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TUBERCULIN.

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THE TREATMENT OF TUBERCULOUS LARYN-  
GITIS WITH MODIFIED TUBERCULIN.

*A Preliminary Report.*

BY

MAX THORNER, M.D.,

OF CINCINNATI, OHIO.

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TUBERCULIN.<sup>1</sup>**

BY JOSEPH EICHBERG, M.D.,  
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THE lamentable failure of the original Koch treatment of tuberculosis is still fresh in the medical mind. Heralded in advance by the one man who had inseparably identified his name with the great scourge of the temperate zone, the treatment was received with confident faith by the entire profession. The circumstances preceding, and the manner of, its publicity savored somewhat of charlatanism; but these were explained and excused on the plea that great political and personal pressure had been brought to bear on the illustrious scientist, to whom modern pathology owes so much. More than any other had he contributed to the establishment and proof of the bacterial theory in pathology as applied to every single member of the group of infectious diseases. It was but natural that to him the world of scientific medicine should turn for some practical result of his great philosophic and experimental work.

<sup>1</sup> Read at the meeting of the Mississippi Valley Medical Association, October 14, 1892.



Nor was he wholly blameworthy. Clinicians of great repute and deserved eminence had closely followed his experiments, to which they lent their countenance, which they copied in detail, and subsequently reported in terms of fulsome praise, with some of their marvellous results. Few in the profession would question any statements emanating from such men as Koch, Bergmann, Gerhardt, and Senator; everyone was excited, and there went up a feverish cry, "To Berlin."

The disillusion came speedily enough. There could be no doubt of the wondrous effects of the new remedy, but their duration was brief, and following the temporary improvement there came a period of increased destruction, with dangerous complications, and not a few fatalities. Where there had been great authority to sanction, there now came the menacing voice of Virchow, commanding a halt, fully justifying, on the post-mortem table, his scathing condemnation of the method, and of its disastrous consequences.

The rocket had soared high, and its flight was hopefully followed by many a poor sufferer; the thud with which it speedily fell carried a corresponding gloom, and seemed to close another avenue of escape to many tuberculous patients, to whom there had come a promise of new life.

However, not all were willing to wholly abandon a method that seemed to rest on so secure and scientific a basis. The whole theory of establishing immunity by inoculation with attenuated cultures, a theory positively proved by Pasteur, seemed to point to some such logical result as Koch had presumably

achieved. True it was, that in one case we were dealing with a healthy organism, and the inoculations were preventive; in the other, the disease was more or less fully established, and the inoculation was to be curative. In the one case we were anticipating the possible development of an infectious disease; in the other, we had to deal with an individual already in the grasp of the destroying malady.

Yet there existed between the two classes an analogy of causation so close as to reasonably suggest that a similar course of treatment would be attended with results positively beneficial. That such a line of reasoning embodies no sophistry has only lately been proved by the brilliant results of Cattani, Tizzoni, and others in the cure of fully established cases of tetanus. By inoculation with an antitoxin obtained indirectly from pure cultures of the tetanus-bacillus, no less than six cases have been reported as cured, a result far beyond the limits of mere accidental recovery.

Consequently, there came to the minds of many a certain doubt as to the expediency of wholly dropping both Koch's plan and his remedy, although the latter was then strongly in disgrace. Efforts were made by a number of observers, as also by Koch himself, to separate from so-called tuberculin those principles that gave rise to the high fever, general malaise, and increased destruction around the tuberculous deposits. If this could be achieved, the remainder might then be counted upon to manifest all of the beneficial and curative properties of the

original lymph, without exposing the patient to any risk from the treatment.

In two instances have these efforts at modifying the lymph been notably successful: in the case of Klebs, who obtained from Koch's tuberculin a compound which he calls tuberculocidin, and for which he claimed great curative powers; and in the case of Hunter,<sup>1</sup> who made a most careful chemical analysis of the lymph, and who succeeded in isolating from the lymph a number of substances, which he designated by letter as modifications A, B, CB, etc.

