SCIENCE

VOL. LXII OCTOBER 2, 1925 No. 1605

CONTENTS

SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. McKeen Cattell and published every Friday by

THE SCIENCE PRESS

Lancaster, Pa. Garrison, N. Y.

New York City: Grand Central Terminal.

Annual Subscription, $6.00. Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the association may be secured from the office of the permanent secretary, in the Smithsonian Institution Building, Washington, D. C.

Entered as second-class matter July 18, 1923, at the Post Office at Lancaster, Pa., under the Act of March 8, 1879.

THE RÔLE OF EPITHELIUM IN EXPERIMENTAL IMMUNIZATION[1]

SOME twelve years ago I became impressed with the idea that the surface epithelium of the body, including the epidermis and the succulent coverings of the respiratory and alimentary canals, must have important functions in mediating between foreign material brought in contact with it and the internal tissues which it covers.[2]

From either a physiological or pathological point of view the surface epithelium forms the "first line of defense" of the body.

Our modicum of knowledge respecting the protective attributes of this covering embraces two certainties—that it is a mechanical barrier intervened to the passage of foreign material, especially when particulate; and that, when part of a mucous membrane, it is a metabolizing organ capable of chemically changing foreign substances in contact with it.

And yet, in the vast majority of experiments designed to elucidate the reactions of the living tissues toward such materials, these are introduced by traumatic methods avoiding the first line of defense.

An animal might conceivably live long without ever suffering a lesion through which foreign matter might be absorbed, but no mammal has ever escaped the necessity of swallowing or inhaling extraneous substances, including proteins which act as antigens when introduced as such within the body.

The following observations are concerned in no way with reactions of the alimentary canal but only with the mucous membrane of the nasal chambers.

The fact is sufficiently extraordinary that, in the healthy subject, the epithelium of the lungs and bronchi is free from microorganisms, untold numbers of which daily enter the nose. What has become of them? What chemical changes have attended their destruction? What tissue reactions have answered the absorption of such foreign proteins or their digested products?

It seems plausible that "natural immunity" might find its extraneous stimulus in such conditions of antigenic absorption.

For three years, with the invaluable cooperation of my colleague, Dr. Cuthbert Powell, I sought to outline experimentally the immunological attributes of the

[1] Chairman's address, Medical Section, Southwestern Division, of the American Association for the Advancement of Science, Boulder, Colorado, June 9, 1925.

[2] Sewall, H., *Archives of Int. Med.*, 1914, XIII, 856.

epithelium covering the mucous membrane of the nose.[3, 4]

It seems advisable to briefly review our results at the present time in the light of important researches more recently conducted by somewhat similar methods in France.

The guinea pig was the animal best adapted to our study and normal horse serum offered a complex of antigens most convenient for use. The guinea pig is unrivalled in constitutional aptitude for quick and clear-cut immunologic reactions; the length of its nasal canals reaches about five centimeters and they present an extraordinary expanse of mucous membrane. Normal horse serum, in convenient holders, is available in unlimited quantity.

The method of experimentation was divided into two correlated stages. There was first a preparatory treatment consisting of a series of instillations of undiluted horse serum into the anterior nares in definite amounts, ranging from 0.02 cc to 0.2 cc at each instillation, and at definite intervals varying from a few hours to twenty-four days between the instillations. The serum was administered from an all-glass syringe capped by a needle with blunted end. The guinea pig was held supine upon a table, its head being clasped gently with the left hand.

The desired number of droplets of serum was allowed to fall upon one or the other naris, care being taken, usually, to alternate the right and left nares at succeeding instillations. It is important, in seeking the immunologic effects to be described, that the instillation be carried out slowly so that each droplet disappear before the next is allowed to fall in the nostril; thus from three to five minutes are consumed in the instillation of 0.2 cc serum. It is also to be advised that the long axis of the animal's head be held nearly parallel with the plane of the table.

It has been proved beyond doubt that a series of instillations of serum as described, while innocuous and provoking no change in the behavior of the normal guinea pig, nevertheless causes a revolution in the internal economy of the animal which alters its immunological state.

