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The Incidence of "Jake" Paralysis in Oklahoma*

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ON February 28, Dr. Earl T. McBride of the McBride Reconstruction Hospital, Oklahoma City, called to ask if we would check his laboratory in the examination of the spinal fluid from two patients who had come to his hospital showing a peculiar paralysis. He stated that there was some resemblance to both anterior poliomyelitis and Landry's disease, but that there were additional features in both cases, characteristic of neither. In both the spinal fluids were negative.

About the same time Dr. W. H. Miles, Oklahoma City Health Officer, and Dr. E. Goldfain, an associate of Dr. McBride, investigated some 60 cases which came to the attention of the City Health Department. It was found that in every instance the condition affected those living in or frequenting the same section of town; that this section was the location of certain drug stores which were suspected of violating the prohibition laws; and it was significant that a number of their employees, and one or two proprietors were afflicted. Careful investigation revealed that the only etiological factor common to all of these cases was a history of habitual indulgence in "Jake."

To Drs. Miles and Goldfain credit should be given for the first indictment against fluid extract of ginger as the causative agent. A number of the druggists selling this product had been visited by federal agents and samples of the fluid extract picked up for analysis. Ordi-

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nary methods showed them to be standard in every respect, but more careful analysis revealed them to be low in ginger extractives. After the appearance of these cases samples were again obtained and analyzed for heavy metals. It was at first announced that the paralysis was due to lead poisoning. The mistake made was in the finding of a so-called "passive" sulphate of iron which precipitated out after sulphuric acid digestion and returned to solution quite slowly.

The authors felt quite certain that the clinical symptoms were not due to lead, and I believe the case histories given here will bear us out. Preliminary chemical work was started, details of which will be given later.

In the meantime numerous facts of interest began to come to light. Cases were reported from other sections of the state. On April 1 cards were sent to about 2,500 physicians in the 77 counties of the state. On April 23 approximately 40 per cent of these had been returned and showed 536 cases in 39 counties. Because of the tendency to be ashamed of the affliction it is safe to assume that this number represents only about one-third of the cases and that there are therefore between 1,500 and 2,000 in the state. Reports and inquiries began to come in from all sections of the country, notably, Alabama, Mississippi, Georgia, Kentucky, Tennessee, South Carolina, North Carolina, Louisiana and Ohio. Different theories were developed as to the cause, all of which broke down under investigation.

Three instances suffice to show how each additional report strengthened our belief in the fundamental truth of our own theory. From Tulane came the report that a physician who was treating several such cases had become paralyzed himself. He denied ever having used "Jake" and the inference was naturally drawn that we were dealing with some type of low grade infection. The cat escaped from the bag when the patients stated that the doctor had purchased his ginger from the same source as themselves. Again—

> The connection of fluid extract of ginger with these cases is being generally definitely established, though there have been some instances where the use of ginger extract has been denied. One such case was the superintendent of a mill in Georgia who was affected with the paralysis, which the doctor diagnosed as the result of ginger drinking, though the patient denied it. The doctor, however, confirmed his diagnosis by means of a ruse, telling the patient's wife that he was writing out a prescription which might be of benefit, but if he had been drinking ginger extract not to give it to him as it might produce fatal results. The patient then announced he would not use the prescription.[1]

Finally, there is the instance of the girl whose mother gave her half

an ounce of fluid extract of ginger to relieve the pains of dysmenorrhea and who later developed the paralysis.

After becoming convinced of the fact that ginger extract was the causative agent we began to cast about for the ingredients at fault. Numerous statements appeared, all of which were considered carefully before being discarded. Among them were the following: that lead or some other of the heavy metals were to blame; that the paralysis was due to water passing through deposits of bauxite; to a fungus growth on the ginger; to another root closely resembling ginger but containing a toxic alkaloid; to use of ginger which had been redistilled, thus rendering the product toxic.

The application of cold reasoning ruled out most of the above, and chemical analysis eliminated the rest. The reasoning followed was based on the fact that the condition made its appearance nearly simultaneously in widely separated parts of the country, that cases originated only during a very brief period of time (no new cases are being reported); that in all the centuries during which ginger in various forms had been used as a condiment, seasoning, flavoring material, confection, or drug, no record of a similar outbreak could be found.

