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OBSERVATION AND EXPERIMENT*

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TWO years ago, in his Cutter Lecture, one of my predecessors pointed out that the object of any science is "the accumulation of systematized verifiable knowledge," and that this is to be achieved through "observation, experiment and thought" — the last including both criticism and imagination. He then added, "the use of the experimental method has brilliant discoveries to its credit, whereas the method of observation has achieved little."[1] This dictum must surely prove, at least at first sight, more than a little disconcerting to the exponent of preventive medicine. In dealing with the characteristics of human populations, in sorting out the features of the environment that are detrimental from those that are beneficial, he does not often find it easy to experiment. The method of observation frequently plays a large part in the particular study of mankind that is his prerogative. Is it, then, quite so useless? Must he give it up as merely a time-wasting hobby?

Looking farther back in time I found that these questions had been considered, as indeed I had expected, by my statistical forebears and teachers in Great Britain. They did not perhaps have quite so pessimistic an outlook as the one I have quoted above, but they certainly did not underrate the difficulties of the observational approach or overlook the value of the experimental method. Thus, in 1924, Yule's[2] view was that the student of social facts could not experiment but had to deal with circumstances operating entirely beyond his control; he must accept records simply of what has happened. He wrote:

> The expert in public health, for example, must take the records of deaths as they occur, and endeavour as best he can to interpret, say, the varying incidence of death on different districts. Clearly this is a very difficult matter...The purpose of *experiment* is to replace these highly complex tangles of causation, [and] the more perfect the experiment — the more nearly the experimental ideal is attained — the less is the influence of disturbing causes, and the less necessary the use of statistical methods.

Greenwood[3] has a characteristic passage, which I quote in full since I believe that the part of it that has no close bearing on my present thesis will nevertheless more than bear repetition today;

> My conception of the statistical method in medicine has changed in the last 20 years; this is especially so with regard to the bearing of statistical method upon experiment. I used to see in the statistician the critic of the laboratory worker: it is a rôle which is gratifying to youthful vanity, for it is so easy to cheat oneself into the belief that the critic has some intellectual superiority over the criticised. I do not think even now that statistical criticism of laboratory investigations is useless, but I attach enormously more value to direct collaboration, the making of statistical experiments, and the permeation of statistical research with the experimental spirit.

The last words — written nearly thirty years ago — are, I suggest, the operative clause in the present setting — the permeation of statistical research with the experimental spirit. Although, as Yule said, facts must often, inevitably, be accepted as they occur, one does not have merely to accept facts as they are reported. One need not accept as final what some third party can give, or chooses to give — for example, a registrar-general or a census bureau. Such reported observations may, of course, prove to be a most valuable indicator of a problem; they may be, thereby, the starting point of research. But when the pattern of cause and effect is complicated they are often not likely to provide a solution. The methods of partial correlation, enthusiastically accepted a quarter of a century ago, no longer seem to have an "unlimited power to penetrate the secrets of nature."[4] One must go seek more facts, paying less attention to technics of handling the data and far more to the development and perfection of methods of obtaining them. In so doing one must have the experimental approach firmly in mind. In other words, can observations be made in such a way as to fulfil, as far as possible, experimental requirements?

Ancient Observation (the Cholera)

It was in this way, nearly a hundred years ago, that John Snow approached his problem, not only as an incomparable master of logical deduction from observations but also, it should be noted, as the