The test and proof of such a constitutional change is to be found in the application of a chemical reagent, horse serum, by intravenous injection. It has long been known that when a guinea pig is given a small subcutaneous injection of serum it undergoes internal changes the effect of which can be demonstrated after eight, and which reach approximately full development in thirty days after the inoculation. If such an animal be given an intravenous injection of, say 0.2 cc to 0.4 cc serum sixteen days after the subcutaneous injection it almost invariably dies in convulsions within a few minutes.

The preliminary subcutaneous injection of *antigen*, horse serum, working through an *incubation period* of eight days or more, has *sensitized* the guinea pig to the proteins in horse serum so that the subsequent intravenous injection is *toxic* and the animal dies in *anaphylactic shock*.

We will suppose that a guinea pig has received a series of spaced instillations of horse serum. Sixteen days after the instillation the animal is given intravenously an injection of approximately 0.3 cc serum.[5]

Two radically different results are obtained, the nature of which may usually be predicted from the experimental conditions which will be detailed later: (1) Within a few seconds of completing the injection the pig breathes deeply, manifests more or less vigorous, fairly localized spasms which pass off within a few minutes, when the animal completely recovers. Every grade in the extent and intensity of these disturbances may be witnessed, resulting in an extreme case in powerful generalized convulsions which may throw the pig, when released, into somersaults and lead to death from asphyxia in three minutes. Opening the thorax the pallid lungs protrude from the chest, respiratory motion is checked, but the heart still feebly beats. This is the classic and familiar picture of anaphylactic death. The guinea pig had been strongly sensitized by the intranasal absorption of serum and the "toxic" injection of the same antigen finds in the circulation a sufficient quantity of allergic or anaphylactic antibodies to develop a quickly fatal poison. (2) But another and apparently completely negative result may follow the toxic injection in a second guinea pig which had received a preliminary sensitizing course of instillation similar to the first. Now the animal lies undisturbed during the toxic injection, except, possibly, for a more restrained and shallow breathing. It would seem that the preliminary nasal instillations of serum had failed to be absorbed.

Further experimentation proves such a conclusion to be premature. From a group of guinea pigs dealt with as above, select two which had survived the toxic injection, one after slight and the other after more severe convulsions, and also two which had withstood the same treatment without disturbance.

Twenty-four days after the first intravenous injection subject all four pigs to a second toxic injection of the same amount of serum as before. Within this period, rising three weeks, the animals which had re-

[3] Sewall, H., and Powell, C., *Arch. of Int. Med.*, 1915, XVI, 605.

[4] Sewall, H., and Powell, C., *Jour. Exp. Med.*, 1916, XXIV, 69.

[5] *Ibid.*, *Arch. of Int. Med.*, 1915, XVI, 605.

acted negatively to the first toxic injection must, if they were normal, have been powerfully sensitized by it and should have promptly died under the second toxic dose. But we would have obtained different results, somewhat as follows: The guinea pig which under the first toxic injection had shown severe convulsions would probably die under the second; the pig which had shown moderate disturbance with the first would probably survive the second after more or less severe spasms, while the two animals which had reacted negatively to the first intravenous injection would probably survive the second with or without convulsive movements.

The repetition of toxic injections could probably be continued indefinitely, but we have not carried them beyond six. For reasons that will be mentioned, a guinea pig may succumb to the third or fourth injection when it might have been supposed to be on the road to complete immunity.[6]

It might be objected that the results described above illustrate nothing more than the condition of tolerance which can be produced in a guinea pig which has received a close succession of massive intraperitoneal injections of horse serum. As is well known, however, such tolerance, while it may be maintained by relatively frequent repetition of the toxic injections, tends always to diminish and hypersensitiveness to redevelop when the resting period between the injections is prolonged. Quite the reverse is found to be the case in guinea pigs which have received their preliminary sensitization through nasal instillations; such have armed the animal fairly completely against the first toxic injection of serum. Here we find that the ability of the animal to withstand the intravenous injection of antigen tends to progressively improve with lapse of time. For example: of two guinea pigs prepared by the same course of nasal instillations both easily survived the intravenous injection, respectively, of 0.31 cc and 0.38 cc of serum given sixteen days after the last instillation.

