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A RATIONALE FOR STUDIES IN THE CONTROL OF EPIDEMIC INFLUENZA[1]

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THAT a lectureship established to perpetuate the influence of an illustrious anatomist should risk contamination by the nebula of influenza is of itself sufficient evidence that he instilled a spirit of broadmindedness and extension into borderline fields. In the study of infectious diseases the usual emphasis is upon the body fluids, while too little attention is directed to the cellular disturbances. Or too little thought is given to interpretation of those disturbances when they are observed. It becomes increasingly apparent, with the viruses particularly, that typical pathological lesions represent injuries induced because of a preference of the invader for certain physiological conditions or because a cell type possesses attributes which selectively attract the infectious agent. The physiology of infection—its pathogenesis—reveals more and more clearly that the purpose of preventive measures is to prevent that union or to modify its effect. This is well illustrated in the problem of influenza.

The recognition that epidemic influenza is a virus disease has constituted a notable advance, but a clarification of all the problems involved has not been accomplished. In fact, there is still confusion in terminology and a diversity of opinion as to what should be included under the diagnosis of influenza. Some tend to include all unidentified respiratory dis-

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ease in the term, adding a greater load than even the much-abused influenza can rightfully bear. There are others who speak of pandemic influenza as something apart and continue to use it in the unjustified sense of severity rather than distribution. "Sporadic" influenza is employed carelessly despite the fact that the last ten years have yielded little evidence of sporadic distribution of the known viruses of influenza. In this discussion influenza will be considered an epidemic disease which occurs at frequent intervals in the same geographic areas, spreads rapidly, subsides promptly and varies remarkably in extent and severity in different years. An attempt will be made to interpret the problem of prevention in the light of evidence gleaned from studies with viruses which have been identified, utilizing this information to establish a rationale for the various approaches directed toward the protection of a susceptible population.

In the control of epidemic diseases chance observation and empirical analogy have been widely followed. The student of a disease, however, seeks by utilizing knowledge of the physiology of the infection to orient efforts toward the most effective site at which to interrupt the sequence of infection. In order to do so major attention must be given to the manner in which infection is induced and the mechanisms by which immunity is effected.

The Pathogenesis of Influenza

The reservoir of epidemic influenza is not established. There is, however, considerable evidence that it may be in circulation in some part of the world at all times. The possibility of carriers has not been eliminated. Nor has a reservoir for human infection similar to that of the lungworm and earthworm demonstrated by Shope in swine influenza been explored. It is clear, therefore, that until further information concerning this aspect is available we are forced to combat the disease as it erupts.

Influenza spreads through a population by the transfer of virus from the respiratory tract of the infected individual to that of a susceptible. In the majority of instances the process is a direct infection, although indirect transfer through contamination is obviously possible. There is little reason to consider the disease air-borne except when in crowded quarters the differentiation between direct transfer and impregnation of the air becomes academic. When virus of influenza gains entrance to the respiratory tract of the susceptible it selectively attacks and destroys the ciliated columnar epithelium. These cells are superficially situated, not intimately bathed in the fluids of the blood stream, and apparently protected to a great extent by their own mechanisms, such as mucous secretions and ciliary action. Following the necrosis of the attacked cells exudate is poured out and the supporting tissues give evidence of acute, edematous, inflammatory changes. These changes are essentially limited to the nose and the larger respiratory passages.

The pneumonia commonly seen in experimental animals is not a necessary accompaniment of the invasion. In fact, during the early passages in which the virus is becoming adapted to ferrets or mice, pulmonary lesions are not observed, although virus is abundantly present. And it is clear that in the human population pneumonia is present in only a minority of the patients. It seems probable that involvement of the pulmonary tissue is a phenomenon secondary to the destruction of bronchial epithelium in which interstitial swelling, peribronchial infiltration and the outpouring of serous fluid and mononuclear cells represent the major change. The necrotic process observed in the respiratory epithelium is not detected in the alveolar walls.

In the absence of invasion by way of the respiratory tract influenza virus does not produce the lesions. From the lungs of mice which have been given the virus intraperitoneally one can recover large amounts of virus without any evidence of pneumonia. When relatively immense doses of the virus are given by the abdominal route, however, the mice may develop fatal pulmonary disease. It seems likely that the result is due to an overflow of virus into the upper respiratory tract whence it proceeds to cause pulmonary disease by the usual sequence observed after the intranasal inoculation while virus present on the vascular side of the alveolar wall fails to produce disease by failing to reach the susceptible epithelium.