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constructor of observations. To recapitulate briefly, his opening arguments are based on vital statistics of the different areas of London. Using the deaths given in the first report of the Metropolitan Sanitary Commission (1847), he first shows the excessive mortality from cholera that in the epidemic of 1832 befell the districts supplied by the Southwark Water Works, a company that drew its water from the Thames at London Bridge and provided worse water, according to Snow, than any other in the metropolis. Even the order of precedence between a flea and a louse is sometimes, it appears, of importance. A death rate from cholera of 11 per 1000 inhabitants stands out starkly amidst the rates of 2, 3 and 4 for other districts of the city, but clearly that unenviable record might be explicable in terms of some quite different local characteristic. The evidence gives a lead but no more. The case is somewhat, but not at all convincingly, strengthened by the events of 1849. The highest mortality rates from cholera were again consistently to be found in the districts supplied by the Southwark Company (now combined with the South London Water Company to form the Southwark and Vauxhall) and also in those served by the Lambeth Company; both companies drew their water from the Thames in its most contaminated reaches. In 1853 there begins to appear reason to sit up and even to take notice. The Lambeth Company had removed its works from central London to Thames Ditton, where the river was wholly free from the sewage of the metropolis; the Southwark and Vauxhall Company continued to prescribe for its customers the mixture as before. In the 12 subdistricts served by the latter 192 persons died of cholera in the epidemic of 1853 — with 168,000 persons living the crude rate is thus 114 per 100,000. In 16 subdistricts served by both companies 182 perons died; among 301,000 living, that is a rate of 60 per 100,000. In three subdistricts of 15,000 persons served only by the Lambeth Company no deaths from cholera were reported.

So far do the statistical observations run; so far but not far enough. On that showing alone one might even hesitate to accept Snow's "very strong evidence" against the water supply. He himself was indeed of that mind, for "the question," he observed, "does not end here" (he had no intention of letting it end there). It was not said without reason that wherever cholera was visitant there was he in the midst. He noted that the Southwark and Vauxhall and Lambeth companies were competitors so that in some subdistricts the pipes of each went down all the streets and into nearly all the courts and alleys:

> Each Company supplies both rich and poor, both large houses and small...No fewer than 300,000 people of both sexes, of every age and occupation, and of every rank and station, from gentlefolk down to the very poor, were divided into two groups without their choice, and, in most cases, without their knowledge; one group being supplied with water containing the sewage of London, and, amongst it, whatever might have come from the cholera patients, the other group having water quite free from such impurity.

Here, then, was an unwitting experiment on the grandest scale, and Snow set himself to learn its results.

In 1854, with one medical man to assist him, up and down the streets, courts and alleys of South London he tramped in the summer's sun, learning for every cholera death the water supply of the household. Thus, by personal, persistent and accurate field work were the basic vital statistics infinitely strengthened. In 40,000 houses served by the Southwark and Vauxhall Company 286 fatal attacks were found in the first four weeks of the epidemic of 1854 — 71 deaths per 10,000 households; in 26,000 houses served by the Lambeth Company 14 fatal attacks were found — only 5 deaths per 10,000 households. In such a way was observation successfully added to observation to form a coherent and convincing whole.

It might be argued that Snow was lucky in having at hand a natural "experiment." Perhaps he was. But such "experiments" or, at the least, effective "controls" would not, I believe, really prove to be so rare if one invariably cast one's eyes round for them after vital statistics, or similar observations, had given an appropriate lead.

Certainly, in the famous Broad Street Pump outbreak of cholera no experiment offered. Its story is too well known to need any detailed reference here, but having brought Snow into my picture, I could not bear to pass it by wholly unsung. It is not so much for persuading the local board of guardians to remove the handle of the pump that Snow here deserves credit — though for this alone it is often paid to him. In fact either through the flight of the terrified population from the stricken area (and Snow himself says that "in less than 6 days the most afflicted streets were deserted by more than three-quarters of their inhabitants") or through natural epidemiologic causes, the outbreak had been steeply declining for five or six days before the well was thus put out of action. That "experiment" provides no useful evidence.

It is again in the field work that his strength lies: the map showing the concentration of deaths around the pump with their number diminishing greatly, or ceasing altogether, at each point where it became decidedly nearer to send to another pump; the demonstration of the escape of the inmates of the workhouse, which had its own well, and, similarly, of the 70 workmen in the brewery who knew better than to drink water — or if somehow driven to do so drew from a well within the brewery. And the striking individual histories, the most conclusive of which Sherlock Holmes might well have called "the curious case of the Hampstead widow." In the weekly return of births and deaths of September 9 published by the Registrar-General of England and

Wales there appeared the following entry: "At West End [Hampstead], on 2nd September, the widow of a percussion-cap maker, aged 59 years, diarrhoea two hours, cholera epidemica sixteen hours." (The times refer to the duration of the fatal illness, then — and again now — entered by the medical practitioner upon the certificate of cause of death.) One of the factories in Broad Street made percussion caps, but on inquiry Snow found that the widow had not been in the neighborhood for many months. However, she still preferred the water from the pump to that of the more salubrious neighborhood to which she had retired, and she commissioned a carter who drove daily between the two points to bring her a large bottle. The bottle was duly delivered on August 31. She drank of it and died two days later. A niece on a visit to her likewise drank of it. She then returned to her home in Islington, where she died of cholera. There was no cholera extant in either neighborhood.

