Public Health Reports

Vol. 61 • JANUARY 4, 1946 • *No. 1*

Printed With the Approval of the Bureau of the Budget as Required by Rule 42 of the Joint Committee on Printing

A CYCLE OF MORPHINE ADDICTION

BIOLOGICAL AND PSYCHOLOGICAL STUDIES [1]

Part I: Biological Investigations [2]

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INTRODUCTION

The extensive literature dealing with the subject of morphine addiction is not a satisfactory index of the amount of available knowledge concerning the biological or psychological aspects of this problem. The bulk of the experimentation has been concerned with research on animals. A few investigators have reported on physiological changes produced by withdrawal of morphine in the addicted human (*1, 2, 3*), but there are no reports available in which a complete cycle of addiction has been studied, i. e., before, during, and after addiction. Data concerned with psychological aspects of addiction are particularly meager.

The problem of drug addiction is manifold. Some of the more important aspects involve psychiatry, sociology, penology, pharmacology, physiology, biochemistry, neurology, and psychology. These are all closely interrelated and interdependent. In adopting a pro-

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[2] Part II: Psychological Investigations, by Ralph R. Brown, Psychologist, will be published in the next issue of PUBLIC HEALTH REPORTS.

gram involving studies only in biochemistry, physiology, and psychology, we were not unmindful of the importance of the other phases.

The purpose of this study was: (1) To shed more light on the nature of opiate addiction, (2) to discover whether the effects of morphine were qualitatively similar to those of addiction, and (3) to determine which, if any, of the phenomena studied were worthy of more intensive investigation.

METHOD OF STUDY

A relatively large number of tests involving the techniques of biochemistry, physiology, and psychology were made on two human subjects throughout a cycle of addiction. The study extended over a period of 2 years. After preliminary tests to establish norms for these patients, morphine was given first in single doses of 20 mg. Later several doses per day were given and the amount was increased. Morphine was then rapidly withdrawn and the patients studied during withdrawal and recovery.

SUBJECTS

This report is based upon data obtained on two patients who were former opiate drug addicts, serving sentences for violations of the Harrison Narcotic Act. They were chosen, from a number of such patients who volunteered for the study, on the following basis: (1) Their sentences were sufficiently long to permit a prolonged investigation and still leave adequate time for recovery, (2) they had long addiction histories, having been addicted and "cured" many times, (3) they showed promise of active and continued cooperation in a long, and at times, uncomfortable experiment. It was realized that the use of post-addicts might open the experiment to some criticism, but this was unavoidable, as it was not feasible to pursue such a study in the nonaddict at that time. Both patients were approximately 40 years of age, and without significant physical defects.

Patient G was "Boston-Irish," and came from a normal home environment. He quit school at the age of 14 and spent 2 years as a laborer in the painting and contracting business. The following 8 years were spent as a guard for an elevated railway company. He had worked as an attendant in a hospital for mental diseases, as a lifeguard, and more recently earned his living selling novelties on the streets of New York City. He never married but made a heterosexual adjustment of the promiscuous type.

He denied the excessive use of alcohol but first used narcotics in 1928 as a means of sobering up after alcoholic "sprees." He had undergone at least one voluntary and a number of involuntary "treatments" but relapsed each time.

Our first impression was that G was a rather stolid, even-tempered individual. During the course of the study, however, we came to know him as a very sensitive, "high-strung" person who was inclined to be overly suspicious and quite jealous of his various prerogatives.

On the Stanford-Binet test (1916 Revision) he attained a mental age of 17 years, 4 months, and scored somewhat below the average adult level on performance tests and on tests in which speed was an important factor.

Patient M was born in New York City, of parents with rather remote Irish ancestry. His parents were separated when he was 13 years of age and his period of adolescence was spent in the "red light district" of Hoboken, N. J., where he earned his living by selling newspapers and serving as an errand boy for the prostitutes with whom he made his home.

He began the use of narcotics at the age of 13 with the smoking of opium, after which he changed to heroin. His life from then on was interspersed with numerous jail and prison sentences, each being followed by his immediate return to the use of narcotic drugs. During the World War (1914–18) he served in the Canadian Army and was promoted to the rank of drill sergeant.

