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ON A CHRONIC CHOLERA CARRIER*

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THE case we are about to offer presents not a few points of interest. More especially we are inclined to think it of import as throwing light upon the existence of "cholera carriers," and as demonstrating the probable mode whereby the cholera vibrio is perpetuated from one season to another and becomes transmitted along trade routes. In the second place, it is of serious import in its bearing upon the efficacy of the international quarantine regulations against this disease. Lastly, it throws doubt upon the value of the routine methods that until recently have been employed for rapid diagnosis of the specific organism. We hesitate to ascribe our abnormal results to imperfect technique, or rather would state that the ordinary technique in our hands has, through the presence of certain other organisms, shown itself unable to separate immediately the specific cholera vibrio with certainty and precision. For this, other methods have been found necessary.

HISTORY OF CASE

For the details of the history of the patient we are indebted to the surgeon of the *Royal George*, to Dr. Bailey, of the American Immigration Service at Quebec, and to Dr. Pagé, Medical Superintendent of the Detention Hospital at Quebec. The patient, a Russian, left the village of Michelsdorf, in the district of Wlodawsky, in the province of Szedlicki, on October 18th, driving to the city of Wlodawa, and thence travelling by rail for two days to Libau. At Libau he was detained in an immigrant boarding-house, with some thirty other immigrants, for a day and a night; then he went on board a Danish

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ship bound for London. The voyage, according to his statement, occupied eight days, and that without call or stop at any intermediate port. During this voyage he ate only food supplied by the ship and no uncooked vegetables or fruit. He knew of no passengers being sick during the voyage. As is the custom with foreign immigrants traversing England, he arrived at the wharf in London, and was taken by an omnibus to an immigrant boarding-house, where with him were many Russians and immigrants of other nationalities. Here he was detained for seven or eight days. On November 8th, the day of sailing, he was sent by rail to Bristol and embarked upon the *Royal George*. He had been at sea four days, when (November 12th) he was taken ill with severe cramps in the extremities and abdomen, chilly sensations, vomiting, and great thirst. These symptoms were apparently not sufficiently severe for him to call for the ship's doctor, or to arrest the attention of the stewards. On the thirteenth, the symptoms were more marked, with weakness and diarrhoea, symptoms which continued with more or less severity until the ship arrived at Quebec on the seventeenth. Throughout this period, however, the man made no complaint, and it is scarcely necessary to point out that frequent vomiting on ship-board does not attract special attention. The same is true regarding frequent retirement to the lavatories. The man never sought treatment, and when the ship arrived at quarantine about midnight on November 16th, it was with a clean bill of health, and clearance was given without examination.

By an agreement between the United States and the Dominion authorities to save trouble and delay at the numerous frontier points by which immigrants may pass from Canada into the neighbouring republic, the United States maintains an examining staff at Quebec, and there all immigrants destined to United States points and entering by the St. Lawrence are disembarked and undergo medical examination. Regarding this case Dr. Bailey reported to his government: "My attention during primary inspection was drawn to this immigrant's unsteady gait, anxious expression, with pinched nose and cheeks, and lips blue. His temperature at the time was 99.2°, weak, thready pulse of 138, and he complained of abdominal cramps and intense thirst. He said he had been unable during the five preceding days to retain anything in his stomach except a few bits of bread he and his travelling companion had brought with them from their village in Russia, and at times had no control over his bowel movements. At no time during his whole journey had he eaten any uncooked vegetables or fruit, except four apples purchased and eaten unpeeled between Wlodawa and Libau." It is but just to add that the symptoms did

not appear so marked to other expert observers on the ship and at Quebec.

In the three or four hours during which the suspect was at the immigration building at Quebec it was not observed that he had to retire. As soon as possible after Dr. Bailey's diagnosis of the case, all the immigrants were ordered back on board, the suspect, perhaps unnecessarily, being conveyed on a stretcher, and now the ship was sent back to quarantine at Grosse Isle. It was only some two hours after reëmbarkation that the patient had an evacuation. This was very watery, being little more than bile-stained, discoloured fluid. The patient was now under strict supervision, and the surgeon placed the fluid in two sterilized glass jars, one of which was delivered to the United States authorities for transmission to Washington, and the other forwarded to Dr. Pagé, at Quebec, for transmission to Dr. Adami at Montreal.