There is little evidence, despite the extensive constitutional symptoms, that influenza is a generalized infection. One might wonder whether the severe myalgias represent damage to the neuromuscular system. While the virus has been demonstrated in the blood of mice for short intervals and after special conditions of inoculation, it has not been recovered from the blood of patients. Furthermore, no significant pathological changes have been recognized in organs other than those of the respiratory tract. The conclusion appears justifiable, therefore, that influenza represents in its pathogenesis a specific injury inflicted by a virus of sharply selective affinities upon a specialized type of cell lining the respiratory tract and that to obtain resistance these cells representing the portal of entry must be afforded protection.

Protection may be conferred by procedures which prevent the virus from reaching the susceptible individual or by procedures which alter the reactivity of the individual so as to render him resistant to the

harmful effects of the infectious agent when it arrives. The latter is usually implied in the term, immunity.

IMMUNITY

What evidence is there that a state of immunity to influenza can be achieved? It has long been said that immunity to influenza is either short-lived or non-existent. It has even been stated that one attack renders an individual more susceptible to subsequent exposures. Statements based upon clinical criteria tend to be inaccurate because of insufficient observation or unwillingness to adopt even those diagnostic criteria which become apparent to the seasoned observer. Owing to the fact that until recently it had not been possible to consider the diagnosis etiologically it is obvious that the question can not be answered on the basis of previous epidemiological data. What appeared to be the same disease clinically or epidemiologically might prove to be entirely different immunologically. Nevertheless, it had been generally accepted that immunity to influenza does exist, that it lasts for a period of some months, at least, but rarely over a long period of years. The tendency for influenza to occur most frequently in children also suggests that resistance increases after that period. Moreover, there is ample evidence that every one exposed, even intimately, in the course of an epidemic does not take sick. The need for such data based upon etiological studies is evident and offers a fruitful field for extended investigation.

At present two distinct types of influenza virus can be identified. The first, originally described by Smith, Andrewes and Laidlaw and confirmed in our laboratory, has been called Type A. This virus has been found to be the causative agent in the outbreaks of 1932–33, 1934–35, 1936–37, 1938–39 and 1940–41. The other, Type B, isolated in 1940 in our laboratory and independently by Magill, was shown also to have been responsible for the wide-spread epidemic of 1936. The disease caused by them has been recognized only in epidemic forms. Each has been implicated in extremely mild and moderately severe epidemics. The two types of virus are similar in that they produce diseases in man and animals which are epidemiologically, clinically and pathologically similar. Magill and Kendall have observed individuals who in successive attacks of influenza had been infected with influenza A and influenza B, respectively. Immunologically, they are so different that infection with Type A virus does not elicit antibodies to Type B virus; immunity to one affords no resistance to the other; nor do serological reactions reveal any evidence of a basic relationship between the two. It is not improbable that still further immunological types will be detected. Until then it seems unwise to test the sales resistance of the physician by the use of terms of misleading accuracy, such as influenza Y.

Beyond the differences in types there is variation in strains of virus belonging to the same type. Some of these differ sharply from others and under specified conditions it can be demonstrated that resistance to one strain of Type A may not give complete protection against another. What role the differences play in epidemic recurrence is not yet established, but the lack of homogeneity observed among strains isolated during different epidemic years indicates that they may be of definite significance. In any case the distribution of multiple types and divergent strains constitutes an inherent difficulty in establishing immunity to the presently unpredictable recurrences of influenza. Fortunately, however, it appears that the basic pattern of pathogenesis and resistance is the same for all the variants so that, apart from their serological behavior, they can be considered as a pathogenic unit.

Most of the accurate information concerning immunity to influenza virus has been obtained from study of the experimental disease. In animals susceptible to the virus, immunity can be induced readily. Vaccination of mice by the intraperitoneal route results in the development of antibodies and immunity without producing infection; subcutaneous vaccination is ordinarily not as effective. The degree of immunity in mice is measured by the survival of the animals and the absence of pulmonary lesions. In the ferret, however, more rigid conditions can be imposed. In addition to the criteria applied to mice, the occurrence of fever, lassitude and nasal signs can be recorded. Vaccination of the ferret does not usually give complete resistance; intranasal test may cause fever and signs of nasal injury. Judging from survival and the absence of pulmonary lesions, however, the vaccinated ferret appears as resistant as vaccinated mice.