All of the above points led to the assumption that some new adulterant was being used in the preparation. That there was reason for suspecting this is supported by the fact that standard preparations of ginger contain such a quantity of ginger extractives that extreme dilutions are necessary before the fluid becomes potable, and such dilutions reduce the alcoholic content until the desired "kick" cannot be obtained. The first adulterant suspected was iso-propyl alcohol. This was found in varying quantities in several samples, but the findings of others[2] convinced us that this was in no way concerned unless there was a chemical combination with some of the ginger extractives. Animals were therefore fed fluid extracts made of African and Jamaica ginger, using as a menstruum ethyl alcohol denatured with 1 per cent iso-propyl. Dogs fed 1 oz. of the above preparations showed no symptoms after from 6 to 10 weeks.

During the course of these experiments, the first autopsies on cases of ginger paralysis were held.

Case I. Male, white, age 68, laborer. Had been heavy consumer of alcohol all his life. No history of venereal disease. No Wassermann. Developed a well marked case of "Jake" paralysis, following debauch. Came into hospital with cough and lung symptoms premonitory of pneumonia, and general malaise. Râles in bases of both lungs. Blood pressure not obtainable because of arteriosclerosis. On the third day he developed stertorous breathing and other symptoms of brain pathology. He died about 48 hours later.

Autopsy showed generalized arteriosclerosis. Some pulmonitis but no definite

pneumonia. Liver somewhat retracted, slightly nodular, darkly mottled. Kidneys not remarkable. Brain described as water-logged. Spinal cord and sciatic nerve, no gross pathology. Cause of death, cerebral edema.

Microscopic sections of the organs showed nothing remarkable. First examination of the material from the nervous system was made by Dr. H. G. Jeter, who reported cellular exudate in some of the fibers of the cauda equina as the only lesion found, and on this basis made a diagnosis of perineuritis. Sections were run by the routine histological methods.

In this laboratory the material was run through special neurological methods using sudan IV-hematoxylin, toluidin blue, and osmic acid stains.

Sudan IV-Hematoxylin. Lower lumbar cord. (1) Brownish red granules packed in marginal area in all nerve cells of the anterior horns. Similar brownish granules in some cells of dorsal horns. (2) Karyolysis, either breaking up of nucleolus—condensation of karyosomes, or complete lysis of karyotin material with disappearance of nucleolus. (3) Migration of the nucleus in many cells. Edema and lymphocytic exudate around the neural canal, desquamation of neural canal epithelium.

Toluidin blue stain shows presence of tigroid bodies—but with frayed margins —in all cells containing a nucleus in good condition, except in regions of the cell occupied by granular material described above. This type of pathological condition of nerve cells was also found in the upper thoracic, lower cervical cord, medulla including the inferior olive, nuclei of the floor of the fourth ventricle at this level, and the dentate nucleus.

Osmic acid-Mueller stain of material from the same regions revealed black granules in all places where Sudan IV had shown brownish red granules.

Marchi stain of the sciatic nerve showed (a) in cross sections some fibers in every fascicle which stained black; (b) in longitudinal section, some fibers were all black, others showed black masses at the nodes of Ranvier, or scattered along in the internodal spaces.

The exudation around the neural canal was found at all levels of the cord examined, but not in the region of the fourth ventricle.

Case II. Male, white, age about 70. Always used alcohol. No history of venereal disease. No Wassermann. "Jake" paralysis, or locomotor ataxia. Came into hospital in semi-comatose condition. Died after short stay. Diagnosed possible uremia.

Autopsy revealed aneurism of ascending aorta, atheromatous aorta, and arteriosclerosis. Other organs not remarkable. Complete central nervous system removed together with sciatic, anterior tibial, part of brachial plexus, and radial nerves. No gross pathology evident except probable swelling of anterior tibial nerve. The special staining methods used in Case I showed identical pathology of nerve cells and fibers with that case.

It occurred to us that if the pathology is due to "Jake," and it has, as in Case I, reached the vital centers, the symptoms and death could be due to the changes described above. The symptoms would be those involving the failure of the vital centers, and death from "Jake" is possible.