To digress for a moment, there was at least one other person who drank of that bottle. The story here is, perhaps, less well known. The first medical officer of health for Hampstead (now one of the metropolitan boroughs of London) dictated as an old man in 1889 some recollections under the title of "The Sanitary Experiences of Charles F. J. Lord, M.R.C.S." It is now held in manuscript in the Hampstead Public Library but was privately printed for circulation among the old man's friends. There is a copy in the library of the Surgeon General in Washington under the title, "Jottings: Some experience with reflections derived through life and work in Hampstead from 1827 to 1877" (Pamphlet Vol. 3807). Lord himself died before making final corrections of the proofs. On pages 36 and 37 of the printed version the following passage is included:

> A memorable case of what we may consider an imported cause of disease happened at West End; Mrs. Eley Mother of the renowned firm "Eley Brothers" had lived in Broad Street Soho, and had drunk with glorification from a deep well there situated. On leaving London, she had a big stone bottle brought daily for the use of herself at West End. Summoned hastily to see the old lady I found her in the early stage of Cholera — remedies were unavailing, though solicitously applied in every way by a daughter and one of her sons. A consultation with the highly esteemed Dr. Farre ensued, the Patient never rallied, died that night. The cause of the disease at that time was never suspected; it was proved afterwards by the untiring investigations of Dr. Snow, that the water from the Broad Street well was contaminated and produced the disease; a sort of practical joke arose among the Teetotalers of the Broad Street district; those who stuck to the Porter especially those of the Brewery were rarely victims to the disease while those who drank the water fell fast around. I myself while attending closely on the old lady, as also was her daughter, was much troubled with Diarrhoea having unsuspiciously sipped some of the imported water. This insipient [*sic*] stage of Cholera soon passed away, in the absence of full or renewed doses.

Here, then, to return to my thesis, is a masterpiece — many persons would say *the* masterpiece — of observation and logical inference, made many years before the discovery of the vibrio of cholera. It shows — as many other examples have shown — that the highest returns can be reaped by imagination in combination with a logical and critical mind, a spice of ingenuity coupled with an eye for the simple and humdrum, and a width of vision in the pursuit of facts that is allied with an attention to detail that is almost nauseating.

Modern Observation (Rubella)

A modern example of acute observation lies in the story of rubella in pregnancy unfolded, almost a hundred years later, in Australia. Again, the story is too well known to need retelling, but it has a facet perhaps less familiar and yet of great interest to the student of public health — in other words, to the observer of group phenomena. It might well be that the congenital defects observed in Australia in the years 1938 to 1941 were something new in medicine, that the rubella epidemic was of a particular virulence, or that the virus had acquired some unusual characteristic at that time. Indeed, there is so much folklore attached to events in pregnancy that if the effects of German measles were an old phenomenon one might possibly have expected to find some old-wives' tale concerning it. I know of none in Britain. That the story was not, however, new in Australia is strongly indicated by the statistical observations marshaled by Lancaster.[5] In each of the reports on the Australian censuses of 1911, 1921 and 1933 there is a section that deals with the enumerated prevalence of blindness and deaf-mutism. The incidence of the latter is revealing; it shows a maximum in each census corresponding to persons born in the years 1896-1900.