As a prisoner, he had learned how to "do time." He knew and understood institutional customs and was constantly, and often successfully, endeavoring to obtain the greatest momentary advantage. If he was frustrated in an attempt to achieve his objective, he took it philosophically, feeling that he had gambled and lost and would profit by that particular experience in his next gamble. He appeared to have no feelings of remorse concerning his addiction and devoted much time to making plans for his future so that he could, with the least amount of risk, return to the use of narcotic drugs.

An outstanding characteristic of M was his tendency to act impulsively. Usually his judgment, though hasty, was sound except in matters of ethics. This open, extratensive, confident, and aggressive personality was in distinct contrast to the inhibited, inwardly tense, fearful, and suspicious personality of G.

A definite animosity developed between the patients during the study. G accepted the leadership of M and allowed him to make decisions for both. He did this grudgingly, however, and his recognition of his own deficiencies led to an increasing resentment of M. M, on the other hand, took delight in "running the show" and in making better records in performance tests than G.

On the 1916 Revision of the Stanford-Binet test, M scored a mental age of 15 years, 4 months. He did well on the Kohs Blocks (score of 83) and Sequin Form Board (10 seconds), but was somewhat below average in those tests in which language played an important role.

FINDINGS

The study indicates that morphine addiction is accompanied by increases in: Body water, erythrocyte sedimentation, carbohydrate intake, and nocturnal activity; and by decreases in body weight, blood concentration, pulse rate, basal metabolism, and diastolic blood pressure. In some instances, e. g., blood concentration, the effects of morphine are qualitatively dissimilar to those of addiction. A reduction in efficiency was associated with addiction. The disturbance value of psychological stimuli was reduced by morphine. Among the items which should be more intensively investigated are: Nocturnal activity, body water, acid-base balance, and psychophysiological reactions.

GENERAL PROCEDURE

Test schedule.—Biological and psychological tests were given to each patient on alternate weeks, one receiving biological and the other psychological tests in any given week.

Dosage schedule.—In order to establish norms and to observe their general behavior, the patients were studied for 2 months before morphine was administered. They were then given single doses of 20 mg. morphine sulfate once weekly for 2 months. During the following 6 weeks the number of doses was increased, first to two and then to three injections per week, after which the drug was administered in single daily doses for 5 weeks. All single doses (20 mg.) were given between the hours of 7 and 9 a. m. At the end of the daily single-dosage period, the drug was withheld for 3 days to determine if physical dependence had developed. It was then given four times per day (6 a. m., 11 a. m., 4 p. m., and 10 p. m.) in increasing amounts reaching 300 mg. per day by the seventeenth day. The multiple injection period (period IV) was divided into four parts (A, B, C, and D) to show progressive changes. The daily average dosage for both patients in part A was 240 mg. per day. G was studied for only 36 days during this period (part A). M was kept on morphine for 6 months, the dosage levels being increased arbitrarily at intervals of 2 to 5 weeks, the highest dose being 4,440 mg. per day for 3 days just before the drug was dicontinued (table 1).

Division of experiment into periods.—In order to simplify reference to the various periods, the following divisions were made:

Period I	Before morphine (post-addiction).
Period II	Single doses of morphine.
Period III	3-day withdrawal.
Period IV	Multiple doses of morphine per day (parts A, B, C, D).
Period V	Withdrawal.
Period VI	Recovery (parts A, B, C, D, E).
Period VII	Post-addiction.

