The pathological and clinical (may I even say surgical ?) approach has thus furnished us with a working hypothesis on which the function of the thymus gland may eventually be elucidated. There are still many difficulties in the way of a final solution, and progress is likely to be slow. It may be thought safer to return for the present to Galen's belief that the thymus is just a cushion to protect the great vessels from contact with the sternum. This would certainly save us all a great deal of trouble.

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THE STATISTICAL SIGNIFICANCE OF BIOLOGICAL DATA

BY

Sir ERNEST KENNAWAY, M.D., D.Sc., F.R.S.

(From the Department of Pathology, St. Bartholomew's Hospital, London)

During recent years increasing reliance has been placed by all biological research workers upon the estimation of statistical significance. This attitude, of course, is very desirable, but it seems to be leading to a deplorable tendency to regard all numerical differences which are not " statistically significant " as in some way unreal or inaccurate, or at any rate as suspect and unreliable, and hence of no value as a basis for any inferences. But such non-significant differences, if observed accurately, are facts, and are entitled to the consideration given to any other facts ; they may be due to chance, but they may also reflect real differences, which may be quite large under some experimental conditions.

We are surrounded by immense numbers of small biological differences which exist, however difficult it may be to demonstrate them statistically. Some very interesting examples of minute differences have been collected from the literature by J. B. S. Haldane (1949). The increase in length of ceratopsian dinosaurs from 1.7 to 6.5 metres in 22 million years took place at a mean annual rate of 6.1×10^{-8} times the length, which was equivalent, at the beginning of the period, to an increase in length of 1 mm. in 10,000 years. A dimension (height of paracone—that is, mesobuccal cusp) of an upper molar tooth in the ancestors of the modern horse increased at a mean annual rate of 3.6×10^{-8}. Man himself has developed from his ancestors through changes of this type, and Haldane gives some estimates of the rate of this process. One is, of course, aware that a statistician is not likely to be consulted on the question of whether any change has occurred between two successive generations of an evolving vertebrate, but the illustration given above shows the fundamental importance of biological changes which, considered as isolated numerical differences, would be utterly " insignificant."

The effects of this aversion to observed small differences is most undesirable in cancer research, because it leads to the use of the strongest possible carcinogens in the largest possible doses in order to get a " result "—that is, something statistically significant which is therefore " something to publish " (Kennaway, 1948).

These very active carcinogens have now an adverse effect upon research. They have set a standard which is apt to induce neglect of less active compounds, although the latter type is that to which we are likely to be exposed ourselves. If a synthetic compound does not yield tumours in, say, 50% of animals in six months it may be supplanted by more active ones. The time has come to concentrate upon naturally occurring compounds, and tissue extracts, which produce tumours in, say, from 5 to 10% of the initial number of animals in two years. Thus the incubation period of 46 sarcomas produced in mice by subcutaneous injection of cholesterol in fatty media ranged from 11 to 29 months, with a mean period of about 19 months (Hieger, 1954). Hence the assessment of the carcinogenic power of such compounds depends upon the number of mice which live through the second year. Such work is wholly unsuitable for short-term grants. One would like to see a whole staff devoted for 10 years, with no obligation to publish anything during that time, to the search for carcinogens and co-carcinogens in human tissues.

The question, What quantities are " statistically significant ? " is, of course, one for mathematicians alone ; one may suspect that many persons use this term freely who have never given any very clear thought to its exact meaning.

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RESPIRATORY FAILURE IN THE ACUTE CASE OF POLIOMYELITIS*

BY

A. B. CHRISTIE, M.D., D.P.H., D.C.H.

Physician-Superintendent, Fazakerley Hospital, Liverpool

In the intellectual history of mankind there are happily periods when the energies of many minds run together and the filament of human thought lights up. These are the moments when an age shakes off the sensibilities of the past and proclaims a new outlook. If, in quality, the scientist cannot vie with the artist, he is not inferior in the intensity of his mental processes, and when the energies of many scientific minds are directed to one end the outcome may be comparable, at a different level, with a shift of thought in the artist's world.