At the census of 1911 the peak lay in the age group from ten to fourteen, and the statistician, writes Lancaster, "was inclined to ascribe the maximum to the more complete enumeration of the deaf at the school ages"; most observers would, I suspect, have taken that view. When, however, in 1921, the peak shifted to the age group twenty to twenty-four the statistician considered epidemic disease as a possible cause. He suggested that the increased incidence of deafness at certain ages might synchronize with the occurrence of such illnesses as "scarlet fever, diphtheria, measles, and whooping cough." In the report on the census of 1933 infective disease was again discussed. But the lead given by the somewhat crude vital statistics was not, it appears, followed up at the time. Lancaster himself has followed it up — in 1951 and therefore, of course, after the clinical observations of 1938-41 — by examining the dates of birth of children admitted to institutions for the deaf and dumb. He finds, to take a single example, that of those admitted in New South Wales 15 were born in 1898 and 16 in 1900. For the intermediate year 1899 the figure soared to 70. Furthermore, these 70 are not evenly spread throughout the year but are concentrated in the months

of April to September. On such evidence, marshaled in detail and with skill, Lancaster concludes that "deafness has appeared in epidemic form in Australia in the past, notably among children born in 1899, 1916, 1924, 1925 and in 1938-41" and that "there is some presumptive evidence that all these epidemics, with the exception of that in 1916, were caused by antecedent epidemics of rubella." It seems so easy *now*, he rightly observes, to suggest a causal relation; it is always easy to be wise after the event. Nevertheless, there was at least a legible scrawl on the wall — additional and accurate data were there for the seeking and, once sought, offered a clear case for a carefully designed field inquiry. The combined observational and statistical approach could have won the day; it could have won it quite a long time ago.

Cancer of the Lung

This approach seems to me to be the only one possible in another matter of community concern today — the etiology of carcinoma of the lung. The starting point is as usual the national registration system. "It is sometimes asked," says Stocks,[6] "how statistics can cure disease," and he suggests that one may counter the question by another question: "how many researches which have led to real advances in Medicine would ever have been started had there not first been some statistics to suggest that here was a problem to be investigated?" In this particular instance it is, of course, admitted that skill in, and modern adjuncts to, diagnosis make more than dubious the whole gamut of changes that the system of vital statistics reveals. But there is, in my opinion, more than enough evidence to regard some of that change as real and to justify a search for a cause of a truly rising mortality in England and Wales. Aided and abetted by the Medical Research Council, Doll and I set about that search in 1947. Our aim was to make the field observations mirror an experimental design as nearly as possible. For each patient with cancer of the lung we sought a "control" patient with some other disease — a patient of the same sex, of the same age group, in the same hospital at or about the same time, but otherwise chosen at random. In other words, we sought, as in an experiment, to limit the variables. We limited them, too, not only in this way but also by employing, in history taking, only a few skilled interviewers, each armed with a prescribed set of questions. We made, of course, no frontal attack upon smoking, which in our original questionnaire formed but one section out of nine — eleven questions out of nearly fifty.

Having admitted to a questionnaire of that magnitude I shall take this opportunity to defend myself. For I have been reported as having advocated, before a conference on the application of scientific methods to industrial and service medicine, "that nobody should be subjected to more than five questions."[7] I am, indeed, in favor of shorter and brighter forms but not always to that extent. What I said on that occasion about the problems of making observations of any value, was this: "broadly speaking, of any twenty questions asked in a field survey not more than five should be put to the surveyed, and not less than fifteen should be put to the surveyor by himself before he enters the field or, indeed, ventures to look over the gate."[8] In other words, I maintained, though doubtless somewhat clumsily, that one may ask as many questions as one believes useful — so long as the ratio one to the surveyed and three to the surveyor is maintained throughout. A basic query in the latter group will be, in every case, "is this question really necessary?" It is surprising how often that will effectively keep down the number incorporated.

On the other hand the observational approach has perhaps been somewhat discredited by a too frequent failure to keep down that number, a pathetically notable lack of the critical and imaginative thought that, as Sinclair noted, must be an integral part of the scientific method, — in other words, and more briefly, too few ideas chasing too many forms. That evil is, of course, no prerogative of the United States of America, but I cannot refrain from citing from Eric Linklater's[9] delectable book (that is, to an Englishman) *Juan in America*. Even twenty-two years ago he was moved to write that "the issuing of questionnaires had become a national habit, and work was provided for many people, who might otherwise never have found employment, in dealing with such returns: that is in docketing them, tabulating, copying, indexing, cross-indexing, rearranging them, according to ethnic, religious, social, geographic and other factors, and eventually composing a monograph on them for the Library of Congress." Perhaps Americans were quicker off the mark. I would, however, warn them that we on the other side of the Atlantic are not being backward and may even overtake them in these national vices and devices.