TABLE 1.—*Dosage schedule*

Period		Dates		Number days in period		Dosage (mg. morphine sulfate)			
						Daily average		Range	
		Patient		Patient		Patient		Patient	
		G	M	G	M	G	M	G	M
I Before morphine	....	Sept. 27, 1938 to Nov. 20, 1938	Sept. 27, 1938 to Nov. 20, 1938	55	55	....	....	....	....
II Single doses	1 per week	Nov. 21, 1938 to Jan. 15, 1939	Nov. 21, 1938 to Jan. 15, 1939	56	56	20	20	....	....
	2 to 3 per week	Jan. 16, 1939 to Feb. 26, 1939	Jan. 16, 1939 to Feb. 26, 1939	42	42	20	20	....	....
	Daily	Feb. 27, 1939 to Apr. 2, 1939	Feb. 27, 1939 to Apr. 2, 1939	35	35	20	20	....	....
III 3-day withdrawal	....	Apr. 3, 1939 to Apr. 5, 1939	Apr. 3, 1939 to Apr. 5, 1939	3	3	40 on 5th	40 on 5th	....	....
IV Multiple doses	A	Apr. 5, 1939 to May 10, 1939	Apr. 5, 1939 to May 14, 1939	36	40	239	245	40–300	40–300
	B	....	May 15, 1939 to Aug. 6, 1939	....	84	....	342	....	300–400
	C	....	Aug. 7, 1939 to Sept. 24, 1939	....	49	....	495	....	400–500
	D	....	Sept. 25, 1939 to Oct. 16, 1939	....	22	....	1,983	....	640–4,440
V Withdrawal	....	May 11, 1939 to May 21, 1939	Oct. 17, 1939 to Oct. 29, 1939	11	13	[1] 75 and 25	[2] 150 and 75	....	....
VI Recovery	A	May 22, 1939 to June 4, 1939	Oct. 30, 1939 to Nov. 12, 1939	14	14	....	....	....	....
	B	June 5, 1939 to July 30, 1939	Nov. 13, 1939 to Jan. 7, 1940	56	56	....	....	....	....
	C	July 31, 1939 to Sept. 24, 1939	Jan. 8, 1940 to Mar. 3, 1940	56	56	....	....	....	....
	D	Sept. 25, 1939 to Nov. 19, 1939	Mar. 4, 1940 to Apr. 28, 1940	56	56	....	....	....	....
	E	Nov. 20, 1939 to Jan. 14, 1940	Apr. 29, 1940 to May 17, 1940	56	19	....	....	....	....
VII Post-addiction	....	Jan. 15, 1940 to May 21, 1940	....	128	....	....	....	....	....

[1] 75 mg. on May 12, and 25 mg. on May 13.
[2] 150 mg. on Oct. 18, and 75 mg. on Oct. 19.

The withdrawal period was arbitrarily chosen as the first 11 days of abstinence for G, and the first 13 days for M. Morphine given during this period was for treatment of the abstinence syndrome and should not be confused with that given at other times. From the end of period v to the ninth month following withdrawal is considered to be the recovery period. It was divided into five parts (A, B, C, D, E) to show progressive changes. The post-addiction period was arbitrarily chosen as beginning after 8 months of abstinence.

Observations made on patients.—Clinical observations, including rectal temperature, systolic and diastolic blood pressure, pulse, and respiration were made on each patient three times daily at 6 a. m., 2 p. m., and 10 p. m. The averages of these observations are reported in this study, except that during period I observations were taken only at 6 a. m., and therefore were not graphed. These observations were made with the patients recumbent after at least 10 minutes of rest in bed. Body weight (stripped) was taken each morning. Nocturnal activity was studied.

LABORATORY TESTS

ANALYSES FOR INTAKE AND OUTPUT

Collecting and Sampling

Foods.—Each serving during the "diet week" was accurately weighed in duplicate, one being given to the patient and the other composited by days and set aside for analysis. Any portion of food left on the plate was reweighed and a like amount removed from the portion set aside for analysis. Milk, cream, coffee, fruit juices, sugar, and butter were also weighed but not added to the composite set aside for analysis.

Urine.—Twenty-four samples were collected in bottles containing 1 cc. toluene. The volume and specific gravity of each sample were determined.

Feces.—Since it is somewhat difficult to obtain a uniform 24-hour specimen of feces, collections were made for 6-day periods, the patients being instructed always to attempt to move their bowels at the beginning and at the end of the collection period. When this was not possible, a plain enema was used. The exact amount of water was recorded and subtracted from the total amount of water found in the feces. The feces were kept in a refrigerator in a covered container with a small amount of thymol as a preservative. At the end of the collection period the weight was determined, the feces were thoroughly mixed, and samples removed for analysis.

Food Analysis

Water.—The water content of milk, cream, coffee, and fruit juices was calculated from the amount consumed and their respective water content as determined by periodic analyses. The solid food set aside for analysis was dried at 70° to 80° C. to constant weight. The water content of liquid and solid foods was added to the water drunk to give total water intake. After drying, the food was mixed, ground, and stored for further analysis.