The employment of modification B seemed to be attended with fewer unpleasant consequences than that of any of the others, an experience that was subsequently verified in the human subject. This modification consists in the isolation of an albumose or group of albumoses, which are re-dissolved, and then employed in a diluted form. Klebs retained the secret of the manufacture of his tuberculocidin, though he allowed it to be sold in the open market. Hunter, guided by a finer, more unselfish professional instinct, at once published his results, and also the method of preparing his modification. It is his preparation B which has been used in our experiments, the same that received the indorsement of Dr. Kinnicutt,<sup>2</sup> whose moderately satisfactory results, together with my own belief that we had not yet exhausted all there was in tuberculin, induced me to subject it to a test, whose results I will give in summary.

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<sup>1</sup> British Medical Journal, July 25, 1891.

<sup>2</sup> New York Medical Record, May, 1892.

First, in defence of these experiments, which might otherwise be open to censure, it must be premised that both Hunter's and Kinnicutt's experience seemed to establish the comparative harmlessness of this peculiar agent. Without such assurance I should not have been tempted to its trial. The mere fact that want and misfortune compel many to seek the asylum of a hospital certainly confers no right upon the physician to trifle with remedies that may possibly aggravate their disorders; and it was solely because of the prominence given to the quality of the remedy, and the freedom from general and local sequelæ of an unfavorable kind, that it was given so thorough a test.

These, then, were the conditions upon which we engaged in these experiments: (1) That the injections should not give rise to any immediate local reaction; (2) that there should not follow fever, or depression, or general lassitude; (3) that there should be no symptoms indicating an increase of destructive process, or a development of fresh inflammatory change in the seat of tuberculous disease; (4) that the dosage should be regulated by careful and repeated observation of the temperature and pulse.

All these indications have been fully met. I can here give only a short *résumé* of the results achieved. Such as they are, they are full of encouragement, and mark the remedy as worthy of more extended trial.

It must be remembered that we were dealing, in the main, with a most unfavorable class of cases, that our experiments were made during an exceptionally hot summer, and that our patients were not

selected with any view as to special fitness for the experiment. All alike received the injections; many were then hopelessly sick, two almost moribund; manifestly little could be hoped for from any treatment at this stage; yet it was desirable to define as nearly as possible the limits within which benefit might be derived, and this could only be done in the way suggested.

Incipient cases, those most likely to be permanently relieved, rarely present themselves for hospital aid during the pleasant weather. Still able to go about, they find some means of eking out an existence until the rigors of winter and increasing helplessness drive them to some charitable institution.

Another feature, connected solely with hospital life, has had its bearing upon our cases. The hospital authorities have no power of imposing restraint upon any patient, except in the cases of such as are under police surveillance. As soon as a patient insists upon his discharge, it must be granted, even though it be against his own interests; and, in most instances, it is useless to appeal either to his reason or to his fears. Thus it happens that some of our most promising cases passed beyond control after the first manifest improvement in their condition had taken place. In private practice, mere self-interest will bind the patient in such a case, so long as there is any hope of further betterment.

The injections were made daily by means of a syringe with asbestos wrapping and packing. The syringe and needles, as also the glass cups for the solution, were sterilized daily before using—a pre-

caution which I believe unnecessary, but which was followed throughout, to avoid any accidental contamination. The solution was kindly prepared for me by Mr. Mark Brown, of Miami Medical College, in the laboratory of the Cincinnati University, according to the directions given by Dr. Kinnicutt.<sup>1</sup> The lymph, from which the solutions were made, was part of an unbroken package, received from Germany about two years ago. In the process of preparation all apparatus was sterilized, and the water used in dialyzing was previously boiled. The dialyzer consisted of fine sausage-casing. The solution was received and kept in sterilized glass-stoppered bottles.