Fourteen days later the former pig received a second toxic injection, increased to 0.38 cc, and died; the latter animal was kept for sixty-eight days before receiving its second toxic injection, increased to 0.5 cc, and easily survived; one hundred and twenty-two days later it tolerated a third injection, increased to 0.75 cc. Again, three young guinea pigs were prepared by six instillations of 0.19 cc serum at intervals of fourteen days. All received the first toxic injection of 0.38 cc sixteen days after the last instillation. Pigs 1 and 3 were not affected; pig 2 responded with moderate shock. Twenty-four days later the toxic injection was repeated. Now pig 1 suffered moderate shock, 2, very severe shock and 3 was but little affected. After a resting period of seventy-five days a third toxic injection was given without affecting either animal. Thirty-six days later pig 1 received a fourth toxic injection increased to 1.1 cc and survived after nearly fatal convulsions. Pigs 2 and 3 were allowed to rest for one hundred and one days after their third injection, when they were given a fourth increased to 1.13 cc serum, and both withstood it with little or no response.[7]

In a group of five pigs sensitized by six massive intraperitoneal injections of serum within ten days, although two of them withstood a series of seven toxic injections, it was obvious that lengthening the periods between the injections, as well as increasing the amount of serum, tended to a fatal result.[8]

I will now briefly survey the factors which appear to determine the nature of the immunologic reactions in animals whose sensitization has been induced by spaced nasal instillations of horse serum.

The following variables obviously offered themselves for study: (1) the number of separate instillations of serum; (2) the time interval between them; (3) the quantity of serum used with each instillation. Subsequently, it was important to note: (1) the number of toxic intravenous injections; (2) the amount of serum employed in each; (3) the intervals elapsing between them; (4) the biologic reactions resulting.

We performed a large number of experiments to determine the relative effects of varying the separate instillations from a total of two to twelve in number, and of increasing the resting intervals between the instillations from fifteen hours to twenty-four days.[9]

We conclude from our observations that the optimum number of nasal instillations of horse serum preparatory to immunization in guinea pigs is four or six, the serum being introduced into alternate nostrils at successive sittings. Probably the most favorable interval between the instillations is one of two to four days. Certainly a period of one day or less or as long as twenty-four days is relatively ill adapted for immunization.

Up to this point we had failed to determine the experimental condition underlying the development, through toxic injection, of anaphylactic shock or death, on the one hand, or prolonged immunity on the other. A more satisfactory outcome attended study of the third variable mentioned above, namely, the *quantity* of serum dropped into the nose or later injected into the vein.

Special consideration was given to this subject in a former article from which is quoted:

[6] *Ibid.*

[7] *Ibid.*

[8] *Ibid., Jour. Exp. Med.*, 1916, XXIV, 69.

[9] *Ibid., Arch. of Int. Med.*, 1915, XVI, 605.

Of nine guinea pigs receiving a course of instillations of 0.2 cc, only one survived the first toxic injection and in this case the amount of serum given by the vein had been reduced to 0.25 cc. From the reaction manifested by the animal it is probable that it would have succumbed to the nasal injection of 0.38 cc. Of twenty guinea pigs receiving a series of instillations of 0.04 cc or less only one succumbed to the first intravenous injection of 0.38 cc horse serum given sixteen days after the last instillation. Twelve of the twenty animals withstood a second intravenous injection fourteen or more days after the first.[10]

It is to be expected that, other things equal, the area of contact between serum and mucous membrane must determine the amount of absorption and consequent reactions. When the serum is dropped slowly, three to five minutes being consumed in administering 0.2 cc, and the head of the animal is extended with its axis parallel to the table, the serum must gravitate among the convolutions of the nose. As the head is inclined toward the vertical and the dose of serum is given quickly, within thirty seconds, the area of mucous membrane covered as well as the duration of contact is probably reduced. By manipulation of these factors it is possible to evoke a stronger sensitizing effect from a series of instillations of 0.04 cc serum administered according to the first method than from a dosage five times as great by the second.[11]

We thus arrived through experimental means to a wholly rational explanation of the conditions determining the operation of the antigen instilled. The effects are, roughly, proportional to the amount of serum actually absorbed by the mucous membrane. Nor is the interval between the successive instillations a matter of indifference. A period of forty-eight hours seems to be the shortest in which the tissues can react to a given instillation so that the succeeding one may add a protective rather than an allergic effect.