On arrival at Grosse Isle early the following morning the patient was able to leave the ship unaided, walking briskly along the gangway and so to the quarantine buildings. His future history may be briefly epitomized. Within two days he was passing normal stools, and from now on till his deportation on May 30th, he had no further attack of a diarrhoeal or choleraic type. In the spring, however, he manifested definite signs of mental aberration. On this account it was that, after his stools had been absolutely negative for a month, he was declared an undesirable, and was transported back to Europe. Lastly, it deserves note that the suspect consistently protested that there had been no cholera known in the district from which he came, and Dr. Montizambert, from official declarations, has been unable to trace the records of any cholera at Libau or within two hundred miles of that port during the last twelve months.

BACTERIOLOGICAL EXAMINATION

In accordance with the recommendations of the International Quarantine Committee, the Canadian regulations regarding cholera are that should a case be detected on board ship the officers and passengers who have been in contact with the case are detained at quarantine, where they are under observation for five days, and if no further cases of the disease show themselves during that period, they are then discharged and permitted to proceed to their destinations. Both on this account, and again for the reason that this was the last voyage of the *Royal George* to Montreal for the year, and because the season was perilously near its close, so that navigation might be interrupted at any moment, it will be seen that it was all important that a

diagnosis be obtained without a moment's delay. Thus the jar containing the faecal fluid was immediately forwarded to Quebec, and on the evening of the seventeenth was sent by express to Montreal, and came into Dr. Adami's hands at mid-day upon November 18th.

The jar contained some 200 c.c. of a thin, dark, greenish fluid, only slightly turbid and with but a small amount of sediment. On centrifugalization with the ordinary hand centrifuge machine the conical end of the tube contained a little over 1 c.c. of greenish deposit, which, on washing with water, swelled to some extent and became pale and mucoid and somewhat stringy, showing under the microscope no evidences of digested food, but occasional cellular débris. At 12.30 p.m., six test tubes of Dunham's medium were seeded both from the supernatant fluid and from the débris and placed in the incubator at 37°C. Immediately smears were made from the centrifugalized sediment and, after fixation, stained by Gram's method, by Loeffler's blue, and by dilute carbol fuchsin. These smears revealed an abundant bacterial flora, the most striking feature of which was the presence of relatively long, thin, Gram-negative, bacillary forms. Every field of the microscope with the immersion lens presented abundant bacteria of this type, many with a double (S) curve, more with the single curve, and, as is common with the cholera vibrio, many straight or with a scarcely recognizable curve. These organisms appeared most clearly and sharply with dilute carbol fuchsin.

At 8.30 the same evening; namely, after eight hours' incubation, the tubes of Dunham's medium were removed from the incubator and examined. Smears were made from drops taken from the surface, and plate cultures were made upon agar and gelatin media, as also streak cultures upon agar. The smears made direct from the broth showed what appeared to be pure cultures of one form, a form, namely, of the same diameter as the vibrios seen in smears from the faeces, in general relatively long, but on the average not so long as those seen in the faeces. Now the majority of the forms tended to be straight; nevertheless, several with double curves were observable. These were always present in little clusters. Hanging drop preparations showed that they were actively motile; further, they were Gram-negative.

Dr. Adami happened to possess at the time only one stock culture of the spirillum cholerae Asiaticae. This had not been transplanted for some months. An agar tube of this was also filled with Dunham's solution and incubated along with the others as a control. This gave, at the end of eight hours, forms which in size and staining power resembled those obtained on Dunham's tube and in the stools. The only noticeable feature was the relative paucity of the vibrios in the field. The

subsequent history of this is interesting. The agar tubes made from this culture gave apparently no growths and were put to one side. Coming to examine the tubes a month later small colonies were found, and since then have been carried through successive transplantations. The remarkable thing about this attenuated and revived form is that it presents individual vibrios with a more pronounced curve than we have ever previously met with. In this it is wholly different from the other three strains now in our possession. In all other respects it is typical.

