Can practising physicians contribute to epidemiologic studies?

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EPIDEMIOLOGY means the study of disease in populations as opposed to patients[1]. It provides a data base from which a physician can assess the likelihood of various possibilities and make proper decisions for the diagnosis and treatment of individual patients. The aspects covered by the epidemiology of a disease include: prevalence (extent) and incidence (occurrence); clinical features; associated conditions; causative factors; indicators of course and ultimate outcome; tests for diagnosis; complications; and treatment.

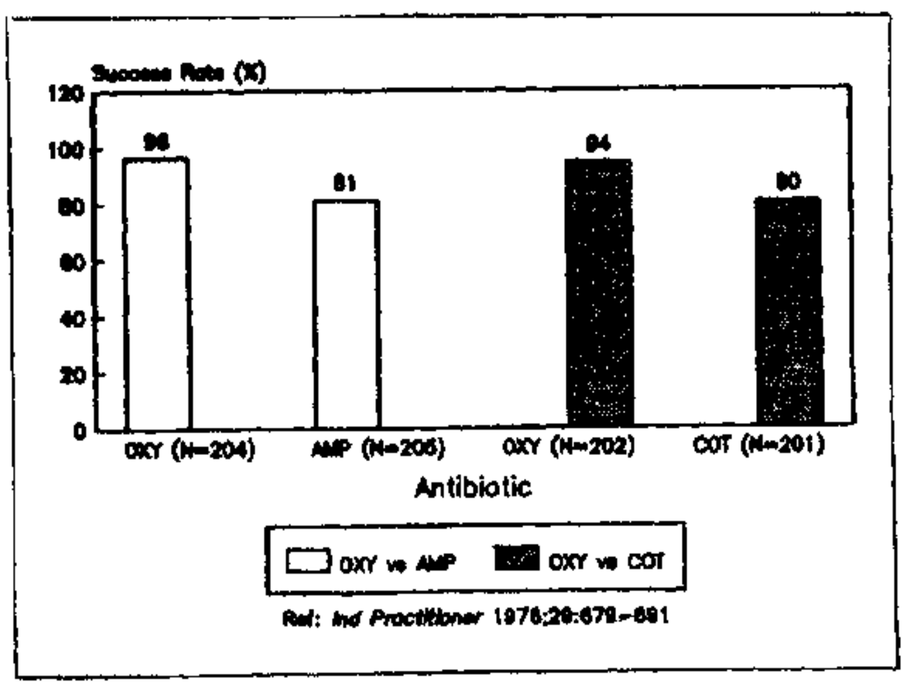
Doctors in private practice possess certain attributes that are essential for good epidemiologic studies. For example, they are spread across the country, and so can cover different segments of the population. This offers a unique advantage for obtaining representative and large samples for study. They see a wider spectrum of disease with respect to age group, stage and severity. They have closer personal contacts with their patients and their families, which facilitates long-term observation. What they lack are an exposure to the scientific method and a managerial support in organizing and monitoring the studies. Given these, they can contribute effectively to epidemiologic studies and help collect valuable data for health care decisions. This has been my experience over the last two decades, and I wish to illustrate this with a few examples.

Respiratory infections

Infections of the bronchi and lungs are common in any community. A variety of microbes are responsible for them, but the common ones are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*. The last of these has been reported to be the cause in about 15% of cases when special diagnostic tests were used[2]. However, a few laboratories are able to isolate it from the sputum and culture it. As a result, many doctors are not aware of its role. This matters because some antibiotics are effective against this microbe, in addition to the others, while some are not. Therefore, awareness of the role of this microbe in respiratory infections can affect the doctor's decision about treatment.

One way to make doctors aware of the role of *Mycoplasma pneumoniae* was to compare the effectiveness of different antibiotics in respiratory infections occurring in the community at large. Assuming that the microbe caused 10% of the infections, one would expect a 10% difference in the efficacy of two antibiotics if one of them acted against this microbe and the other did not. If this turned out to be a fact, then one would have a sound basis for choosing one antibiotic in preference to another for the initial treatment of respiratory infections in the community. Statistical calculations showed that to detect a 10% difference in efficacy ($\delta = 10$), if it existed, in the range of 80% to 90%, would require about 200 patients per treatment if the chance of getting a false positive result must be as low as 5% ($2\alpha = 0.05$), and the chance of missing a real difference must be as low as 20% ($\beta = 0.20$). Such a study could only be done with the help of doctors in practice.