The prophylactic virtues of the two days' interval of rest would seem from clinical experience to stamp also the evolution of bacterial infection. Thus, in a valuable paper,[12] L. Heidenhain urges every operator who suffers an accidental prick with an infected instrument to instantly put the member at rest for two days; an injury to the hand demands that the arm be carried in a sling for that period. In his experience no instance of blood poisoning has followed such treatment, while septicemia has been frequent without it. I have elsewhere pointed out the expediency of limiting tubercular patients who easily develop fever with exertion to exercise on alternate days.[13]

[10] *Ibid., Jour. Exp. Med.*, 1916, XXIV.

[11] *Ibid.*

[12] Heidenhain, L., *Münch. med. Woch.*, 1915, LXXII, 1482.

[13] Sewall, H., *Amer. Rev. Tuberculosis*, 1921, V, 236.

There is an objective sign of allergic reaction which may appear in the course of nasal instillation and which, under known conditions, becomes invariable. This reaction is best brought out by intranasal dosages of 0.2 cc of serum.

. . . Pigs which, after daily treatment for three or four times, are allowed to rest for sixteen days before the next instillation, or pigs at about the fourth treatment in a series with twenty-four days' intervals . . . are apt to manifest characteristic symptoms of sensitization. Two or three minutes after beginning the instillation more or less active movements of intestinal peristalsis are seen. If the pig is a noticeably pregnant female twitching of the lower abdominal wall is obvious, and if pregnancy is far advanced, within a few days of term, there are very active fetal movements which seem, when felt by the hand, to be active fetal contractions.

I have not been able to assure myself that these movements are not imparted to the fetus by vigorous uterine contractions. . . . *During the fetal turmoil the mother remains passive.* Succeeding the onset of intestinal peristalsis the respiratory movements are apt to become deeper, and in about one fifth or more of the cases clicking rales are felt in the throat, then rales are heard in the nose and extend to the bronchial tubes, the animal coughs, becomes dyspneic and is involved in the throes of a bronchial asthma which is almost identical in its symptoms with an asthmatic attack in the human subject. The respiratory urgency gradually passes off in about half an hour, but the animal may still be disturbed after several hours.

We can state definitely that the more marked are these signs of *quasi*-local sensitization the more likely is the animal to succumb to the toxic intravenous injection. In pigs which have been previously highly sensitized by a single subcutaneous injection, serum dropped into the nose is apt to cause, after a small number of treatments, immediate frantic signs of distress to be succeeded in a few minutes by an urgent asthma.[14, 15]

Blood serum, of course, contains a number of different antigens; it was therefore gratifying to receive a personal communication from Dr. V. C. Vaughan that he had confirmed the above observations, using pure edestin or egg-white as antigens.

It is worth noting that when a sensitized pig is made to inhale serum in a nebulized form, driven into a pasteboard funnel encompassing the face of the animal, severe asthma is likewise produced; but in this case, in our experience, no rales were heard; the asthma was *dry*.[16]

In pondering the reasons for the extraordinary biological difference betwen the extremes of our anaphylactic and immune guinea pigs the most reasonable explanation seems to be found on the assumption of

[14] *Ibid., Arch. of Int. Med.*, 1915, XVI, 605.

[15] Sewall, H., *Jour. Lab. and Clin. Med.*, 1817, II, 874.

[16] *Ibid., Arch. of Int. Med.*, 1914, XIII, 856.

two antagonistic antibodies generated in response to serum instillation. One of these is an allergic or sensitizing antibody; the other is an inhibitory resistant or, as we prefer to call it, an immune antibody.

If this supposition be correct it ought to be possible to determine the specific characters of a circulating antibody by bleeding an experimentally prepared animal and injecting its serum into the peritoneal cavity of a normal guinea pig.