Recovery from even mild infection is accompanied by complete immunity. But this resistance wanes so that after a few months the previously infected ferret behaves like the one which had been vaccinated. Antibodies persist, but the respiratory epithelium destroyed by the primary infection has returned to anatomic normalcy and with that return has again become susceptible to infection. Immunity tests are followed by fever and the other milder features of the disease but pneumonia does not occur. Following the second infection the antibody titer rises to a much higher level than that attained as a result of the primary infection and the animal is once more immune.

It is of interest, however, to note that by repeated intranasal doses of small amounts of the infectious

agent at short intervals after an original mild disease it is possible to maintain a state of complete resistance in ferrets without significantly affecting the level of antibodies. There is evidence, moreover, to indicate that the normally susceptible epithelium itself has been modified so that as a result of repeated stimuli it has developed a functional resistance independent of antibodies in the circulating blood. These facts have been briefly recounted in order to furnish a background for the various directions which may be taken in attempting to prevent influenza in man.

Active Immunization

Let us first consider the induction of specific immunity. Preventive specific immunity is related in most minds to the action of specific antibodies in the blood, actively acquired through vaccination, or through subclinical infection with a modified virus; passively conferred by the parenteral administration of antibodies. The thesis which I propose is this: In order to function most effectively specific antibodies must be available to prevent the virus from attacking the cells to which it is specifically attracted. When the agent must be transmitted by way of the blood to reach its site of localization, circulating antibodies can exert their greatest effect. When, however, the portal of entry is superficial and also constitutes the area of primary injury it is apparent that antibodies can prevent disease only if they are immediately present in that area.

It has been uniformly observed that a high percentage of patients who develop influenza have antibodies in the blood at the time of onset. Since in the majority of such instances the titers are relatively low it has been the tendency to conclude that resistance is proportionate to the antibody level. The experiments of Smorodintseff *et al.*, Burnet, and Stokes and Henle were based upon experimental infection of human subjects. They, too, state that a relationship between susceptibility and antibody titers exists. Since vaccination of human subjects with influenza virus in the active or inactive state is followed by a sharp increase in circulating antibodies it has been assumed that resistance might be increased proportionately. This is the basis on which most vaccinating efforts have been projected but concerning which little explanation has been offered as to how the supposed result is accomplished. On the other hand is the evidence from experimental animals that vaccinated or previously infected animals may not be immune to the homologous virus and that the respiratory epithelium may be destroyed even though antibodies are present in the blood. How, then, can circulating antibodies prevent the pathogenic influence of the virus on these superficial cells?

In seeking information concerning the question our attention was directed to a consideration of factors which might be available in the environment of the vulnerable tissue. A study of the nasal secretions of human subjects revealed in them a substance capable of inactivating influenza virus. This substance has the characteristics of antibody both in its immunological and physico-chemical properties. It is present at birth, lost rapidly thereafter but beyond two years of age the frequency of its presence increases so that by school age it is present in a high proportion of human nasal secretions. It makes its appearance or increases in amount as a result of infection with the virus. In comparison with titers of neutralizing antibodies of the blood the substance is present in low concentration but in general those individuals with high levels of circulating antibodies have the more potent nasal secretions.

It was of interest to determine then whether subcutaneous vaccination exerted any influence upon the inactivating capacity of nasal secretions. A series of experiments was conducted last spring in which, before and after vaccination with influenza virus, both the blood and nasal secretions of a group of subjects were tested for their neutralizing capacity. It was found in those patients in whom a sharp response of humoral antibodies was observed, that the inactivating capacity of the nasal secretions was also enhanced.

The results suggest, therefore, that subcutaneous vaccination serves as a preventive by its influence upon the local protective mechanism which offers a more effective physiological defense than antibodies in the blood themselves. This concept attributes to circulating antibodies a secondary role of limiting the spread of the virus. After the virus has become established and engorgement and serous discharge takes place they may prevent the infection of other cells, as in the experimental animal they contribute to the prevention of pulmonary involvement by virtue of the lung's high vascularity. In the presence of an epidemic with marked incidence of pneumonia due to the virus that effect might result in a marked limitation of severity and mortality without comparable influence upon the incidence of infection. The experiments of Stokes and Henle, previously referred to, suggest that this was their major result.