In a kind letter from Dr. Kinnicutt, he says: "Both Dr. Trudeau and I deemed it prudent to still further dilute the 10 per cent. preparation B and CB. The formula which we adopted was as follows: 1 c.c. of the 10 per cent. solution was diluted with 10 c.c. of  $\frac{1}{2}$  per cent. carbolic acid solution, and of this 0.002 gram was used by me for the initial inoculation; 0.005 gram by Trudeau. By me the dosage was increased by 0.002 gram

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<sup>1</sup> Method of preparation of Hunter's modifications. Modification B: 1 c.c. of tuberculin, 5 c.c. distilled water, saturation with preferably large crystals of ammonium sulphate for twenty-four hours in the cold, the precipitate filtered off and freed as far as possible from any crystals of ammonium sulphate, placed in the dialyzer, and dialyzed just so long and no longer in running water, and then in distilled water until all trace of ammonium sulphate has disappeared. Crystals of thymol are added to the solution to prevent any putrefactive change; the solution is then made up to such bulk that 10 c.c. shall correspond to each c.c. of tuberculin employed. (Title: B, 10 per cent.)

daily, by Trudeau by 0.005 gram. If any elevation of temperature above 100° F. followed an inoculation in an apyretic case, the same dosage was retained until such a rise ceased to be developed. In pyretic cases the daily range without inoculation was carefully studied for several days, and any rise above the daily range, following an inoculation, was regarded as an indication to diminish the dosage or hold it at the same amount. As I stated in my lecture, the B preparation only should, in my judgment, be used."

These directions have been carefully followed, except that the increase of dosage, begun at 0.0025 gram, was afterward changed to 0.005 gram daily in cases in which tolerance was well established. In no case did the amount injected exceed 0.100, which, as we were dealing with a 1 per cent. solution of the original lymph, represents a very minute dosage. In some later experiments reported by Trudeau,<sup>1</sup> the initial dose was 0.003 gram daily, which was finally carried to 0.7 or 0.8, the increase being slowly kept up as long as no rise of temperature occurred; but there seemed to be no indication in our cases for any larger dose than the one mentioned. Indeed, symptoms of decided improvement set in in a considerable number of cases before the dose reached 0.03 gram of the diluted solution.

The clinical material embraces twenty-nine cases of undoubted pulmonary tuberculosis, one of lupus, and one of tuberculous peritonitis. With reference to the latter, some doubt may be expressed as to

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<sup>1</sup> THE MEDICAL NEWS, September 10, 1892, p. 299; September 24, 1892, p. 364.

the accuracy of the diagnosis. The only reply that I can make is that all of the symptoms ordinarily manifested in tuberculous peritonitis were present ; that there was at the same time incipient pulmonary tuberculosis, with continued fever ; and that the patient was a negro, chronic tuberculous processes being especially common in the colored race. In this case perfect recovery ensued.

The case of lupus, which had been treated a year before with the original tuberculin without success, remained under observation for too short a time to furnish any reliable data, the patient being expelled from the hospital for insubordination. Another patient, a case of pulmonary tuberculosis, with beginning excavation of the lung, improved so much that he felt obliged to celebrate the change in his condition by assaulting the cook, whom he thoroughly worsted in a fistic encounter ; though, at the time of his admission, this patient was unable to leave his bed. One case of pulmonary tuberculosis, with elastic fibers in the sputum, was discharged perfectly well ; fever, cough, expectoration, all had disappeared, and there was a gain in weight of fifteen pounds.

Of the 29 cases of pulmonary tuberculosis, 22 were males, 7 females ; 4 of the latter were colored. The ages of the patients ranged from twenty-one to fifty-one years, 11 being below thirty, and 9 below forty years of age. Six patients died ; one had, in addition to the pulmonary changes, chronic interstitial nephritis ; one died twelve days after admission from a complicated tuberculous laryngitis, which rendered swallowing very difficult ; another had

total adhesion of the pericardium, with fatty kidneys; a fourth was almost moribund on admission, but lived seventeen days.

In no single instance could it be said that death was hastened by the injections; nor, in the case of tuberculous laryngitis was there any change for the worse in the local ulceration. In no case was hemorrhage observed to follow the injections. In general, all patients, without exception, declared that they felt better, breathed with greater freedom; a weight seemed to be lifted from the chest, and the general condition seemed to indicate a better tone.

Of the remaining cases, three are still in the hospital; one was discharged at her own request in a condition little better than when she came; one was discharged well; one nearly well, and fourteen were greatly improved.