It is well known that when the serum is thus transferred from an animal "immunized" in the ordinary way, by subcutaneous or intraperitoneal injection of the serum, the recipient normal animal becomes "passively hypersensitive," so that when it is given an intravenous injection of serum, after a period of one to three days, it usually dies in anaphylactic shock.

We performed, with the invaluable aid of our colleague, Dr. W. C. Mitchell, a few experiments in this field and the results were so remarkable that an excerpt from them is given here.[17] Two guinea pigs were prepared by the instillation of horse serum six times on alternate days. Pig A received 0.04 cc serum at each dose. According to hypothesis this animal should have developed, especially, protective or immunizing antibodies during the course of incubation. Pig B received the same number of instillations but of five times the quantity as A, namely, 0.2 cc. Twenty-one days after the last instillation both pigs were bled and their serums were injected intraperitoneally into six normal young guinea pigs.

Forty-eight hours later each of the latter was given an intravenous injection of 0.25 cc horse serum. Normal pigs 1 and 2 had received serum from donor A; pigs 3 and 4 from donor B. All survived the toxic injection after more or less shock. When the toxic injection was repeated in fifteen days all four recipient pigs died.

But normal pigs 5 and 6 were prepared differently. In their case the serums from the donors A and B were mixed in varied proportions and incubated for some minutes at body temperature. The total amount of serum injected into 5 and 6 was less than that used in either 3 or 4.

Pigs 5 and 6 to which had been transferred the mixed "immune" and "sensitized" serums, both withstood, not only the first toxic injection after forty-eight hours but also a series of other toxic injections following at intervals of 15, 14, 17 and 59 days. The quantity of serum in the last two injections was raised to 0.38 cc, but the tolerance was nearly complete, though profound shock had been excited earlier in the series. It should not be overlooked that the pigs which furnished the serum in the above experiments had been prepared only by the nasal instillation of serum and had lacked in their treatment those aids to the multiplication of antibodies that must come from the enormously greater doses of serum employed in our usual series of toxic injections.

The procedures described above were repeated on groups of guinea pigs as donors of serum which had, on the one hand, been strongly protected by intravenous injections after a preliminary course of instillations, and, on the other, of pigs which had been "immunized" by a succession of massive intraperitoneal injections of serum without previous nasal instillations.

The detailed results must be found in the original paper. Suffice it to say that in these experiments the transfer of serum from the first class of immune donors, those which had received preliminary nasal instillations, protected normal pigs against a succession of toxic injections; while the transferred serum from the second class of (non-instilled) immunes caused death of the recipient pigs under the first toxic injection. Mixtures of the two donated serums obviously protected the recipients.

Apparently the only work that bears definitely upon our conclusions is that of Gurd.[18] His researches were carried on independently and, apparently, somewhat antecedent to our own.

Gurd's experiments consisted in the transfer to young normal guinea pigs of the serum from rabbits which had received injections of sheep's blood serum and were kept for a sufficient time for development in the rabbit of antibodies against sheep's serum.

A normal guinea pig thus inoculated should within twenty-four hours become passively sensitized toward sheep serum and should show anaphylactic reaction when given an intravenous injection of the latter. Gurd found, however, that according to the amount of immune serum transferred and the amount of antigen injected into the guinea pig the response of the latter was positive or negative. He assumes from his results the "presence in the circulating blood of immune animals of bodies which are potent to induce the hypersensitive state when introduced into normal animals and also of bodies which, if injected in sufficient quantities, are able to render normal animals immune."

He writes further that when a guinea pig is made hypersensitive by the inoculation of foreign serum, "subsequent inoculation in sublethal doses results in the stimulation of the production of a second order of ferments whose activity is directed more particularly toward the more complete cleavage of the toxic split product."[19] One familiar with the literature will

[17] Sewall, H., Mitchell, W. C., and Powell, C., *Jour. Amer. Med. Assoc.*, 1916, LXVII, 95.

[18] Gurd, F. B., *Jour. Med. Res.*, 1914, XXXI, 205.

[19] Vaughan, V. C., "Protein Split Products," 1913, Lea & Febiger.

recognize that the "toxic split product" is a result of the interaction of the "first order of antibodies" which had been developed under stimulus of the sensitizing antigen, commonly known as the "anaphylactic antibody," and the protein introduced with the toxic injection.