From each of our 45 operating areas in the country, we selected two doctors who agreed to study 10 consecutive patients according to the plan of study. By random assignment, one doctor was requested to compare ampicillin (AMP) against oxytetracycline (OXY), and the other was requested to compare cotrimoxazole (COT) against OXY. Each doctor's patients were again randomly assigned to the two treatments, five to each. The criteria of success or failure were defined beforehand, based on symptoms, signs, chest X-ray and blood white-cell count. When the results were analysed, the success rates were[3]: OXY 96% vs AMP 81%, and



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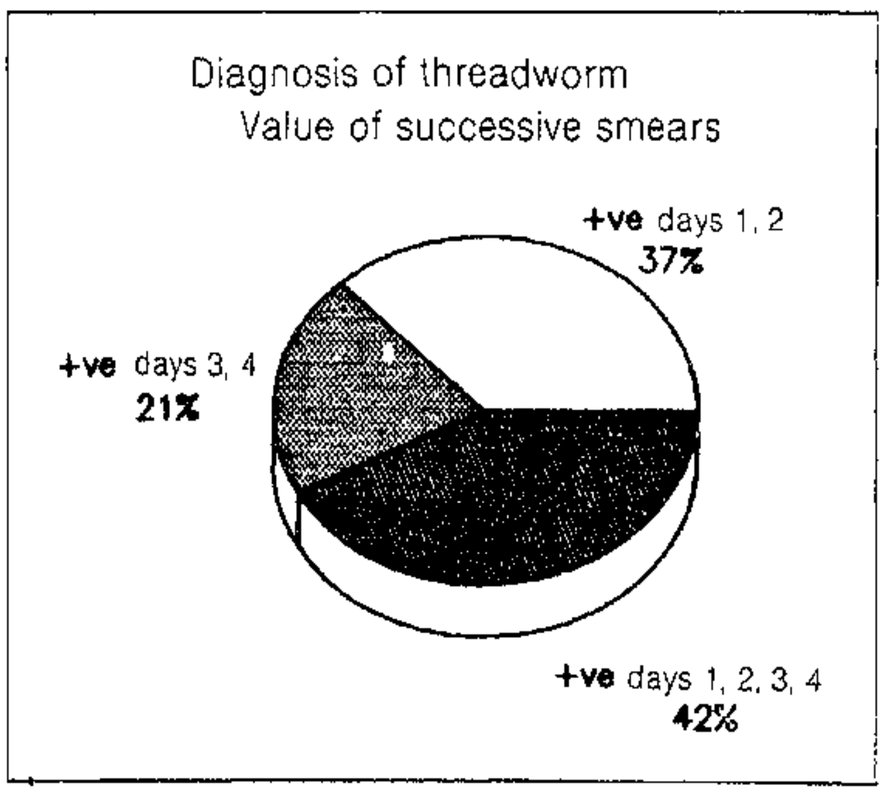
OXY 94% vs COT 80%. This was consistent with the knowledge that OXY is active against *Mycoplasma pneumoniae*, but AMP or COT are not. An unintended byproduct was the finding that the success rates with OXY were closely similar (96% and 94%) in the hands of two different groups of doctors.