As a result of these first studies, late on the evening of November 18th, a telegram was sent to Dr. Montizambert at Quebec, stating these facts and concluding, "Must provisionally diagnose cholera. Absolute diagnosis to-morrow night."

The examination next day of the agar plates and streak cultures and of the other media further confirmed the diagnosis. The streak cultures on agar showed the translucent, somewhat milky growths characteristic of the cholera spirillum. With twelve and twenty-four hour cultures on ordinary broth, stained by Pitfield's method, characteristic organisms were observed possessing a single polar flagellum. Regarding the presence of forms with a single polar flagellum there could be no doubt. These additional data led Dr. Adami in the afternoon of the nineteenth to telegraph to Dr. Montizambert at Grosse Isle that these properties of the organism forced him to conclude that he had definitely to deal with a case of cholera. All the Dunham tubes tested in forty-eight hours gave well-marked cholera-red reaction.

So far, then, the following positive results had been obtained; namely: 1. Presence of characteristic vibrio forms in the stools. 2. Presence of similar vibrio forms on the surface of Dunham's medium after eight hours' incubation. 3. Presence of forms possessing a single polar flagellum. 4. Active motility on the part of organisms possessing the vibrio type. 5. Gram-negative staining of the organism. 6. Character of growth upon agar-agar. 7. Presence of the cholera-red reaction.

It may be asked whether this collection of data was sufficient to justify a positive diagnosis. Certainly it would have been better to wait another twenty-four or thirty-six hours in order to report upon the nature of the growth of individual colonies on gelatin plates and the nature of the stab cultures on gelatin. It so happens that had the diagnosis been delayed until these had been waited for, this definite diagnosis could not, at that period, have been ventured upon.

As we shall proceed to point out, the gelatin liquefying power of the vibrio was singularly weak, and was only developed to a characteristic

extent by a repeated subculture. Nevertheless, our subsequent studies show that the diagnosis was correct. Here we would note that gelatin plates made from the surface of the eight-hour Dunham tubes gave in thirty-six hours an abundance of finely granular colonies, together with fewer colonies of a similar appearance to the naked eye, but, seen under the lower power, of a more coarsely granular type. Both forms presented the concentric layers noted by other observers and ascribed to commencing peripheral liquefaction: only a few showed at most depression of the surface colonies but without progressive development of a zone of liquefaction. There were no lobate surface colonies, no whetstone deeper colonies. The more coarsely granular, rounded colonies showed this concentric appearance, though not more markedly than did the others. This same want of liquefaction was true with gelatin stab cultures. Variation in liquefying power of different strains of the sp. cholera has been noted by many observers,* as again variation in the appearance of isolated colonies, but we were not prepared to find such deficiency in early growths.

As above indicated, with repeated transfer from colonies of the more coarsely granular type showing the most marked concentric arrangement, we have eventually exalted the liquefying power and have obtained cultures which now, in every respect, conform to typical cholera spirilla.

A litre bottle of drinking water from the water tanks of the *Royal George* gave negative results.

In the meantime, Dr. Vallée was engaged independently at Quebec making periodical examination of the stools of the suspect, which were sent to him regularly from Grosse Isle. Almost from the moment of his return, the patient appeared to be wholly recovered and in excellent health, with well formed stools. But from these stools, by the employment of Dunham's medium, the same motile, slightly curved form continued to be isolated, agreeing in general characters with those originally isolated by Dr. Adami, and, as with Dr. Adami's forms, showing little liquefying power.

Here it deserves note that on the fourth day after the isolation of the patient, his effects were forwarded to Montreal for examination. Those effects were curiously meagre. They were contained in a small, reed hand-basket and consisted of: three small, plain, cotton handkerchiefs; two larger coloured; one small rag; one briar pipe; one bottle of eye medicine with dropper and Russian label, and one small, paper-covered book of evangelical hymns (German). These, according

*See Zlatogoroff's observations given latter.

to an attached label signed by Dr. Pagé, were all the effects with which the suspect landed at Quebec.