Gurd's experiments seem to me to furnish insufficient ground for his sweeping conclusions, nevertheless he has recently made them the basis of a most stimulating and suggestive monograph.[20]

The deductions drawn from our own work confirm, in the main, the conclusions envisaged by Gurd, but I believe that our method for the primary production of antibodies, by the instillation of serum into the nose, possesses specific advantages for increasing either the numerator or denominator of the ratio of the sensitizing or anaphylactic to the immune or protective antibody.

It is the great merit of Gurd to have conceived the existence of a "second order of antibodies" having protective powers. But his assumption is gratuitous that this is a *ferment* and that its function is that of a lysin of the toxic split product, or that, if so, it is destroyed in the process.

We seem to have demonstrated, also, that, contrary to Gurd, this second order of antibodies is generated preferably by minute doses of antigen and that its formation begins with the very first introduction thereof.

There is little doubt that the method of choice in attempts to determine the special properties of the respiratory epithelium as a portal for the introduction of foreign protein is to apply the antigen, as we did, in a non-living liquid form.

For many years the opportunity has been denied us to test our conclusions in the field of bacteriology.

Fortunately Besredka, at the Pasteur Institute, has taken up this phase of the subject with the most definite results confirming the specific immunological relations both of the respiratory and alimentary epithelium.

More than five years after our work was published Besredka studied the reactions to horse serum introduced into the larnyx or directly into the trachea of the rabbit and guinea pig.[21] His conclusions as to the immunological advantages of this method, dependent on absorption through the epithelium of the middle respiratory tract, were so favorable that he strongly advises this avenue of treatment in human serotherapy. He also studied on rabbits the effect of introducing cultures of killed tubercle bacilli into the trachea.[22] Enormous doses could be administered without sensible harm because of the filter-like protection offered by the intact epithelium. But the bacilli were evidently at least digested *in situ* and the products absorbed, for the treatment gave rise to a much more abundant and lasting formation of antibodies than could be obtained by any other mode of inoculation. He found that the intestinal epithelium has specific relations with the activity of certain microorganisms.[23]

The germs of dysentery, for example, inoculated into rabbits by whatever method, never cause septicemia but they are always eliminated by the intestine, with local lesions.

He dwells also on the specific relations of the dermal epithelium with the virus of smallpox. In order to vaccinate an animal the skin itself must be inoculated. Vaccine virus introduced into the body without coming in contact with the skin does not vaccinate the animal, for this responds to subsequent inoculation of the skin.[24]

Sanarelli prepared powders containing killed cultures of the bacilli of typhoid, cholera or dysentery.[25] He insufflated the dried powders into the nares of rabbits. Immunity to the respective living germs was aroused by this method, as was evidenced both by the production of a high agglutination titer in the blood and by the resistance offered by the animals to intravenous inoculation with lethal doses of virulent bacilli.

This résumé by no means exhausts the French literature of the past few years confirming the postulate of specific local and general immunities set up by absorption of antigens through surface epithelium.

Summary and Conclusions

When a small amount of blood serum is dropped into the nose of a guinea pig the serum is absorbed by the mucous membrane and, after a definite period of incubation, the animal can be shown to have become profoundly changed.

Depending upon the number of instillations, the interval between them and, especially, the quantity of serum instilled, the animal becomes either highly hypersensitive or strongly resistant to a toxic injection given by the vein. This resistance withstands a considerable series of increasing toxic injections and is strengthened with lapse of time,—contrary to the state of tolerance produced by traumatic methods.

[20] Gurd, F. B., "Infection, Immunity and Inflammation," 1925, C. V. Mosby Co.

[21] Besredka, A., *Ann. de l'Inst. Pasteur*, 1920, XXXIV, 51.

[22] Besredka, A., *Ann. de l'Inst. Pasteur*, 1920, XXXIV, 361.

[23] Besredka, A., *Ann. de l'Inst. Pasteur*, 1919, XXXIII, 301.

[24] Besredka, A., *Paris Medical*, 1922, Dec. 2, p. 496.