Returning to my theme it is, of course, possible that the relative absence of nonsmokers and the relative frequency of heavy smokers that Doll and I found in our patients with cancer of the lung (and that other workers have also noted) is really a function of some other difference between the two groups. We do not ourselves, for several reasons, believe that to be so, and it is certainly worth noting that patients with pulmonary cancer and controls are remarkably alike in other characteristics that we have recorded. Nevertheless, here lies, I admit, the weakness of the observational as compared with the experimental approach. With the former we can determine the most probable explanation of a contrast in our data; given the provision that we have taken sufficient care to remove disturbing causes, that probability can be very high. But with a well de-

signed experiment it should be possible to eliminate (or allow for) nearly all disturbing causes and thus to render the interpretation of the contrast even more certain.

Yet in this particular problem what experiment can one make? We may subject mice, or other laboratory animals, to such an atmosphere of tobacco smoke that they can — like the old man in the fairy story — neither sleep nor slumber; they can neither breed nor eat. And lung cancers may or may not develop to a significant degree. What then? We may have thus strengthened the evidence, we may even have narrowed the search, but we must, I believe, invariably return to man for the final proof or proofs.

In this instance one other method of inquiry is now being applied both in the United States and the United Kingdom: a "looking-forward" investigation. Up till now investigators have taken already marked subjects — together with a control series — and have inquired into their antecedents. That has been the method not only, of course, in this particular inquiry but in many others. It is a natural approach and one likely to yield quick returns. Adult patients with peptic ulcers are questioned concerning whether they came from broken homes; those with rheumatoid arthritis are questioned on their previous shocks and ills; and the views of the victims of neurosis upon the habits of their fathers are sought. The resulting picture, the contrast between marked and unmarked, may be clear cut, and yet it may be difficult to distinguish between effects and causes, between horse and cart. Memories may well be more profound and more retentive in the "marked," and they may indeed be more highly colored — what the adult neurotic thinks of his father may not always be the truth. Even with the method at its best one can rarely hope to make a prognosis by these means, to measure the probabilities of events. But that is what is usually needed: first to observe the broken, and unbroken, home and then to record the subsequent history of its youthful inmates. That is clearly difficult to do and calls for a considerable degree of patience, which most investigators do not possess. But if the forward approach can be employed, it is, I believe, almost always the right way to go to work; in any observational inquiry its possibility should invariably be considered.

In the particular investigation that Doll and I now have under way — broadly into the deaths in the next few years of men and women on the British medical register whose smoking habits are already characterized at a defined point of time (late 1951) —it again, of course, would not follow that any association we might find between death from carcinoma of the lung (or other causes of death) and smoking habits must be a direct association. The heavy smokers may be differentiated from the light smokers in some other way, which might have some bearing on the risks of a bronchial carcinoma. We are still faced with the most probable explanation. But we may, I submit, have further narrowed the field of possible variables, of errors of omission or commission.

The Field Experiment

There is today an increasing resort to the field experiment, a district, a town, a school or a factory being used as the laboratory. It is a striking development of the present age and, if the requirements of an efficient experiment can be met, a most valuable one. But those requirements *must* be met; a poor experiment serves no purpose. Yet it seems that the very magic in its name may serve to mislead those who worship at the experimental shrine.

As an example, in a recently reported study of vaccination against influenza, the subjects for inoculation were chosen on a voluntary basis and "without any great propaganda 32.8% of the total employees involved in the Survey voluntarily requested the inoculations." This one third, self-selected group is compared with the remaining two thirds, who, like Gallio, "cared for none of those things." Of the 1148 inoculated persons 10.80 per cent were attacked by influenza, and of the 2349 remaining population 15.02 per cent. The difference is "statistically significant" with a "P of 0.00567." And yet does this ritual and do all these decimal places mean anything at all? Admittedly, the technical test says that the two groups had experiences that differed by more than one would expect to occur by chance; equally, it tells nothing else. As it stands I do not myself believe that it gives any support whatever for the author's conclusion that here is evidence "strongly in favor of the immunization of large groups in industry." Yet I have no doubt that it will be cited in the literature under the caption "it has been shown by experiment."