To those of us who deal with poliomyelitis there can be little doubt that the advances of recent years are of basic importance. The virologist and the epidemiologist have each contributed, fortunately in a complementary manner. Tissue culture is obviously an immense aid to the virologist in his laboratory research, but it also enables him to promise increasing help to the epidemiologist in the field. The epidemiologist has traced the path of the virus and has worked out many of the probable details of infection: much is still uncertain, but the importance of close contact and the significance of the minor illness seem established. These points are, in turn, of direct importance to the virologist: tissue

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culture may result in a safe and abundant vaccine, but without knowledge of epidemiological detail he could not use it with intelligence. And the same applies to the possible uses of gamma-globulin. It is fortunate, then, that both in the laboratory and in the field advances so full of promise have been made together.

In the laboratory and in the field—but at the bedside, what has been achieved? It is doubtful if, to date, a single case of poliomyelitis has been prevented. Nor can we feel assured that the incidence or the severity of the disease is decreasing: the contrary seems to be true. The attack rates per 100,000 population in the United States for the years 1949–53 were 28.3, 22.0, 18.5, 37.2, and 22.8 (Report, 1953). Denmark had its worst epidemic in 1952: the attack rate for paralysed cases alone was 58 per 100,000 for all Denmark, and for Copenhagen itself the figure was 106; of these paralysed cases, approximately one-third had respiratory embarrassment. The epidemic in 1953 was on a smaller scale, with an attack rate for paralysed cases of 13 per 100,000, yet in total numbers it had been surpassed only three times in Denmark (*Lancet*, 1954). In 1951, as in the rest of Europe, the non-paralysed cases greatly outnumbered the paralysed. In Liverpool the number of cases has always been, in comparison, quite trivial, but the figures indicating the relative severity of epidemics are of some interest. For the years 1948, 1950, 1951, and 1953 the percentages of cases with paralysis of those admitted to hospital were 71, 66, 33, and 72; the percentages with respiratory paralysis were 14, 7, 8, and 12.

There seems to be no definite pattern. Epidemiologists may disagree, but clinicians, I think, feel they have little to guide them with regard to either the size or the severity of the next epidemic. When it comes to treatment, we have seen not even the shadow of a specific remedy. The clinician must make his own preparation.

Factors in Respiratory Embarrassment

Death in poliomyelitis results almost entirely from respiratory embarrassment; in fact, in the diagnosis and management of the acute case there is no major difficulty or any fundamental difference of opinion until respiration is involved. When this occurs the clinician is faced with an acute clinical emergency in which there are many involved problems and only a few indefinite answers. Two primary principles are clear and may be stated at once: (1) when the muscles of respiration are weakened by paralysis they must be mechanically assisted; and (2) when the patient's airway is obstructed, it must be cleared. These two principles are simple, but their application to a patient may raise the most baffling problems. A consideration of the factors involved may at least help to illustrate the difficulties.

The free ventilation of the human body depends on (1) the ability of the respiratory muscles, mainly the diaphragm and intercostals, to carry out the essential thoracic movements; (2) an unobstructed airway; (3) the integrity of the respiratory centre; (4) the retention of the normal elasticity and plasticity of the lungs and thorax and the presence of a healthy respiratory epithelium across which gaseous interchange can take place; and (5) the unimpeded return of venous blood to the heart and the free flow of blood through the pulmonary bed.

In a case of poliomyelitis any or all of these factors may be involved, some as a direct result of the disease, some as a result of treatment, and some as a result of both. I propose first briefly to review each factor from the point of view of causation, and then to attempt to analyse some of the clinical states with which we have to deal.

Paralysis of Respiratory Muscles.—Involvement of the respiratory muscles results from direct damage by the virus. The clinical picture is relatively simple and the indications for treatment are clear—some form of mechanical assistance will probably be required. One must not be misled by *apparent* paralysis, when the real trouble is in the pharynx and the patient is afraid, consciously or unconsciously, to breathe.

Obstruction of Airway.—The airway may be obstructed by accumulation of mucus in the pharynx due to pharyngeal paralysis—a direct result of the disease. Here again the indications for treatment—postural drainage—are clear. Obstruction to the airway may result apart from pharyngeal paralysis: inability to cough as a result of respiratory muscle paralysis may lead to excess of secretions in the air passages, plugging of bronchi, and atelectasis. It is essential to sift out the factors concerned and to apply the appropriate treatment, as treatment of only one factor may add to the damage.

Involvement of Respiratory Centre.—The respiratory centre may be directly damaged by the virus; oedema of the brain due to circulatory changes may also play a part. The centre may also be subjected to gross biochemical abnormalities, especially in respect of oxygen and carbon dioxide concentration, and these may be due either to difficulties of ventilation as a result of paralysis or to mistakes in treatment.