One large and one small handkerchief were crumpled and presented clear evidence of use; the others were relatively clean. Three of them were placed separately in sterile flasks, covered each by 150 c.cm. of Dunham's solution, and incubated for eight hours. Two of the flasks remained absolutely clear, with no surface film, and on microscopic examination the films made from the broth were wholly negative, devoid of any growth. The other, which contained the larger, soiled handkerchief, was recognizably more turbid at the end of the eight hours, and drops taken from the surface layer exhibited what, by simple staining, appeared to be a pure culture of an organism identical with that obtained from the stools in the first instance. Nevertheless, gelatin plates from this yielded four varieties of colonies. Two of them gave definitely stumpy bacilli, a third, of more granular type, afforded short, relatively thin bacillary forms, with two, not one, polar flagella. This form died out and could not be further studied. The dominant organisms had characters not distinguishable from those first described as being obtainable from the stools.

In order further to test the nature of these organisms, it became necessary to undertake agglutination tests, and independently Dr. Vallée obtained from Washington, and Dr. Adami, first through the courtesy of Dr. Park, and later direct from the New York Pasteur Institute, received some desiccated, agglutinating serum prepared by the Swiss Serum and Vaccine Institute of Berne, under the direction of the well-known bacteriologists, Professors Kolle and Tavel, and with this both obtained positive results. Here a few words may be said regarding the serum in question. It is prepared by immunizing horses with cholera spirilla until their serum develops such powerful agglutinating properties that it causes clumping even when diluted ten thousand times. It is sent out desiccated in sealed glass tubes, and is an exquisite product. Its only disadvantage is that it loses its power slowly, in the course of a few months becoming relatively insoluble. Thus, for example, the tube which Dr. Park courteously sent to Dr. Adami had been opened previously and was found to give no results with high dilutions, using a known cholera culture as a control, and employing the test tube or macroscopic method. Employing the microscopic method, with less extreme dilutions, similar clumping results were obtained with various cultures from our case and with known cholera spirilla, a strain obtained by Dr. Park from one of the New York cases, and another which Messrs. Parke, Davis and Co. were so good as to send us, coming originally from Krahl's collection.

MACROSCOPIC TEST

Agar growths twenty-two hours old from nine different cultures isolated from the original stools and from the handkerchief above mentioned were now taken along with similar agar growths of the Park, and Parke, Davis strains, and were compared by the macroscopic agglutinating test, dilutions being employed of 250, 500, 1,000, 2,000, 4,000, and 8,000. The cultures, it may be added, were chosen for their dissimilarity in growth on other media, some obviously were not cholera spirilla, others were doubtful, but all, save the stock cultures, had been originally obtained from eight-hour Dunham flasks.

The results were as follows: (See page opposite).

The results are, in the light of later results, not a little interesting. The cultures D8 and D9 were those of the cholera spirillum obtained from Dr. Park and Messrs. Parke, Davis respectively. They gave typical agglutinations, becoming incomplete (in twelve hours) at a dilution of one in eight thousand, although complete in twenty-four hours. D7, obtained from a gelatin tube derived from the stools, which, at the end of a week's growth, showed slight evidences of liquefaction, and which on plates showed spherical, concentric, more coarsely granular colonies, behaved identically. This form now, after repeated subculture, gives typical liquefaction, shows a single polar flagellum, and comports itself generally as a true cholera vibrio. In character it appears more nearly allied to the Parke, Davis than to the Park strain, although showing a faint, but perceptible, difference in the action upon litmus milk after twenty-four hours. While neither turned the milk acid, the colouration of the milk with D7 was fainter than with D8. The relatively high dilution with which D2, D3, D4, D12, and D13 gave precipitation by the macroscopic test has caused us considerable debate as to their nature. Further cultures have shown that while all these forms are actively motile they are not cholera spirilla. They are one and all gas producers and provided with peritrichous flagella. In the early growths, certain individuals were recognized having a faint curvature, although the majority were straight. This is an example of the difficulty in making a perfectly unbiased decision. Undoubtedly certain of the organisms had a faint curve. Indeed, control studies on known bacillary forms show a certain proportion with similar slight curvature. Here the problem was complicated by earlier experience that known strains of the cholera spirilla are, at times, singularly devoid of curve. It must now, we think, be taken as a safe guide and principle in connexion with agglutination work that a given serum will agglutinate different strains of the same species to the same extent, and, if it fails to do this, suspicion must at once

be aroused. Thus, further studies of these dubious forms have shown that, although they are those commonest in plates, they are motile bacilli and not spirilla. In other words, the method of concentration by means of Dunham's solution, while it had preserved the cholera