In my view this is not an experiment at all. Some observations have been made of the recorded incidence of "influenza" in two groups. The investigator knew (and so incidentally did the two groups) that they differed in one respect — inoculation; they may well have differed in a score of others — even, for all one is told, in such simple respects as age and sex. None of the other possible variables of importance were controlled, and it is well known that in trials of vaccines a self-selected group is most unlikely to be a representative sample of the total. Field experiments are not, unfortunately, as easy to design and carry out as all that. In this particular field — vaccination against influenza — I speak with conviction, for the Medical Research Council has during the last winter carried out some experiments in industry, — trials of methodology, I should say, as much as of vaccines. We too, of course, have had to rely upon volunteers for our basic material. There is (fortunately) no other way of setting up a trial.

But the volunteers were divided at random into two groups — an inoculated group given the influenza vaccine and an inoculated group given a dummy vaccine. We had their general consent to that procedure, but in the individual case it was unknown. It was also unknown to the medical practitioner diagnosing such illnesses as occurred — influenza, possibly influenza and other diseases. In such ways we have endeavored to equalize our groups *de novo* — to eliminate bias from the subsquent observations. Whether, having to cast our epidemic net wide, we have succeeded in obtaining accurate and comparable records from a score of factories and still more doctors remains to be seen. Such experiments involving human beings are, I repeat, not easy to carry out; they are, as a rule, costly. Yet in relation to the returns rendered they are relatively cheap. A well designed plan may in a few months, or years, forestall years or decades of indeterminate, unplanned observation.

Conclusion

There is one thread that runs — or it might be more accurate to say wanders — through this lecture. I have been unable — even if I would — to conceal my preference in preventive medicine for the experimental approach. At the same time that preference does not lead me to repudiate or even, I hope, to underrate the claims of accurate and designed observations. But I would place all the emphasis at my command upon those adjectives. In this field of preventive medicine I share, on the whole, the view regarding the curative aspects recently expressed by Platt,[10] professor of medicine in the University of Manchester. Records in clinical research are likely, he suggests, to be disappointing;

> Unless they have been kept with an end in view, as part of a planned experiment...Clinical experiment need not mean the subjection of patients to uncomfortable procedures of doubtful value or benefit. It means the planning of a line of action and the recording of observations designed to withstand critical analysis and give the answer to a clinical problem. It is an attitude of mind.

In appropriately exploiting that attitude of mind one may well need, in this age of technicalities, close and constant collaboration. Today, as Joseph Garland[11] pointed out in this city of Boston, "the mathematics of research has expressed itself in a multiplicity of graphs, charts and tables with the aid of which the average reader at a quick glance can often learn next to nothing." The biostatistician must therefore acquire a taste for lying down with the epidemiologist, and the bacteriologist with the medical officer of health (I speak in fables).

There are, of course, no grounds for antagonism between experiment and observation. The former, indeed, depends on observation but of a type that has the good fortune to be controlled at the experimenter's will. In the world of public health and preventive medicine each will — or should — constantly react beneficially upon the other. Observation in the field suggests experiment; the experiment leads back to more, and better defined, observations. However that may be, it is difficult to see how one can wholly, or ever, escape from Alexander Pope's epigram. How else but by observation upon man himself being born, living and dying, can one set about the solution of such problems as prematurity and stillbirth at one end of life and cancer and coronary thrombosis at the other? However tangled the skein of causation one must, at least at first, try to unravel it in vivo. As Pickering[12] has said: "Any work which seeks to elucidate the cause of disease, the mechanism of disease, the cure of disease, or the prevention of disease, must begin and end with observations on man, whatever the intermediate steps may be."

The observer may well have to be more patient than the experimenter — awaiting the occurrence of the natural succession of events he desires to study; he may well have to be more imaginative — sensing the correlations that lie below the surface of his observations; and he may well have to be more logical and less dogmatic — avoiding as the evil eye the fallacy of *post hoc ergo propter hoc,* the mistaking of correlation for causation.