While it is obviously a simple matter to stimulate circulating antibodies in man, it is much more difficult to demonstrate that immunity results from the procedure. A summary of evidence obtained with one form of vaccine has been recently presented by Horsfall. In these groups vaccine which was said to induce unusually high yields of antibody reduced the incidence of the disease by one third at most; in some groups no effect was discerned. The studies are still

in their primitive stage and there may be too great conservatism as to the nature of vaccinating material. As has been seen, however, there is more than a traditional basis for indicating the possibilities.

A second method adaptable to preventive use is the creation of active immunity by infection with modified virus or the setting up of subclinical infection. It represents the principle involved in the virus vaccines which have been most successfully utilized in human disease—smallpox, rabies, yellow fever. The application to influenza is readily seen. Introduction of influenza virus by routes other than the respiratory does not produce the disease. This has been demonstrated by the fact that human subjects given the fully active virus subcutaneously or intramuscularly do not give evidence of infection. In general, immunity resulting from infection by the natural route is a firmer immunity than that derived from vaccination by abnormal routes. The reasons are that under the former conditions the naturally susceptible cells are affected by the virus and receive the benefit of that stimulation while the systemic defenses also are subjected to the antigenic stimulus. The inoculation of active influenza virus into the respiratory tract would afford an opportunity for the respiratory epithelium to participate in the reaction. The possibility of initiating an epidemic is immediately put forward as an objection. Smorodintseff *et al.*, Burnet, and Stokes and Henle have, with the use of recently isolated strains of virus, caused frank disease of considerable severity. However, in the past few years, using the PR8 strain cultivated in tissue culture or fertile eggs, we have demonstrated that the virus can be sprayed into the nostrils or introduced by packs soaked in virus, without producing clinical disease. In fact, the difficulty has been that the virus has been too greatly attenuated and results as measured by the development of circulating antibodies have been irregular. It may be, of course, that the response in terms of circulating antibodies is not a proper measure of the effect and that the influence upon the respiratory epithelium is much greater than the systemic evidence would indicate. This remains to be shown.

There is additional theoretical reason for suggesting the advantage of subclinical infection. In the fields of both plant and animal viruses it has been shown that the inoculation of an attenuated or mild strain of infectious agent will protect the host against a highly virulent strain given at the same time or shortly thereafter. This protection has been called interference, connoting that the mild virus competes successfully with the lethal strain for the privilege of occupying the susceptible cells, and is not based upon rapidly developing serological activities. Intranasal vaccination with the attenuated culture strain in the face of an outbreak might very well exert a similar influence.

There is need for further systematic exploration of vaccination by the intranasal route. *A priori* it presents a more rational and simpler opportunity than inoculations made by para-respiratory routes.

PASSIVE IMMUNIZATION

Turning from the question of active immunization it is of interest to consider the possibilities of conferring specific protection by means of passive transfer of antibody to the threatened individual. Since many subjects possess circulating antibodies at the time of illness, it is clear that to influence resistance by intravenous or intramuscular administration of serum would require relatively large concentrations of immune substances. Early in experimental studies when efforts were being made to develop technics for the measuring of antibody titers it became clear that serum given intraperitoneally was much less effective in preventing intranasal infection than when serum and virus were mixed and given by the intranasal route. This was further demonstrated by the studies by Laidlaw, Smith, Andrewes and Dunkin using the serum of immunized horses. Smorodintseff and Shiskhina reported for the first time in 1938 the observation that when immune serum was given intranasally before the virus infection and even for a period thereafter it was much more effective in protecting mice than the same serum given in much larger doses by other routes. Since then Stokes and his associates, Taylor, Hare and others, have adequately confirmed the results. In 1938 Nechaev published the results of the use of intranasal sprays of immune serum as a therapeutic agent in man. According to his statements, where given intranasally to patients in the first two days of illness, the serum was of definite therapeutic value. The following year Smorodintseff reported prophylactic studies on 650 men—again with favorable results. These were amplified by Smorodintseff, Gulmow and Tshalkwa, who reported that prophylactic administration reduced the incidence of influenza in 501 treated individuals to 8 per 1,000 while in 1,825 untreated an incidence of 82 per 1,000 was observed.

