old notes. A fresh line of clinical research may start at any time if a doctor looks with new insight at an old problem. One good observation, recorded and thought about and published, is worth any number of ill-considered statistics. Churning out figures can be meaningless or helpful, according to your wisdom in asking the right questions of the computer. Sooner or later, of course, Koplik had to see how many cases of measles had spots in their mouth; and this could be done in any one practice in one epidemic. Doll and Bradford Hill had to see whether all or only some heavy smokers died of lung cancer; that study had to be spread over very many practices and several years. But remember, in the progress of medical research, however great or small, " what " and " sometimes " always come before " how often " and " how many ".

Acknowledgement

I am grateful to the Medical Research Council for a personal grant, held since 1961.

The isolation of viruses from acute respiratory infection. HIGGINS, P. G., ELLIS, EILEEN M., and BOSTON, DOREEN G. Monthly Bulletin of Ministry of Health and P.H.L.S. 1963. **22,** 71.

This paper gives a concise account of laboratory findings in 1962 from the Epidemiological Research Unit at Cirencester, of which Dr R. E. Hope Simpson is director. Ninety viruses and 12 strains of *Streptococcus pyogenes* Group A were isolated from 100 of the 384 patients investigated. The viruses were strains of influenza virus type B, parainfluenza virus types 1, 2 and 3, R.S. virus, adenovirus, M and H types of rhinovirus, herpes simplex virus and poliovirus. Only two viruses were isolated from 44 control persons without respiratory symptoms.

The excellent harvest of viruses undoubtedly depends in part upon good clinical and laboratory techniques but also in part on the close proximity of the virus laboratory—in fact above the practice premises—so that specimens were being cultured within three hours of collection. There are probably just as many different viruses in every other practice, if only they were studied.