Lastly, I quote the words of Professor William Topley,[13] a British worker for whom I had a profound admiration and from whose wisdom I endeavored to learn:

> A great part of clinical medicine, and of epidemiology, must still be observation. Nature makes the experiments, and we watch and understand them if we can. No one will deny that we should always aim at planned intervention and closer control. Here, as elsewhere, technique — the way we make our observations and check them — is half the battle; but to force experiment and observation into sharply separated categories is almost as dangerous a heresy as the science and art [of medicine] antithesis. It tends to make the clinician in the ward, the epidemiologist in the field, and the laboratory worker at his bench, think of themselves as doing different things, and bound by different rules. Actually they are all making experiments, some good, some bad. It is more difficult to make a good experiment in the ward than in the laboratory, because conditions are more difficult to control; but there is no other way of gaining knowledge... Controlled observation in the ward or in the field is an essential part of medical science, shading through almost imperceptible stages of increasing intervention into the fully developed experimental technique of the laboratory.

Mr. Winston Churchill, revisiting the Niagara Falls after more than forty years, was asked by a reporter "Do they look the same?" "Well", he is said to have replied, "the principle seems the same." General principles are obstinate things; they do tend to remain the same generation after generation. Yet one element of that sameness — their fundamental importance — perhaps justifies their being brought out into the light of day from time to time and, if one cannot weave fresh clothes, at least in a newly

dyed costume. In accepting the honor of delivering this Cutter Lecture I indeed trusted that that was so. If I was wrong I must comfort myself like that charming character described by Anatole France: like Monsieur Bonnard, I have the satisfaction of believing that, in following my distinguished predecessors, I have at least "utilized to their fullest extent those mediocre faculties with which Nature endowed me."

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NONSYPHILITIC INTERSTITIAL KERATITIS AND BILATERAL DEAFNESS (COGAN'S SYNDROME) ASSOCIATED WITH ESSENTIAL POLYANGITIS (PERIARTERITIS NODOSA)*

A Review of the Syndrome with Consideration of a Possible Pathogenic Mechanism

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CHICAGO

In 1945, Cogan[1] described a syndrome consisting of nonsyphilitic interstitial keratitis with deafness. Subsequently, a number of other cases were reported, mostly in the ophthalmologic literature. Although these authors speculated on an association with systemic disease, no definite etiology could be found in fifteen cases [1-6] reported up to the present. We have had the opportunity of observing an additional case in which two episodes of oculo-aural symptoms occurred before the onset of extensive vascular lesions, pointing to a possible association between essential polyangitis (periarteritis nodosa) and the initial symptoms. In view of the rarity of the syndrome, it may be useful to describe its manifestations as observed.

The syndrome usually occurs in young adults and is of sudden onset, either with ocular or aural symptoms. The presenting ocular symptoms may include redness of the eye, blurring of vision, ocular pain, lacrimation, blepharospasm and subconjunctival hemorrhage, and may involve one or both eyes at the onset. The vestibuloauditory signs, which are similar to those of Ménière's syndrome, appear suddenly, with nausea, vomiting, tinnitus, vertigo and rapid development of deafness. With the onset of deafness, the associated vestibular signs diminish. The symptoms of both systems may occur within a few hours of each other, or there may be an interval up to five months, though in the majority of cases, it is between one and two weeks.

Examination of the eye early reveals a granular type of corneal infiltrate, patchy in distribution, found predominantly in the posterior half of the cornea. The endothelium of the cornea may be boggy. There may be little or no reaction in the anterior chamber or the iris, although cases with iritis, uveitis, and secondary glaucoma have been reported. The cornea usually is not thickened; the retina is not involved. Late in the disease, vascularization of the cornea develops. There may be a sluggish reaction to mydriatics, and there may be extraocular muscle paralyses. The vestibuloauditory signs are those of inner-ear deafness, either unilateral or bilateral, with diminished to absent vestibular responses. The neurologic examination, except for the findings mentioned above, is negative. In 8 cases, leukocytosis was present, and 5 of these were associated with a mild eosinophilia; usually, the eosinophil count was from 5 to 8 per cent, although in 1 patient it ranged up to 28 per cent. The serologic reaction for syphilis is negative, nor is there a history of the infection in either the family or the patient. The cerebrospinal fluid reveals no abnormal findings. Additional clinical facts are noted in Table 1.

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