[25] Sanarelli, G., Comptes Rendus de la Société de Biol., Dec. 19, 1924, p. 1302.

It is inferred that the absorption of foreign protein by the nose causes the formation of two different antibodies. One of these is *allergic* and excites to anaphylaxis; the other is *protective* and leads to true immuuity. The relative amount of either antibody can be regulated by modifying the amount of serum instilled.

Added to a state of general allergy it is easy to produce, in the guinea pig, a special sensitization of the respiratory apparatus which leads, under appropriate stimulation, to attacks resembling those of bronchial asthma in man.

No conclusion can be drawn at present concerning the nature or mode of action of the protective or immunizing antibody; but the indications are that its relations to the circulation and to tissue fixation resemble those which have been developed by other investigators in regard to the anaphylactic antibody.

Evidence has been submitted that the living epithelium mediates between foreign protein and the organism in a way to favor specifically the elaboration of true immunity.

HENRY SEWALL

DENVER, COLORADO

SUPERFICIAL FACTORS IN EARTHQUAKES

IN considering the earthquakes in New England and eastern Quebec of this last winter, especially the quakes of January 7 and February 28, attention is called to a factor which has been too much neglected. Several writers have written on this subject of the superficial factors, such as barometric pressures, diurnal hours of high and low barometric pressures or the "so-called" tropical hours, the tides and rainfall. The earthquake of February 28 is particularly interesting in that two of these factors, barometric pressure and deficiency of rainfall, appear to have played an important part. Before going into details of this quake a few geological observations must be made.

During the ice advances of the Glacial period, the land of New England and adjacent territory was depressed considerably below its present stand by the tremendous weight of the great glaciers, which had an average thickness of about 3,000 feet. The land was more depressed in the region of Maine, New Hampshire and Vermont and southern Canada than in southern New England, on account of the greater thickness of the ice in the more northern region. In fact, in southern New England the ice pressure is supposed to have uplifted the land near the terminal moraines instead of depressing it, in the way that a ridge is produced around your boot when stepping in soft mud. Thus Long Island, Block Island and the Cape Cod region were higher than now at the close of the Glacial period. In the region about Montreal the land was depressed about 600 feet below its present stand. On the Maine coast around Penobscot Bay it was depressed about 300 feet. Since the ice left New England about 30,000 years ago the more northern part has been uplifted and the southern part has been depressed. There has been a kind of tilt, the northern part going up and the southern part going down. The northern part has risen much more than the southern part has sunk. At the present time, therefore, there is a tendency for most of New England to rise. It was Woodworth[1] who proved these facts in 1905 in his great work on the "Ancient Water Levels of the Champlain and Hudson Valleys," and since that time other workers have proved that Woodworth was right. It is to be noted that the tendency to rise is the important point to bear in mind in considering the superficial factors discussed, in these New England and Canadian quakes.

The earthquake of January 7 was probably to the east of Cape Ann, and not many miles off shore. The fault on which this movement took place has not been located. The earthquake of February 28 appears to have had its origin near the mouth of the Saguenay River. The large amount of destruction in the villages near the mouth of the Saguenay, and the records of the distance on the Harvard and Ottawa seismographs indicate that here the greatest intensity took place. Strains that finally result in earthquakes usually go on for a long period of time, sometimes measured in many years, before the final crack comes, so in the quake under discussion the release came suddenly when conditions were just right. If New England is a rising area, anything which would tend to make its land lighter would increase the strain along the fault. A deficiency of rainfall and a low barometric pressure would be the two most effective ways of making the land lighter.

According to the data collected at the Blue Hill Observatory, we had a deficiency of about 8.1 inches of rainfall in New England during the five months previous to March 1, 1925. Reservoirs had been low, hydraulic power plants had had to shut down in many cases for lack of water, wells had gone dry and in many places there had been good cause for worry. The quake of January 7 was preceded by three months of very dry weather and immediately followed by rain and a normal rainfall for that

1 Woodworth, J. B., "Ancient water levels of the Champlain and Hudson valleys," New York State Museum, Bull. 84, Geology 8, 1905.