Since the microscopic findings in the above cases seemed to us to

be unique, and—with only 2 cases autopsied—characteristic, we set about to determine, if possible, the causative agent. On April 25 one of the authors (D. T. B.) visited L. T. Hoyt, Chemist in Charge Federal Prohibition Laboratory at New Orleans, La., where he learned that some samples seized had shown the presence of a phenol compound which had not been positively identified but was thought to be tricresyl-phosphate. Analysis up to this time, by the methods of Fuller and Authenreith & Warren, had failed to disclose anything unusual. This may have been due to the fact that the samples analyzed by us had actually not contained the adulterant. Taking advantage of the findings of Mr. Hoyt, an attempt was made to isolate and identify the phenolic substance suspected. No tests could be found in the literature available, and after some experimentation the following procedure, modified from Fuller, was adopted:

Sixty c.c. of the fluid extract of ginger was placed in a small distilling flask, connected with a condenser and placed in a water bath. The alcohol was distilled and collected for examination. The residue was diluted with water, transferred to a separatory funnel and extracted with ether. The ether solution was then extracted with a 5 per cent alkali solution, washed with distilled water, extracted with dilute sulphuric acid, again thoroughly washed with distilled water, filtered, and the ether evaporated on the water bath.

After the beaker and contents had cooled, the residue from the ether solution was thoroughly extracted with petroleum ether. Upon evaporation of the petroleum ether, a rather viscid, slightly yellow residue was obtained. The distillate from this residue when warmed with alkali and distilled after acidification with sulphuric acid gave strong positive tests with Millon's reagent, bromine water, and the formaldehyde and sulphuric acid reagent. The precipitate was amorphous with the bromine water and did not give the pink color that is obtained with phenol. In other words, the indications are that it was a cresol rather than a phenol.

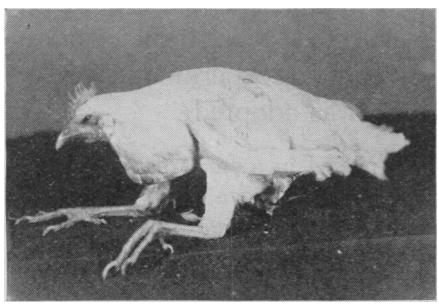
The residue in the flask still contained a large amount of undissolved material which was washed with concentrated sulphuric and nitric acids until a colorless solution was obtained and tested for phosphate with ammonium molybdate. A very positive test was obtained. From the manner of the extraction and the tests, it was assumed that the substance was tricresyl-phosphate. Quantitative analysis showed the substance to be present in a strength of about 3 per cent.

Having convinced ourselves of the identity of the adulterant chemically, experiments were made to substantiate our belief by pharmacological and pathological methods. Ten chickens and four dogs have been used.

Technical tricresyl-phosphate was secured and administered to young, full grown chickens and dogs. The dosage for chickens was 5 c.c. administered orally with a catheter. In about a week there were symptoms of unsteadiness in the use of the legs of the chickens, which became more pronounced in 24 hours; at this time another dose

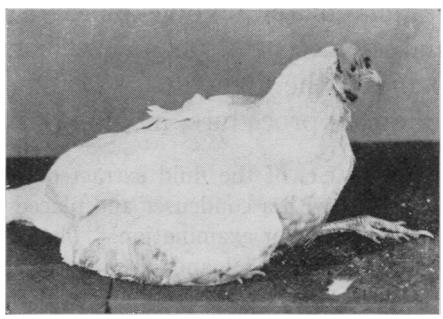
was given. The 9th day from the initial dose, foot drop and difficulty in using legs were very marked in all chickens; 2 days later cyanosis of the comb and respiratory embarrassment were present, and about the 11th day, the chickens died. Since the behavior of the chickens and the symptoms which developed were identical with those which had received dosages of Jamaica ginger that had produced paralysis in human beings (see Figures I and II), we felt assured that the deleterious substance that had caused the epidemic of paralysis in humans was tricresyl-phosphate.

FIGURE I



Chicken 1. 5 c.c. Tricresyl-phosphate, 6/5/30—Repeated 6/13/30, Photographed 6/16/30—Died 6/16/30, P.M.

FIGURE II



Chicken 2. 15 c.c. Deco Ginger, 6/5/30; 10 c.c. Deco Ginger, 6/13/30, Photographed 6/16/30, Killed for Pathological Study 6/21/30.

Misfortune overtook the dogs before we had finished our studies. One was taken by some students by mistake and used in an experiment in another department. A second, which at the end of the 8th week had developed marked loss of use of hind legs and feet, also respiratory embarrassment including almost complete loss of voice, was likewise destroyed prematurely. The third escaped just after it had begun to show symptoms; and the fourth, though showing early signs of poisoning, has not advanced sufficiently at this time to warrant pathological examination. However, our experiments showed that while paralysis of dogs by the use of Jamaica ginger containing small percentages of tricresyl-phosphate was attained with great difficulty; nevertheless, they could be paralyzed by the drug alone, although the onset is slow. The dosage was 10 c.c., administered by mouth at 3-day intervals. Two doses were given to each animal.