Protein.—Nitrogen was determined in 5-gm. samples of the finely divided dried food by a macro-Kjeldahl method, and the protein content calculated. The amount of protein in liquid foods, such as fruit juices, milk, and cream, was determined by calculation, using tables which were prepared by analyzing representative samples about once a month. The sum of the results determined by calculation and by chemical analysis gave the total amount of protein in the food.

Fat.—The fat content of the ground dried food was determined on 5-gm. samples by the Soxhlet extraction method; other ether-soluble substances which may have been extracted with the fat were considered to be insignificant. The fat content of liquid foods was calculated from their known composition and total weight. The sum of the fat content of solid and liquid foods represents the total weight of fat in the diet.

Carbohydrates.—Food was analyzed for ash, protein, fat, and water. Fibrous or undigestible matter was determined in feces. The total weight of the dried food minus these substances was taken as the weight of carbohydrate in solid food (it was assumed that no carbohydrate was present in the feces). The carbohydrate of liquid foods was calculated from tables of standard analyses.

Moisture content of the ground, dried food used for analyses.—After the oven-dried food had been weighed, it was ground as finely as possible with a meat grinder and transferred to glass fruit jars. This procedure resulted in absorption of some moisture in addition to the small amount of residual water not removed by the drying procedure. The moisture content of the ground, dried food was determined by weighing approximately 2 gm. in small crucibles before and after heating in an oven at 105° C. for 24 hours.

Ash.—The food dried at 105° C. was heated at a temperature sufficient for complete ashing without volatilizing minerals. The amount of ash was determined gravimetrically.

Fibrous and other undigestible matter.—Fibrous and other undigestible materials were approximated by calculation. Feces, dried on a water bath, contain, in addition to the fibrous material, ash, residual water, small amounts of fats, other ether-soluble matter, and nitrogenous matter calculated as protein. The total weight of these items was subtracted from the total weight of dried feces to obtain the weight of fibrous and undigestible matter.

Caloric intake.—The total caloric intake was calculated from the total protein, carbohydrate, and fat content of the diet, using the factors 4.0, 4.0, and 9.2, respectively. The percentage of calories derived from each food constituent was also calculated.

Water of oxidation.—Calculations for the determination of water of oxidation were made on the basis of the composition of the metabolic mixture. The total heat production was calculated as 2.42 times the weight of 24-hour insensible water obtained under conditions of normal activity. The amount of protein oxidized was calculated by

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multiplying the excretory nitrogen by 6.25. After a few days on any given diet, the carbohydrate of the metabolic mixture is considered to be equal to the carbohydrate of the diet. The number of grams of fat oxidized was obtained by taking the difference between total heat production and the sum of heat derived from the oxidation of protein and carbohydrate, i. e., 4 calories per gram for each, divided by 9.54.

The water produced in the oxidation of this mixture is calculated by means of the following constants: Proteins and fats each yield 0.41 and 1.07 gm. of water, respectively, for each gram of material oxidized. The average factor for water of oxidation of carbohydrates was taken as 0.60, even though it varies slightly for the different carbohydrates. The sum of the values obtained from each dietary constituent constitutes the total water of oxidation.

Analysis of Urine

The total nitrogen was determined by the macro-Kjeldahl method, using 5.0-cc. samples. The water content was determined gravimetrically after the dehydration of 5.0-cc. samples.

Analysis of Feces

Water.—Approximately 100 gm. of the wet feces were placed in an evaporating dish with about 25 ml. of a 15-percent solution of acetic acid in ethyl alcohol. This was thoroughly mixed, and the contents evaporated to dryness on a water bath. The dried fecal material was thoroughly broken up and further dried in an oven at approximately 80° C. to constant weight.

Residual water.—Samples of the dried feces were thoroughly ground in a mortar and placed in jars for analyses. Approximately 2 gm. of the finely divided dried feces were placed in a covered crucible and weighed. This was then heated in an oven at 105° C. to constant weight, and the residual water calculated from the loss in weight.

Fibrous and other undigestible material.—It was assumed that the difference between residual water, ash, fat, and other ether-soluble matter and nitrogen (as protein) and the total dry weight of feces represents the weight of fibrous and other undigestible material.