	$\frac{1}{250}$	$\frac{1}{500}$	$\frac{1}{1000}$	$\frac{1}{2000}$	$\frac{1}{4000}$	$\frac{1}{8000}$
D ₂ ¹	<u>+</u>	<u>+</u>	++	+	+	<u>+</u>
D ₃	++	++	++	+	-	-
D ₄ ²	+	+	+	+	○	○
D ₅ ²	-	-	-	-	○	○
D ₇	++	++	++	++	++	+
D ₈	++	++	++	++	++	+
D ₉	++	++	++	++	++	+
D ₁₀ ²	-	-	-	-	○	○
D ₁₂ ²	++	++	+	<u>+</u>	○	○
D ₁₃ ²	+	+	+	○	○	○
D ₁₄ .	-	-	<u>+</u>	-	-	-

Note I: These numbers, it may be noted, were given to the series by the laboratory assistant, in order that a knowledge of the origin of the growths might not be known to Dr. Adami. It is a coincidence, probably due to close similarity in the agar growths, from which the dilutions were made, that has brought together the stock cultures and the typical *Sp. cholerae Asiaticae* from the stools.

Note II: From their dissimilarity to typical cholera cultures, these were selected originally largely as controls, and, as the amount of diluted serum was growing low, they were purposely not employed for the higher dilutions.

spirillum, had also led to a more active proliferation of other forms of organisms that are not specific.

An interesting phenomenon was observed in connexion with one of these forms; namely, D2, and to a slighter extent, D14, a phenomenon usually ascribed to the existence of pro-agglutinoids; namely, whereas there was no agglutination in the dilutions of two hundred and fifty and five hundred, higher dilutions afforded definite precipitation.

Independently Dr. Vallée, studying samples of the stools sent periodically from Grosse Isle, obtained parallel results. The eight-hour cultures on Dunham's broth afforded vibrio forms, but the plates made from Dunham's broth in the main yielded gas-producing organisms of the colon type. We can only conclude that, with an attenuated organism, the vibrios, while multiplying with fair rapidity on Dunham's medium, have, to a large extent, grown faintly at first upon transplantation to other media. Similarly, up to the end of April, eight successive examinations afforded smears giving vibrio forms. The ninth failed to show vibrios in smears made directly from the diluted stools, although cultures on Dunham's medium, like all the previous cultures, afforded forms which by the microscopic method of examination showed agglutination with dilutions of from two to three thousand. The tenth and the eleventh examinations, made in May, gave negative results with Dieudonné's medium (see later), although, even in this last examination, growth was obtainable on the surface of Dunham's medium. Dr. Vallée confirms Dr. Adami in obtaining, as a result of Dunham's concentration method, a dominant growth in subsequent cultures of bacillary forms, motile, Gram-negative, and which do not liquefy gelatin.

Why these forms agglutinate in so high a dilution is an interesting problem. A few years ago Drs. Adami and Chopin isolated from a suspected water an organism of the colon type, which was further studied by Dr. Klotz, and which agglutinated with similar high dilutions of typhoid serum. They suggested then that the existence of this aberrant reaction might be regarded as possibly indicating that the organisms had been derived from human discharges, that, in short, this phenomenon of agglutination with human blood serum to this very high degree indicated at least that the microbes had been accustomed to grow within the human organism. Possibly a similar suggestion can be made in this case. Indeed, we may even go a step further, and suggest that the high agglutinating capacity of these cultures has some relationship to their symbiotic growth in the human body along with the true cholera spirillum; that with this growth they have become, as it were, sensitized.