Involvement of Respiratory Epithelium.—Anoxia due to any of the foregoing factors may lead to oedema of the pulmonary epithelium. This will impede gaseous exchange and also decrease the elasticity of the lungs, and both these will increase the anoxia. The use of a tank respirator against oedematous lung tissue or an obstructed airway will further increase the pulmonary oedema. Finally, it is possible that pulmonary oedema may be caused centrally by vagonuclear involvement by virus.

Reduction of Cardiac Output.—Artificial methods of ventilation affect not only the lungs but the other contents of the thorax. Both tank respirators and positive-pressure appliances may by pressure effects impede the return of venous blood to the heart and so add to anoxia from a fall in cardiac output as in shock. But shock may also result from involvement of cerebral centres by virus or from the gross biochemical abnormalities already mentioned. Diagnosis of shock is obviously not enough; it is essential to attempt to assess the primary cause. Astrup *et al.* (1954) admit that "there can be little doubt that manual positive-pressure ventilation . . . has given rise to many cases of shock."

The combined effects of the two foregoing factors may be seen in Table I.

TABLE I.—*Intrapulmonary Defects in Poliomyelitis*

Alterations in pulmonary epithelium	due to oedema—due to	Anoxia Changes in blood pressure due to shock Vago-nuclear involvement
Diminution of ventilating surface of lung	due to blocking of bronchi leading to atelectasis—due to	Increased secretions Inability to cough
Alterations in vascular flow	due to Shock—due to	Anoxia CO_2 retention Virus invasion of brain
	due to Poor cardiac return—due to	Effect of mechanical ventilation

Clinical Analysis

It can be seen that the background to the clinical picture may be very complex, and in practice the clinical analysis of a case is often extremely difficult: if a symptom is wrongly interpreted, disastrous errors in treatment may result. Anoxia, for example, although usually easy to diagnose in a patient, cannot be regarded as a clinical entity for which there is one clear remedy: it may result in several different ways in one patient, and several factors may be involved at once. Table II illustrates some of these factors.

Anoxia is often only one part of the clinical picture: carbon dioxide retention frequently accompanies it, and the relief of the anoxia alone will not lead to clinical improve-

TABLE II.—*Anoxia in Poliomyelitis: Causes*

- *Mechanical difficulties of ventilation* due to
  - Paralysis of respiratory muscles
  - Obstruction of airway
    - *Pooling* in the pharynx from inability to swallow leading to aspiration of mucus
    - *Increased* bronchopulmonary secretion due to inability to cough, leading to plugging of bronchi and atelectasis
  - Unhealthy pulmonary epithelium, due to anoxia
  - Poor venous return to heart
- *Shock*— due to
  - Anoxia
  - High CO_2 concentration in blood
  - Cerebral damage by virus
- *Therapeutic mistakes* due to
  - Unsuitable types of respirator, or wrongly applied, leading to underventilation

ment. The administration of oxygen to such patients may in fact produce coma: the anoxia is relieved by the oxygen and the patient becomes pink, but the anoxic stimulus to respiration is removed, with the result that respiratory excursions decrease and carbon dioxide retention increases. Whereas slight increases in the concentration of carbon dioxide act as a stimulus to the respiratory centre, very high concentrations have a narcotic effect leading to medullary depression, decrease in respiration, fall in blood pressure, and so to the anoxia of shock. Some of the factors involved may be seen in Table III.

TABLE III.—*Changes in Blood pH and in CO_2 Concentration in Poliomyelitis*

- *Acidosis*—due to
  - CO_2 retention—due to
    - Respiratory paralysis
    - Obstruction of airway
    - Underventilation
    - Administration of O_2 without relief of other factors
  - Lactic acid—due to Anoxia of tissues
  - Retention of fixed acids—due to Renal vasoconstriction of shock
- *Alkalosis*—due to Low CO_2 tension—due to Mechanical overventilation
- *High CO_2 concentration in blood* —leads to: Medullary depression and shock
- *Low CO_2 concentration in blood* —leads to: Cerebral vasoconstriction leading to cerebral anoxia

It will be seen that, in all the cases considered, difficulties may arise both from causes due to the disease itself and also from wrongly applied treatment. It is easy, for example, by using a tank respirator, to reproduce the movements of respiration, but it is extremely difficult to match the respiratory circulation or ventilation so produced to the pulmonary vascular circulation, which is beyond our control. Although the mechanical movement of the chest wall may appear to be adequate, underventilation or overventilation may in fact be present, adding greatly to the complexity of the clinical picture. It may be an advantage to consider briefly some of the ways in which this may come about.