Ash.—The crucible containing the dried sample of feces heated to 105° C. was placed in a muffle furnace and heated to a temperature at which ashing would be complete. From the loss in weight after ashing the percent of ash in the sample was calculated.

Fat and other ether-soluble matter.—Ten grams of the dried feces were placed in a Soxhlet extractor and extracted with ether for 2 hours. After the evaporation of the ether in the receiving flask, the flask with its contents was placed in a desiccator over calcium chloride for 24 hours and then reweighed. The percent of ether-soluble substances consisting of fats, pigment, and so forth was calculated in the sample.

Nitrogen.—The nitrogen in feces was determined on a fresh, wet specimen, using approximately 0.5 gm. of the thoroughly mixed sample. Analyses were made in triplicate, using the macro-Kjeldahl method.

ENERGY METABOLISM

Insensible Water Loss Per 24 Hours

Insensible water loss was determined and heat production calculated according to the method described by Newburgh (*4*). The computations were derived from the results of 6-day runs made on alternate weeks. The sum of the weight of the man at the end of the period, the total 6-day weight of urine, feces, and the metabolic carbon dioxide equivalent of the diet was subtracted from the sum of the weight of the man at the beginning of the period, the total weight of the food and liquid consumed, and the weight of the metabolic oxygen equivalent of food. This figure, divided by the number of days, represents the insensible water loss per day.

The total weight of oxygen and carbon dioxide equivalents of the metabolized food was calculated as follows (*4*): Each gram of metabolic protein, during its oxidation in the body, involves 1.38 gm. of oxygen and 1.46 gm. of carbon dioxide; each gram of fat involves 2.86 gm. of oxygen and 2.78 gm. of carbon dioxide; each gram of carbohydrate involves 1.13 gm. of oxygen and 1.54 gm. of carbon dioxide.

Insensible Weight Loss Under Basal Conditions

The weight loss was determined by means of a Sauter balance with an electromagnetic damping and mechanical recording device as described by Andrews, Oberst, and Williams (*5*). The insensible weight loss under basal conditions was calculated from the time required for a man to lose 10 gm. Immediately after a weight-loss run, collection of respired air was made which was analyzed for carbon dioxide and oxygen. From these analyses insensible water was calculated by the formula:

Insensible water = insensible weight loss — (CO_2—O_2).

Respiratory and Gaseous Exchange

The volume of the respired air was measured by drawing it through a wet test gas meter. Expired air was collected in a Douglas bag from which samples were removed and analyzed for oxygen and carbon dioxide by means of a Haldane, Henderson, Bailey (*6*) gas analysis apparatus. During the collection of the gas the respiratory rate was determined. Immediately after the run, body weight and height were taken in order to calculate the surface area.

BLOOD STUDIES

Blood Constituents and Properties Tested

Oxalated whole blood was analyzed for cell volume, sedimentation rate, hemoglobin, water, and specific gravity. Blood to be analyzed for carbon dioxide content, chlorides, phosphates, pH, and nonprotein nitrogen was collected under oil in oxalated tubes. Specific gravity and water content were determined on plasma. Serum was analyzed for sodium, calcium, potassium, and protein.

Sedimentation rate was determined by the method of Wintrobe and Shumacker (*7*), and settling of the cells was read 60 minutes after the tubes were filled. The cell volume was then determined by centrifuging the blood at 3,000 r. p. m. for 30 minutes.

The carbon dioxide content was determined by the manometric method of Van Slyke and Neill (*8*), using the gas apparatus and technique of Van Slyke (*9*). The pH of plasma was determined by using a photoelectric colorimeter, according to the procedure described by Evelyn and Malloy (*10*).

Hemoglobin was determined by means of the Evelyn photoelectric colorimeter (*11*). The method described by Clark and Collip (*12*) was used for the determination of calcium. Inorganic phosphorus was determined by the method of Fiske and Subbarrow (*13*), the final solution was read in a photoelectric colorimeter. The total nitrogen of serum was determined by a macro-Kjeldahl method (*14*), and the nonprotein nitrogen of plasma subtracted to give the protein nitrogen. This was then multiplied by the factor 6.25 to obtain the total protein. The nonprotein nitrogen was determined by the procedure of Folin and Wu (*15*). The Wilson and Ball (*16*) procedure for chlorides in plasma was employed.