A rating as to improvement was based upon a gain in weight, a diminution in the frequency and severity of cough, diminished quantity of expectoration, and cessation of night-sweats. The physical signs were altered, inasmuch as dry sounds took the place of coarse, moist râles and fine crepitations, showing clearly an arrest of the destructive changes in the lung-tissues. The computation of the bacilli was not made, owing to the uncertainty attending such estimates.

The average stay in the hospital of all cases subjected to the treatment by inoculation was 56.6 days. Few cases received inoculations for more than fifty days, many leaving earlier—as soon as they had in a measure regained their strength. In

no instance did a patient suffer any local inconvenience about the point of inoculation. For the most part, the injections were given in the infra-clavicular region; for no other reason than that the parts, being already exposed by the examination, offered a convenient surface. The strength of the solution was gradually increased, so that the amount given never exceeded the contents of one syringe.

The effect on the urine was, in many instances, decided; an increased flow rapidly followed the inoculations, and the daily average remained higher during the time of the experiments. The first effect on the sputum was to cause an increased expectoration, to be followed later on by a gradual diminution. Parallel with this was a change in color and composition, the sputum becoming less viscid and more distinctly mucous in character. The cough became less troublesome. Three of the cases were interrupted in their convalescence by a prostrating diarrhea, which seemed in no way connected with the inoculations.

The most surprising effect was observed in the temperature. By the exercise of great industry the nurses in the respective wards kept records for two weeks of hourly observations of the temperature before and after the injections. Subsequently, these were supplemented by records taken every three hours.

In but the fewest instances was there noted any decided rise, *i. e.*, to, say, more than  $2^{\circ}$ ; while in the larger number there was, within the six hours immediately following the injection, a decline of between  $2^{\circ}$  and  $3.5^{\circ}$ ; this decline followed whether

the injections were made early or late in the day, so that it was not due to diurnal variation. In cases in which originally there had been continuous fever, it was noted that in all, save the most advanced, the mean daily temperature steadily declined, approximating the normal line during the entire twenty-four hours. In cases that were apyretic at the outset the thermal line remained subnormal during the greater part of the twenty-four hours.

The experiments were sometimes interrupted for a day or two, when it was noted that the maximum of the intervening days was higher than when the injections had been given. It was a common experience to find the temperature after midnight subnormal. The pulse-rate was slowed, but without much gain in the volume or force of the circulation. In apyretic cases there was never any increase of temperature.

In conjunction with the inoculations all patients received five-drop doses of creasote, with oil.

Our present position has been well expressed by Trudeau in the paper already quoted. "More extended research and clearer knowledge of the various elements, both beneficial and injurious, contained in bacterial products, as well as of their effects upon tuberculous animals, may in the future lead to still further improvement in this as yet tentative method of treatment. At present its limitation to early and apyretic cases seems indicated." On the strength of our own experience we would go somewhat further. The greatest benefit—indeed, complete restoration with cicatrization of tuberculous deposits—may be hoped for in incipient cases during the apyretic

stage ; but even in advanced cases some improvement, with consequent prolongation of life, will be frequently observed. Experiments hitherto reported have, in the main, been carried on in localities in which the altitude and climate contribute greatly to favor a cure. Yet the fewest of patients will be so situated financially as to avail themselves of climatic changes ; indeed, the majority will not be able to do so. It is especially with a view to again call attention to the possibilities of prompt treatment in the incipient stage of such cases that I have reported this comparatively limited number of observations.



**THE TREATMENT OF TUBERCULOUS LARYNGITIS WITH MODIFIED TUBERCULIN.<sup>1</sup>**

*A Preliminary Report.*

BY MAX THORNER, M.D.,  
OF CINCINNATI, OHIO.

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NOT more than twelve years ago tuberculosis of the larynx was considered an incurable disease—so hopelessly incurable, in fact, that nobody attempted to treat the local affection with the view of healing it, but simply for the purpose of alleviating, if possible, the agonizing sufferings of the patients. It was in the year 1880 that Prof. Moritz Schmidt, of Frankfurt, reported sixteen cases of tuberculous laryngitis that he had cured (of which number, after thirteen years, there had been no recurrence in the larynx in two).<sup>2</sup> Then, for the first time, it was strikingly emphasized that one should enter upon the treatment of laryngeal tuberculosis with the view of a possible cure, and subsequent events have proved the correctness of this position. I need only mention the names of Heryng, of Warsaw, and Krause, of Berlin, who, by their surgical treatment

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<sup>1</sup> Read before the Mississippi Valley Medical Association, October 14, 1892.