Intestinal worm infections

This is an important public health problem in our country. It may not cause many deaths, but it causes much ill health. However, there are no national data about their relative prevalence in different parts of the country. We needed this information because we were about to market a drug for intestinal worms. So we decided to collect it in the best way we could[4]. In each of our 45 operating areas across the country, we listed the pathology laboratories under three categories: public free hospitals, private paying hospitals and personal pathology laboratories. The assumption was that these categories serviced different segments of the population. From each category, then, we selected one laboratory randomly and requested them for the stool reports of 100 consecutive specimens examined by them from the date of request. The percentage of samples positive for different worms was calculated for the whole country as well as for individual states. This helped us to rank the worms in descending order of prevalence nationally as: *Ascaris lumbricoides* (large roundworm) 16.3%; *Enterobias vermicularis* (threadworm)* 14%; *Ancylostoma duodenale* and *Necator americanus* (hookworm) 7%; and *Trichuris trichiura* (whipworm) 3.7%. The variations in regional prevalence were also revealing. For example, roundworm was common almost throughout the country; threadworm was more common in Madhya Pradesh, Rajasthan, Assam and Tamil Nadu; hookworm was very common in Tamil Nadu and Kerala, but relatively rare in Madhya Pradesh and Rajasthan; and whipworm was found mainly in certain pockets such as Calcutta, Bombay and Kerala. This data base can be a rational basis for public health measures such as mass deworming and periodic deworming campaigns.

Diagnosis of threadworm

As mentioned earlier, threadworm eggs are not usually found in the stools. They are laid by the worm at night on the skin around the anus. To detect them, it is necessary to apply a piece of scotch tape to the area in the morning, before the patient gets up and washes, and to examine the tape under a microscope. Further, a single test may not be successful because the eggs may not be laid every day. One test detects about half the patients whereas tests on five *consecutive* days detect about 95% of the patients. In practice this is very cumbersome to do. However, we had access to a Japanese device that allows an adult patient to collect his own specimen on two consecutive days in a hygienic manner, and to bring the sealed tape to the laboratory for examination. A parent can take similar specimens for a child. Using two such devices for each patient to do the test on four consecutive days, we screened the families of 100 consecutive patients with the help of five paediatricians[5]. The results showed that in 80% of the families, about 58% of the members were infected. Further, of those found infected, only 42% had a positive test on all 4 days, 21% were missed on days 1 and 2, and 37% were missed on days 3 and 4. This brought home the importance of proper methodology in studying the efficacy of anthelmintic drugs in threadworm infection. If only a single test is done after treatment, many patients will be found negative and assessed as cured; a good trial must use at least four consecutive tests after treatment to justify the result as cure.



Post-operative infections

The human gut normally harbours anaerobic bacteria which, along with other microbes, can cause wound infections after abdominal and pelvic operations. Until the last decade their role was not much appreciated because the facilities to isolate them from the wounds and grow them in the laboratory were not available.

To prevent post-operative infections, many surgeons use antibiotics (usually a combination of ampicillin (A) and gentamicin (G)) before, during, and after the procedure. However, these are not effective against a

*Eggs of this worm are found in the stools in only 5% of cases. Hence this figure was obtained by multiplying the prevalence in stools by 20. The problem of diagnosing this infection is discussed in a later section.

common anaerobe, viz. *Bacteroides fragilis*. To cover it, it is necessary to use a nitroimidazole compound such as metronidazole (M) or tinidazole (T). These compounds can be given by intravenous infusion, but this is quite expensive. If the drugs are to be given orally, the dose must be given 12 h prior to operation since patients are generally fasted from the 12th hour before operation. Further, they should provide effective concentrations in the tissues for 48–72 h. Of the two, tinidazole has a longer duration of action because it is eliminated more slowly than metronidazole, produces higher blood concentrations for a longer time, and has been used to prevent post-operative infections in a dose of 2 g by mouth, 12 h before operation. Would it be more effective than antibiotics alone? And would it be more effective and acceptable than metronidazole?

Statistical calculations showed that a trial to answer these questions would need a very large number of patients because, with proper aseptic precautions, the incidence of post-operative infections is low. Assuming this to be 10–15%, and assuming further that nitroimidazoles would reduce it by five percentage points ($\delta = 5$), about 700 patients would be required in each group (control and test) if the chance of missing such a difference (if it exists) must be as low as 10% ($\beta = 0.10$) and the chance of getting a false positive result must also be as low as 5% ($2\alpha = 0.05$). Obviously, such a study could only be done in the community, i.e. a private practice setting.

Here, we went to the smallest operating areas, which number 300, and from each we selected a surgeon who agreed to conduct the study as planned. Then we divided the 300 investigators randomly into two groups of 150 each: one would compare antibiotics (AG) alone against antibiotics plus tinidazole (AGT); the other would compare antibiotics plus metronidazole (AGM) against antibiotics plus tinidazole (AGT). Each surgeon was requested to study 10 consecutive patients, and these were randomly assigned to the test and the control groups. The criteria of post-operative infection were defined beforehand.