The specific gravity was determined by weighing 2 cc. of plasma or whole blood in a 25-cc. covered crucible. The water content was obtained by drying the specimen at 105° C. to constant weight.

Potassium was determined on the dried material remaining in the crucible by treating with one or two drops of concentrated sulphuric acid and ashing overnight at a low heat. The ash was dissolved in a few drops of dilute hydrochloric acid and water. The solution was transferred to a 15-cc. centrifuge tube and evaporated to dryness. The residue in the tube was analyzed for potassium by the method of Shohl and Bennett (*17*). The viscosity of serum was determined at 25° ± 0.02° C. by means of a Poissule viscosimeter as modified by Ostwald, using 2-cc. portions. The corresponding time of flow for 0.90-percent sodium chloride was 70.6 seconds.

Blood Volume and Thiocyanate Fluid Volume

These determinations were made simultaneously by combining the method of Gibson and Evelyn (*18*) for blood volume with that of Crandall and Anderson (*19*) for thiocyanate fluid volume.

NOCTURNAL ACTIVITY

Nocturnal activity was determined by having each patient sleep alternate weeks on a bed which was mounted on the floor of a Toledo platform scale. The beam of the scale was extended and arranged so as to write on a smoked paper kymograph. With this arrangement the apparatus was sufficiently sensitive to record small movements such as that of the hand at the wrist or of the foot at the ankle. The patient went to bed at 10 p. m. and got up at 6 a. m. Movements were counted from 11 p. m. to 5:30 a. m. The total number of movements was counted. Another measure of the degree of the activity was made by measuring the length of each excursion exceeding 2 mm. on the kymograph paper and computing the sum. It was found that the results of the two methods, when charted on graph paper, gave almost identical curves; consequently, only the number of movements is reported in this study.

RESULTS

For purposes of clarity the data obtained in this study are divided into two parts: (1) Those reflecting changes incident to continued use of morphine, (2) those indicating changes resulting from single injections of morphine. The data representing the continued use of morphine are shown in graphic form in figures 1 though 11, and those

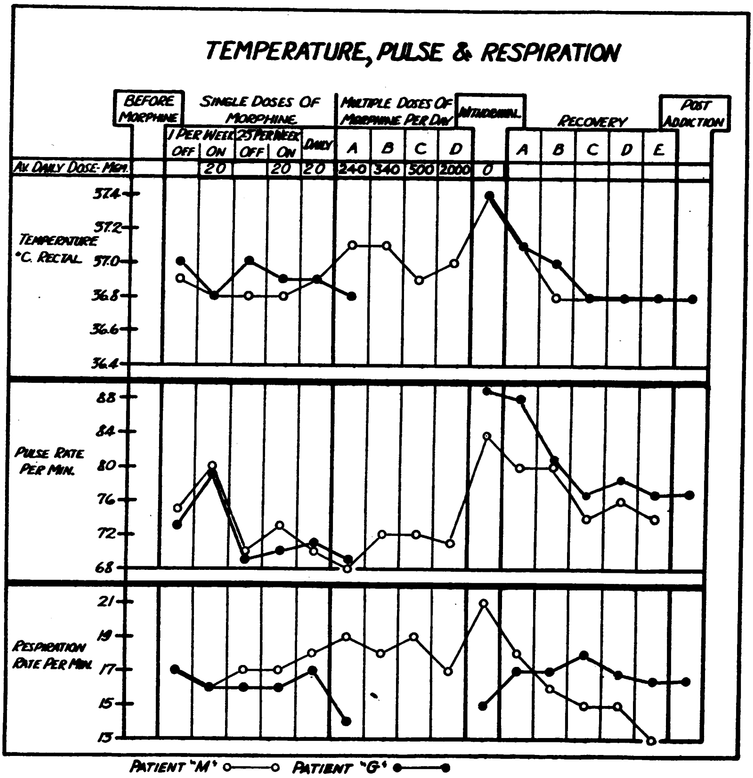

FIGURE 1.