Recognizing the fact that the protective value of serum so administered is a temporary expedient it, nevertheless, may be found of considerable value in otherwise unprotected populations faced with an epidemic. The results all emphasize again the primary need of protecting the respiratory cells and the greater efficacy of immune substances available at the portal of entry. The addition of antibodies to the surface of susceptible cells by the use of immune serum is essentially a heightening of the virus-in-

activating capacity of the nasal secretions. Thus, local passive immunity, selectively applied, provides general immunity by breaking the infectious chain at the site of localization of the virus.

BARRIERS

Protection may be more than enabling an individual to combat an infectious agent which reaches him, but may represent, on the contrary, the use of agencies which have no immunological meaning. They do not give the susceptible individual resistance but serve to interrupt the passage of infectious material from the infected to the susceptible individual. The practices of isolation, quarantine and disinfection represent efforts in that direction. The first attempted, by limiting the quarters and associations of the sick individual, to decrease the opportunities for distribution; the second, quarantine, by curtailing the movements of a patient and his associates during a period in which disease might be incubating, has sought to limit the spread. The limitations in application are to a great extent those imposed by practical considerations of inability to restrain an individual sufficiently long to eliminate his participation as a spender of infection —as with streptococcicosis. Disinfection meant in many respects fumigation. It became apparent that disinfection of the premises had little effect when the human subject served as the chief distributor. Gradually, terminal disinfection was largely discontinued. Recently, however, it has reappeared under different guises intended for constant disinfection of the atmosphere.

The problem of the control of infections transmitted by way of the respiratory tract has been of increasing concern to pediatricians in charge of children's wards and institutions. The knowledge of the efficacy of ultraviolet light in killing bacteria and viruses suggested the application to nurseries, wards and schools. Under these conditions recent reports have attempted to create an erythematous opinion. While it is apparent that sterilization of the air may proceed, radiation has been most effective in small spaces in which motion is at a minimum and ventilation rigidly controlled. In fact, recent evidence indicates that satisfactory results are obtained only when the air is brought directly to the lamp. Moreover, some of the evidence is weighted by dissimilarity between control and test groups. Briefly, its application rests primarily on the assumption that air-borne dissemination is the important mode of spread of these diseases. In limited spaces with controlled ventilation and heavy contamination this may be true, but under normal conditions of activity, with open windows or outdoor associations, the probabilities of general control by ultraviolet irradiation can scarcely be anticipated.

Of greater promise because of simplicity is the use of aerosols. In the early days of the present conflict, French and British investigators drew attention to efforts toward air sterilization in bombproof shelters, barracks and hospital wards. Due again to their proven bactericidal properties, synthetic detergents in various vehicles were used for sprays. Decrease in the bacterial content of the air was accomplished, but various disturbances such as dust interfere with their efficacy. It was further noted that certain fumes, such as incense, were even more effective than aerosols. The next step was introduced by Robertson and his associates, who recognized that propylene glycol, which had been used merely as a base, was more effective than the agents mixed with it. It is readily volatile, requires no expensive equipment for its distribution, acts apparently in the gaseous phase rather than by changing surface tension and is active in high dilutions against pathogenic bacteria and viruses. At present there is excellent reason to believe that this non-toxic agent will fulfill a valuable function indoors but the out-of-doors is not readily subject to similar control. Disinfection revived is claiming important attention.

And now the lowly mask, after progressive decline and discard, has been dusted off, remodeled and shown by accurate physical measurements to fulfill a real function in preventing a ready distribution of minute particles of infected material. The ordinary gauze mask is not only *not* beneficial but actually harmful. The revised masks containing flannel filters which fit properly are shown to prevent deflection of infectious particles and to filter them out of the air; they become more efficient with use and laundering; they provide protection to the wearer and to the exposed susceptible. The new mask deserves place in the field of prevention.

Still another barrier is being earnestly sought—a drug which may be taken prophylactically and be available so as to render the arriving virus inert. Or, if rapidly effective, it may be employed so early after infection as to abort the incipient disease. Although this is anticipation, in view of rapid progress in the field of chemotherapy the period of waiting may be terminated at almost any time.