The patient may be simply overventilated.—Loss of carbon dioxide is excessive, but oxygenation is adequate. This will develop when a tank respirator is used at too great pressure or speed.

The patient is overventilated but anoxic.—(*a*) Changes in the alveolar membrane reduce the transfer of oxygen but affect very little the excretion of carbon dioxide. (*b*) There is a deficiency of oxygen, relative to the patient's needs, in the inspired air. A patient with a high temperature and increased metabolism requires more oxygen than a patient with a normal temperature.

The patient is simply underventilated.—Carbon dioxide accumulates in the blood stream and there is some hypoxia.

The patient is underventilated but well oxygenated.—This can result when using a rich oxygen mixture: ventilation may be sufficient to maintain an adequate oxygen tension in the alveoli, but insufficient to remove enough carbon dioxide, which therefore accumulates in the blood stream.

These are far from being theoretical considerations. They are problems presented by every case undergoing treatment. If not thoroughly understood, they may readily lead to a completely false clinical assessment of a case, and to the continuance or exaggeration of therapeutic mistakes. Two examples will illustrate this tendency. (1) Drowsiness may be caused by CO_2 retention due to underventilation, but may also be caused by an encephalitic or thalamic element in the disease. (2) Restlessness may be due to anoxia, but may also be a symptom of overventilation. The necessity for correct diagnosis is literally of vital importance.

Team-work

In a superficial way the poliomyelitis patient with respiratory paralysis resembles patients suffering from other diseases. With his cyanosis and anoxia he may recall the chronic bronchitic bordering on cor pulmonale, and the administration of oxygen may be equally dangerous to both. With the grossly disordered chemistry of his blood stream he may resemble the patient with uraemia. In his disordered consciousness he may suggest a patient with brain abscess. But he differs from all three in that he is essentially a healthy patient with healthy organs, battling with an acute respiratory and circulatory crisis. His life depends on correct treatment. At the bedside, physician and anaesthetist aim at accurate clinical assessment, and not too far away they require assistance from many colleagues. To the physiologist and clinical pathologist they look for methods of measuring and interpreting the changes in their patient; at the bedside there is too much guesswork. To the virologist and pathologist they look for further understanding of the way the virus affects the brain; it is so difficult to distinguish pathological damage from physiological distress. The pharmacologist must advise on sedation and the use of drugs controlling blood pressure and temperature. With the microbiologist, he may yet find the secret within the cell itself; there respiration finally takes place and there virus competes with cell life. To understand the problems of respiratory poliomyelitis we need clinical co-operation and clinical imagination: *omni nunc arte magistra.*

Summary

The contributions of epidemiologist and virologist to the study of poliomyelitis have been complementary. The clinician, however, still has to rely on his own clinical resources.

The cause of death is respiratory embarrassment, and the clinical picture presented by a patient suffering from respiratory failure may be very complex. The factors necessary for the free ventilation of the body are efficient respiratory muscles, a clear airway, an intact respiratory centre, a healthy pulmonary epithelium, and a free flow of blood through heart and lungs. Any or all of these may be involved. Treatment directed to improve one factor only may cause clinical deterioration.

Anoxia must always be considered along with carbon dioxide tension, the *p*H of the blood, and shock. An understanding of respiratory physiology is essential to the safe use of any form of assisted respiration.

The problem of respiratory failure in poliomyelitis cannot be dealt with by clinicians alone. At the bedside, team-work between physician, anaesthetist, surgeon, and pathologist is essential.

In writing this account, I had a background of reading and discussion the sources of which I cannot now acknowledge. I have found the articles by Astrup *et al.* (1954) and by Steigman (1954) of immediate use. Some of the material was included in a report to the Liverpool Regional Hospital Board, under whose auspices I visited Copenhagen in 1953: it was written jointly with Dr. J. R. Esplen, consulting anaesthetist to the Fazakerley Group of Hospitals, and to him I am indebted for permission to use it, but far more for constant advice and collaboration in the management of our cases.

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