The results (under publication) showed the incidence of post-operative infections as: AG 14% vs AGT 5%; AGM 17% vs AGT 6%. Thus it was possible to show the benefit of adding T to the regimen, and also its superiority over M, in a conclusive manner.

Treatment of amoebiasis

Amoebiasis is another common condition in our country. Although effective drugs such as metronidazole and tinidazole are available, their side-effects such as nausea, vomiting and bitter taste dissuade patients from completing a proper course of 5--10 days. Trials in the late 1970s had shown that, because of its long duration of action, tinidazole can shorten the duration of treatment to three days if a dose of 2 g is given once daily. When the drug was marketed, it was desirable to know how it would perform in the real world. Would patients willingly take four tablets of 500 mg each at a time? Would the treatment be completed or would side-effects be a hindrance? To answer these questions, 300 doctors (one from each operating area) were requested to study five consecutive patients each, according to a written plan. The results (under publication) showed that 1% failed to complete the treatment because of side-effects, and 4% were lost to follow-up, which means at least 95% could complete the treatment, and in these the parasitic cure rate was 91%.

Special situations

So far I have described how epidemiologic studies through practising doctors can help obtain information of practical value to health care delivery and decisions —information that cannot be obtained in any other way. I would now like to point out some other therapeutic problems and situations to which solutions can only be found through co-operative research in practice, combined with routine patient care.

If you see the manufacturer's prescribing information on a new drug, you will find statements such as 'safety for use in pregnancy has not been established', 'there are insufficient data to recommend usage in children below 12 years of age', and 'dosage for elderly patients over 70 years of age has not been established'. These may protect the manufacturer legally, but they do not solve the real-life problems of doctors and patients. However, it is also true that there are ethical constraints in setting up studies of new drugs in these 'therapeutic orphans'. Now let us see what happens in practice. A doctor faces a pregnant woman, a child, or an old person in need of a drug on which information is limited. What does the doctor do? He consults his colleagues or seniors, refers to whatever related literature he can get, uses his common sense and judgement, takes the patient or his/her relatives into confidence, and then uses the drug cautiously. In most cases probably nothing terrible happens, and slowly the doctor builds up his own experience and confidence. But alas, it is rarely documented, and lost to therefore lost to the medical world. In such instances, if doctors could write up the case histories and either publish them in medical journals, or send them to manufacturers, what a wealth of information we could have in a short time!

Another area of concern is the lack of information about placental transfer of drugs, and the safety to the baby of drugs given to the mother during labour. Again, planned experiments may be fraught with

problems. But surely the obstetric departments of good hospitals can collaborate with clinical pharmacology departments, and set-up a routine of collecting from each labour case (i) a history of all drugs taken during the last month of pregnancy, or given during labour, (ii) a sample of the mother's blood, and (iii) a sample of cord blood before the cord is cut[6]. The samples can be stored in deep freeze and analysed later to correlate the mother's and the baby's plasma concentrations. What a wealth of data we can generate with a little planning, a little co-operation, and a little desire to combine patient care with research.

Recording and reporting of all adverse clinical experiences is another good habit we need to cultivate. It could help either to detect rare but serious drug reactions at the earliest, or to dispel doubts and engender confidence.

Formation of in-practice research groups interested in a common problem could also help discover unforeseen opportunities. I recall how, while I was working on the clinical programme for a drug that blocks post-synaptic α-receptors of epinephrine, some perceptive investigators discovered its utility in patients with chronic heart failure[7], in scorpion sting[8], in sickle cell crisis, and in reducing the time for peritoneal dialysis (unpublished personal communications). The history of medicine is full of serendipitous discoveries. But, I believe, such discoveries are not entirely serendipitous. They may stare the doctor in the face, but he needs more than eyesight to see them. He needs a perceptive mind that is groomed by constant reflection. And that is the real aim of research. I long for the day when every doctor will realize that practice and research are two sides of the same coin: good patient care!

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