SUMMARY

Influenza has long been a field conducive to fancy and speculation. At present, however, through increasing knowledge of the pathogenesis of the disease and the factors influencing resistance, the collected

data are beginning to take form. In this discussion an effort has been made to point out the trends, to interpret their possibilities on the basis of the mechanisms involved, and to give some intimation as to their relative applicabilities and limitations. It is clear that certain of them offer reasonable promise of exerting a real effect in the prevention of influenza; it remains only to prove them.

OBITUARY

FRANK DAWSON ADAMS

ON December 29, 1942, Dr. Frank Dawson Adams died at his home, 1173 Mountain Street, Montreal. Dr. Adams was one of Canada's foremost men of science and one of her most distinguished citizens.

Born in Montreal, in September, 1859, he was educated at the Montreal High School and McGill University. Choosing geology as his major subject of study, a science then just coming into its own in Canada, he graduated with first rank honors in natural science in 1878, when only nineteen years of age. He subsequently studied at Yale University, Johns Hopkins and finally at Heidelberg. From the latter university he received his Ph.D. degree "summa cum laude" in 1892. From McGill he received the doctor of science degree in 1902 for distinction in science and later the LL.D. degree for distinguished public service.

His first appointment was in 1880 to the staff of the Canadian Geological Survey. He was appointed lecturer in geology at McGill in 1889 and Logan professor of geology in 1893. He was last but one of those who, receiving their inspiration from the late Sir William Dawson, by far the greatest principal McGill has had, was appointed to the staff of McGill by Sir William, whom he ultimately succeeded as head of the department of geology. During the succeeding years he arose step by step to merit almost every distinction which a man of science can hope to attain.

In Canada, Toronto, Queen's, Bishop's and Mount Allison Universities similarly honored him with the LL.D. He was early elected fellow of the Royal Society of Canada and later became its president. In Britain he was elected a fellow of the Royal Society of London and also of the Geological Society of London. By the latter society he was awarded the Wollaston Gold Medal, the greatest distinction the society has to offer. It was characteristic of him that when he received the cable telling him of the award, he first thought it was a mistake and that it must be meant for some one who happened to have the same name as himself.

He was equally recognized outside of Canada and the British Empire. He received honorary degrees from a number of American universities and had the unique distinction of being the only Canadian foreign associate member of the American Academy of Science. He was also elected foreign member of the Swedish Academy of Science, honorary member of the Mineralogical Society of Russia, of the Geological Society of Belgium and of many other scientific societies of equal distinction in other foreign countries. The International Geological Society elected him its president in 1913. The Geological Society of America elected him to a similar honor in 1918.

In Canada every effort to utilize more fully our economic resources received his loyal and hearty support. He was an active member of the Canadian Conservation Commission in the days when it was an active force in Canada and before political manipulation put it out of business. From the foundation of the National Research Council until his retirement from the university he was an active and distinguished member of that body and for a short time its executive chairman.

As a geologist he ranked first among his profession in Canada. For years a constant stream of papers came from his pen, covering almost every phase of Canadian geology. These appeared in the publications of the leading scientific journals in America and Britain, dealing with natural science problems. Altogether approximately ninety papers so appeared. From this long list it is difficult to select what might be considered most important. Perhaps the papers which gave him the greatest satisfaction were: "The Transfusion of Matter from one Solid to Another under the Influence of Heat"; "An Experimental Investigation in the Flow of Marble" (with J. T. Nicolson); "Experimental Investigation of the Compressibility and Plastic Deformation of Certain Rocks" (with Ernest C. Coker); "Experimental Work on the Flow of Rocks"; "An Experimental Contribution to the Question of the Depth of the Zone of Flow in the Earth's Crust"; "On the Origin and Nature of Ore Deposits—an Historical Study"; "On the Amount of Internal Friction Developed in Rocks during Deformation, and of the Relative Plasticity of Different Types of Rocks" (with J. A. Bancroft).

These researches, extending over a number of years, dealing with the flow of rocks under changing conditions of temperature and pressure, carried on with the support of the Carnegie Foundation, remain a permanent contribution to our knowledge of the manner in which internal changes in the structure of the earth were brought about in geological time. They were