These facts are deserving of note as indicating that the agglutinating test can only be regarded as final when the form under observation agglutinates to the same limit of dilution as does a known strain. We have thus sought for some surer method of isolating the spirillum, and believe that we have found it in the employment of Dieudonné's medium.* As pointed out by Arens, the cholera vibrio grows best in a strongly alkaline medium. Dieudonné takes equal parts of defibrinated ox-blood and normal KOH solution. The results are a dark, laked, alkaline blood solution which can be sterilized in the steam sterilizer. Thirty parts of this solution are now added to seventy parts of ordinary peptone agar, the latter made neutral to litmus. The mixture is poured on to agar plates, which, in order to solidify, are dried gradually in the incubator at 37°C. or more rapidly by exposure to a temperature of 60°C. The plates are made twenty-four hours before intended use, and the material to be examined is then spread on the surface. On this medium we find that the type *B. coli* has either a feeble growth or none at all, whereas cholera vibrios proliferate abundantly, forming good colonies in the course of twenty-four hours, and showing a tendency to surface spread in consequence of the semi-solid nature of the medium.

The forms D2, D3, and D4 were derived from the gelatin plates from the original stools, and from the more finely granular colonies. D12 was from a similar colony from the handkerchief. All these it may be recalled had passed through the Dunham tube, gave thinner growths upon agar than are characteristic of *B. coli*, agglutinated with relatively high dilutions of a cholera serum, and now, what is striking, they also grow upon Dieudonné's medium in twelve to eighteen hours in a manner which is indistinguishable to the naked eye from the cholera spirillum. We present these plates before the Association† just as, we may add, our agglutination results were presented before a meeting of the Lister Laboratory Club at McGill in the early spring.

Happily, smears from these plates are quite characteristic; the strongly alkaline character of the medium serves to accentuate the morphological difference between the true vibrios and these doubtful forms. We cannot, however, but call attention to the existence, in this case, of bacilli which, by all the methods highly recommended for the rapid isolation of the cholera vibrio, possess characters closely resembling those of the true organism. It might easily happen that,

**Centralblatt f. Bakt. Abt. I.* Orig. 50, page 107, 1909.

†NOTE: These were demonstrated before the Laboratory Workers' Section of the Association along with a comparative series of preparations of the form isolated from our case of the old laboratory stock culture and the Park and Parke, Davis strains.

depending on these methods in circumstances similar to those of our own case, where a diagnosis is urgent within thirty-six hours, the observer would be led astray. As in our case, morphological characters become the safeguard,—the presence in the stools of definite spirilla, particularly of those with a double curve, the obtaining from early cultures of forms with unmistakable single polar flagella.

The fact that in the last two examinations of Dieudonné's method Dr. Vallée obtained wholly negative results, demonstrates that at last the patient's stools are free, both from the cholera and from these associated germs.

THE PUBLIC HEALTH ASPECTS OF THE CASE

We have, thus far, dwelt upon the bacteriological aspects of the problem, which, in our opinion, present several features of interest. From the point of public health, what is of the greatest significance is the fact that here we deal with a cholera carrier, similar to the now well-known typhoid carriers. These cases, we may point out, are not unknown. The earliest recognition of this existence, if we mistake not, occurred during the great Hamburg epidemic of 1892, when Dunbar, in an examination of several hundred stools of healthy individuals, gained cultures of the characteristic vibrio from six cases. As noted by Professor Connell* in the suspects quarantined in New York in September and October 1910, two were cholera carriers: it is the culture from one of these, isolated by Dr. Park that we have used as control. The careful routine examination of returning Mecca pilgrims at El Tor in Egypt has afforded half a dozen or more cases of cholera carriers. One convalescent afforded the spirilla fifty days after his illness.† Other cases are recorded in the French literature.

The fullest study of these cholera carriers known to us has been by Russian observers. This is summed up in a recent paper by Zlatogoroff‡ who himself, during the epidemic of 1908 and 1909, made periodic examinations of three hundred and twenty-four cholera patients to determine how long the vibrios persisted in the stools. Sixty-nine of these patients died within ten days. Out of the remaining two hundred and fifty-five, no less than fifty-one per cent. gave vibrios on the fourteenth day, five of them as long as the twenty-second day, seven until the twenty-seventh day, two until the thirtieth day, two until the thirty-third, and six for longer

*This JOURNAL April, 1911, p. 333.