<sup>2</sup> M. Schmidt: Tuberculin bei Kehlkopftuberculose. Verhandl. d. X. Cong. f. inn. Medicin. Wiesbaden, 1891.

of this affection, have established the fact (as many others, too numerous to mention, have also done by other methods of treatment) that there is a possibility of laryngeal tuberculosis being cured. Unfortunately, the number of such cases cured and remaining so is exceedingly small.

It is, therefore, not to be wondered at that, when the first enthusiasm over Koch's tuberculin had subsided, the disappointment was so much the greater. The agent had not done for the larynx what had been expected; for the larynx was the very region to demonstrate *aa oculos* the curative action—to allow the study of every phase of any change that might take place. It was in this sense that Lennox Browne wrote in his early monograph on Tuberculin: “*Not only is the larynx the most appropriate place for the study of true tubercle, but it is also the most appropriate and convenient site for accurate observation of the various stages of its development toward reparation which takes place under Koch's treatment.*”<sup>1</sup> The outcome of the numerous experiments is yet fresh in our minds. Referring to the larynx alone, the cases in which improvement or cure followed the administration of the lymph were few, while evil results followed in many cases. Not only did new tuberculous eruptions occur in situations in which previously the tissues appeared healthy, but swellings and edema developed in many cases, causing threatening dyspnea, which, in a few cases, necessitated tracheotomy.

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<sup>1</sup> Lennox Browne: Koch's Remedy in Relation specially to Throat Consumption, 1891, p. 3.

When "crude tuberculin" (as it was afterward called) had fallen into disuse, there were quite many observers who were at heart convinced that the underlying principle of the treatment was correct, and that it would finally be triumphant. This idea is very prettily expressed by Prof. M. Schmidt in his concluding remarks on "Tuberculin in Laryngeal Phthisis," when he says:<sup>1</sup> "If this experiment should fail, we shall be compelled to bid farewell for some time to the light that shed so brightly its warm rays of hope into the most profound depths of human misery. The road, however, opened to us by the great Robert Koch is sure to lead us some day to our goal."

Since that time experiments have been made with some modifications of tuberculin, the details of which have already been entered into. The following two cases have been treated with Hunter's modification B of tuberculin,<sup>2</sup> for the supply of which I am indebted to Dr. Joseph Eichberg, who has also seen the cases several times with me. The injections were always made between the shoulder-blades, with carefully sterilized syringes and needles. The temperature was taken every two hours, from 7 A.M. to 9 P.M., the patient always sleeping soundly through the night.

CASE I.—Charles V., forty-three years old, was first seen March 24, 1892. He had been discharged from St. Mary's Hospital but a few weeks previously, where he had been under treatment for pulmonary tuberculosis. At the time of his discharge from the hospital the cough had improved. At the time of

<sup>1</sup> Loc. cit.

<sup>2</sup> Brit. Med. Journal, 1891.

his first visit he was coughing incessantly, was very hoarse, complained of pain in the laryngeal region, and had some dyspnea. He was a typical case of pulmonary tuberculosis. He weighed 123 pounds. His temperature ranged from 98.4° to 101.6° F. Physical examination revealed the presence of an active process in the lungs. Tubercle-bacilli were found in the sputum.

The entire larynx was congested; the left vocal band was intensely swollen to double its normal size, especially so in its posterior portion; the upper surface and free edge were rough and uneven, having the appearance of being covered with small excrescences, which assumed a bunch-like shape near the inter-arytenoid fold. The process vocalis was marked by a small yellowish ulcer; beginning at this particular spot there was considerable swelling, confined to the laryngeal side of the mucosa covering the left arytenoid cartilage; this infiltration was also the seat of several superficial ulcers; the lower surface of the left band was considerably infiltrated, presenting the appearances seen in an attack of chorditis vocalis inferioris acuta; while repeated examination, with the aid of Prof. Killian's excellent method,<sup>1</sup> failed to disclose any affection of the posterior laryngeal wall, a favorable oclation for tuberculous deposits.