Further to prove the question in point, it seemed advisable to try the effect of Jamaica ginger containing tricresyl-phosphate. For this purpose a sample of Jamaica ginger was secured which contained no cresyl or phosphate and was known to be of U. S. P. Standard. Four groups of two each of chickens were used. To one Jamaica ginger not containing tricresyl-phosphate was given; to the other three Jamaica

ginger containing various percentages of tricresyl-phosphate. The results are shown in Table I.

DISCUSSION OF TABLE

The results of these experiments are interesting for a number of reasons. The experiments showed: (1) Jamaica ginger not containing tricresyl-phosphate produced no paralysis or paralytic symptoms, and aside from the initial intoxication following the administration had no effect on the well-being of chickens; (2) Jamaica ginger containing as little as 1.5 per cent of tricresyl-phosphate would cause paralysis and even death of chickens; (3) in proportions greater than 3 per cent, death would occur in a few days—in our experiments, 14 days.

Another interesting point was the difference in the resistance of the different chickens to the ultimate effect so far as time was concerned. It will be noticed that chicken No. 6 received 1.5 per cent of tricresyl-phosphate and died in about 19 days, while chicken No. 8, which was

TABLE I

Chicken No.	6/2/30	6/24/30	6/30/30	7/3/30	7/9/30	7/10/30	7/12/30	7/14/30	Ultimate Fate
3	Gin. 1	Gin. 1	Well	Well	Well	Well	Well	Well	Dead 7/20*
4	Gin. 1	Gin. 1	Well	Well	Well	Well	Well	Well	Killed 8/15†
5	Gin. 2	Gin. 2	Leg weakness	Leg & foot weakness marked	Paralysis severe	Feet weakness	Feet useless, swelling of eyes	Condition same, respiratory trouble	Killed 8/15†
6	Gin. 2	Gin. 2	Leg weakness	Leg & foot weakness marked	Paralysis, respiratory trouble	Dead			
7	Gin. 3	Gin. 3	Leg weakness	Leg & foot weakness marked	Paralysis, respiratory trouble	Condition worse	Dead		
8	Gin. 3	Gin. 3	Leg weakness	Leg & foot weakness marked	Paralysis, respiratory trouble	Feet useless, respiratory trouble same	Condition same	Condition same	Dead 8/14
	6/21/30	6/24/30	6/27/30	6/30/30	7/5/30				
9	Gin. 4	Gin. 4	Leg weakness	Paralysis marked	Dead				
10	Gin. 4	Gin. 4	Leg weakness	Paralysis marked	Dead				

Different samples of ginger are marked: 1, no tricresyl-phosphate; 2, 1.5 per cent of tricresyl-phosphate; 3, about 3 per cent; and 4, about 4 per cent tricresyl-phosphate. The doses were 5 c.c. of each mixture with 15 c.c. of water administered by mouth.

* The cause of death of chicken No. 3 on July 20 was not determined. It was apparently all right at 5 P.M., July 19. It had not at any time shown any effect of the ginger, and at autopsy none of the pathology found in those showing the effects of ginger.

† Chickens Nos. 4 and 5—One well and one paralyzed. Since they had shown no change for over 3 weeks, it was decided that it was more valuable to make microscopic examinations of them than to keep them living for a longer period.

given 3 per cent, lived 53 days. The time of the appearance of initial symptoms was practically the same for all concentrations used, in this series being about 9 days. Another similarity was that, regardless of the duration of life following the onset of symptoms, all of the chickens developed respiratory difficulties; all died in coma; and all developed edema of the orbital region with watering of the eyes. The paralysis in all cases was very similar to that found in humans in "Jake" paralysis—toe drop, inability to use the feet, and while the legs could be moved they could not be used for ambulation. So far as we were able to discern the chickens' wings were not affected.

We were somewhat disappointed in the microscopic examination of the central nervous system, in that we did not find the fatty degeneration which was present in the human cases. We did, however, find karyolysis, karyorhexis, and degeneration of the nerve cells as shown by the difficulty or inability to stain them by any method. We may say that the typical pathological lesions so far as the central nervous system is concerned in cases of intoxication resulting from tricresyl-phosphate are karyolysis, karyorhexis, and degeneration of the cell bodies, the exact type depending on the animal affected.

A very interesting series of experiments on rabbits, dogs and calves, by Smith,[3] arriving at similar conclusions, differs from our work in that we were able to produce symptoms in dogs and were able to compare human and animal pathology.

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