†See Ruffer, *Brit. Med. Jl.* 1907: i: 735 and Gottschlich, *Lancet*, 1905: ii: 549

‡*Centralblatt f. Bakt. Abt. I. Orig.* 58, 1911, 14.

periods, fifty-six being the longest. He quotes Kulescha and two other Russian observers as having demonstrated that, like the typhoid bacilli, the cholera vibrios remain for a long time in the gall-bladder and bile ducts, and confirms the observation by feeding newly born rabbits with virulent cholera cultures. In two cases he obtained the vibrios from the bile at the end of fourteen and twenty-one days, respectively. Though in his longest case the vibrios isolated in the stools on the fifty-sixth day after recovery were morphologically unaltered, in another case vibrios obtained on the thirty-second day exhibited very weak curvature and feeble staining. Often, also, he noted that the growths from these carriers were very weak and soon died out, and though, in general, growths obtained at the beginning of the disease were quite typical in gelatin, those recovered after twenty-one days not infrequently *either liquefied gelatin weakly or not at all*. The indol reaction also became weakened. This is interesting in comparison with our case; on the other hand, most often the vibrios retained their original agglutination power, although in fifteen per cent. there is a definite diminution.

It is thus evident that the existence of cholera carriers is well established. Indeed, we are strongly inclined to attribute to these, rather than to those actually suffering from the disease, the gradual spread of cholera along trade routes. If Zlatogoroff's figures are to be accepted, the indications are that less danger is to be expected from them than from typhoid carriers. As we know, the latter may continue to yield typhoid bacilli over a space of many years. On the other hand, the tendency is that the cholera vibrios in general disappear within two months. Conditions are not always so favourable, however, as indicated by this case, in which a man who gave no history of the disease afforded vibrios twenty-six days after leaving an infected country and continued to pass these spirilla for five months longer. Another important observation of Zlatogoroff's is that while in one case he found no diminution in the virulence of the vibrios isolated from the stools on the fifty-first day, in three others, on the seventeenth, twenty-second, and twenty-fourth days, respectively, the virulence was found reduced from two to three times. The tendency would thus seem to be for the spirilla in these carrier cases to be distinctly weakened, and the variations in their morphological and culture characters confirm this view. We cannot but believe that during the course of the last few years cholera carriers must have repeatedly landed on this continent, but whether through this weakening of the microbes, or through the better hygienic conditions now prevailing in civilized countries, no ill results have ensued. Some day it may happen that an individual

bearing highly virulent vibrios may effect a landing, and then, if, by chance, he passes to some place where his fæcal matter can contaminate a water supply, we may find the development of an apparently spontaneous epidemic of cholera. No quarantine regulations, it seems to us, can be devised against such a possibility. Fortunately, the chances of such an event appear to be singularly slight.

“OUR notions as to the place of uric acid in metabolism have undergone profound change in recent years. It is recognized that this substance can no longer be looked upon as an intermediate product in the formation of urea, but that it is a special product of the breaking down of one particular class of protein substances, the nucleo-proteins. A second mode of origin, by synthesis, is perhaps operative, to some extent, in the human body, and must play an important part in birds and reptiles, the bulk of whose nitrogenous excretion is in this form. Obviously this change of view cannot fail to modify profoundly our ideas as to the optimum diet of gouty patients. Our aim will be to avoid adding to the excess of uric acid in the blood, by limiting the intake of its parent substances, the purin bodies and nucleo-proteins. To this end it no longer appears necessary to restrict protein foods generally, unless the kidneys be actually diseased, but rather to restrict such foods as are rich in the constituents referred to; namely, the extractives of meat, the glandular organs, such as sweetbreads and kidneys, and the varieties of meat which are specially fibrous, and therefore rich in nucleo-proteins. Other restrictions which are imposed, and with good cause, are made upon empirical grounds, and mainly on the testimony of those best qualified to judge of their desirability; namely, gouty sufferers themselves.”—*The British Medical Journal*.