Surgical treatment being contra-indicated on account of the extremely weak condition of the patient, the larynx was treated locally with lactic acid and menthol. Internally the man took beechwood creasote. This treatment seemed to hold further advance of the local trouble in check, whilst the general condition had improved mate-

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<sup>1</sup> G. Killian: Die Untersuchung d. hint. Larynxwand. Jena, 1890. Rudolf Keller: Zur Tuberculose der hint. Larynxwand. Inaug. Dissertation, Freiberg, 1892.

rially at the time when the injections were begun. He had gained ten pounds; felt stronger; coughed very little, at times not at all. There was not quite so much hyperemia of the larynx, and some of the small superficial ulcers had healed. Otherwise the condition was unchanged. The temperature ranged from  $98.6^{\circ}$  to  $99.4^{\circ}$  F.

On September 5, 1892, the first injection of 0.0025 of tuberculin was practised. This amount was gradually increased until, on October 8th, 0.1 was reached. The injections were made every day. The temperature ranged from  $98^{\circ}$  to  $99.6^{\circ}$ . Only on one day was there a temperature of  $100.2^{\circ}$ , and this was the second day after I had commenced injecting 0.1; after that the temperature returned to  $99.6^{\circ}$ . The highest temperature was usually found from two to four hours after the injections, which were generally made between 10 and 11 A.M. The lowest temperatures were registered in the early forenoon. Ordinarily, the temperature did not rise above  $99^{\circ}$ . The general condition of the patient was always good. Only during the first few days did he complain of general malaise, sometimes of headache; but these soon left him, never to return.

The laryngoscope at no time revealed any increase of the hyperemia, any new swelling, any evidence of tuberculosis in places previously free. There was, in fact, at no time any untoward symptom noticed in connection with the larynx. After the fifth injection it was possible to notice a subsidence in the congestion. The congested mucosa gradually assumed a paler color, while the infiltration of the vocal band, especially in its anterior portion, had greatly diminished at the end of the third week, when Dr. Eichberg saw the case again; the large superficial ulcers over the arytenoid had

healed, and the lobular swellings around the processus vocalis had decreased in size; the subglottic swelling had also greatly abated. This improvement continued, though slowly, but in an unmistakable manner. On October 6th, one month after the first injection, the patient volunteered the statement that he experienced much less dyspnea when walking up hill. On October 14th, the improvement had continued; there remained only a small portion of the excrescences in the posterior part of the cord; the subglottic swelling, though still visible, was materially reduced, and the mobility of the left cord was greater. The voice was clearer than before.

CASE II.—Mrs. S. M. H., thirty-five years old, has had pulmonary tuberculosis for a number of years, an exacerbation usually taking place in the autumn. For two months she had complained of pain in swallowing. Tubercle bacilli were found in the sputum.

On September 20, 1892, laryngoscopic examination showed the epiglottis to be considerably thickened; on the laryngeal surface, near the left upper border, was a yellow ulcer as large as a split-pea. There was also considerable pear-shaped swelling of both arytenoids, and some slight swelling of the inter-arytenoid membrane. The temperature ranged between  $98.8^{\circ}$  and  $99.8^{\circ}$  F. On September 27th, a first injection of 0.0025 was practised. The dose was gradually increased every day until it was 0.035. There was never any untoward symptom in connection with the larynx. The small ulcer healed; the infiltration of the epiglottis slightly diminished; otherwise the condition remained unchanged. The temperature ranged from  $98.6^{\circ}$  to  $99.6^{\circ}$ . The patient became able to swallow without pain.

These two cases are insufficient, and the time of observation is yet too limited to permit of any definite conclusions. They seem, however, to encourage further research in the same direction with some of the modifications of tuberculin. I shall certainly continue to investigate the effect of this powerful preparation, deprived of its toxic constituents, and I confidently hope that many others will do the same, for, as the late S. D. Gross has said: "In an inquiry of this kind individual experience amounts to nothing; collective experience is everything."









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