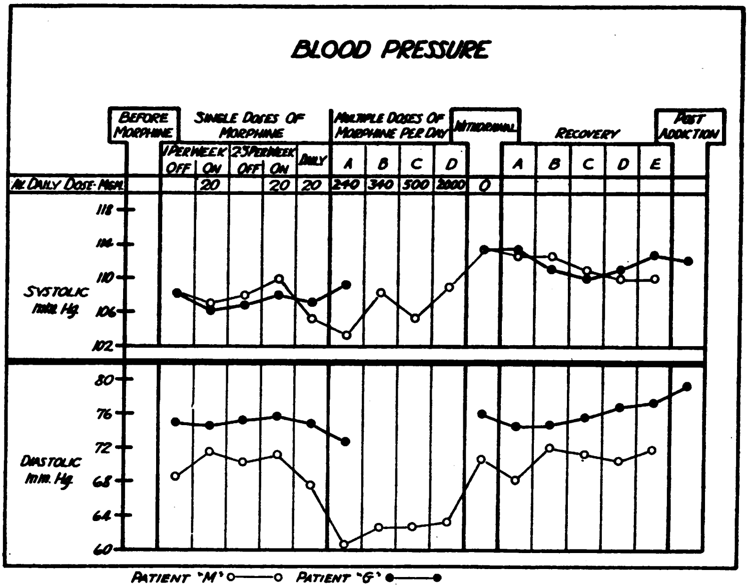

FIGURE 2.

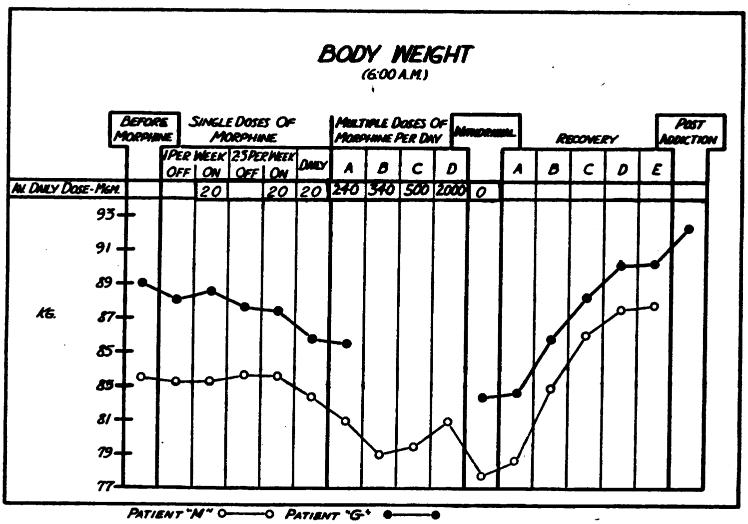

FIGURE 3.

representing the effect of a single injection of morphine are presented in tables 2 and 3. A more complete presentation of some of the data is given as follows.

Nocturnal Activity

The results of this study are shown in figure 4. When morphine was given two to three times per week, the activity during the nights following a morning injection was less than that during other nights.

Table 2.—*Average of changes in respiratory gaseous exchange and in insensible water loss under basal conditions 30 to 60 minutes after a dose of morphine*

Patient	Period of study	Dose (mg.)	Rate of respiration (per min.)	Volume of respired (cc. per min.)	Volume of carbon dioxide produced (cc. per min.)	Volume of oxygen consumed (cc. per min.)	Respiratory quotient	Basal metabolic rate (per cent)	Insensible weight loss (gm. per hr.)	Insensible water loss (gm. per hr.)	Heat production: Calculated from gas analyses (calories per sq. m. per hr.)	Heat production: Calculated from insensible water (calories per sq. m. per hr.)
	Period II											
G	2-3 per week	20		−320	−20	−1	−0.07	−2.6			−1.0	
M	2-3 per week	20		+40	+3	+1	+0.01	0.0			+0.1	
G	Daily	20	0	−850	−31	−22	−0.07	−10.2	−5.0	+0.9	−3.9	+0.2
M	Daily	20	−1	−1,200	−14	−14	−0.02	−6.1	−2.1	−2.2	−2.2	−2.8
	Period IV											
G	A	66	−1	−400	−2	0	−0.01	0.0	+6.3	+6.0	0.0	+7.4
M	A	66	−2	−410	−1	+3	−0.01	−0.3	0.0	−0.2	+0.2	−0.2
G	B											
M	B	75	+1	−120	0	+3	−0.01	+0.5	−1.2	−0.6	+0.2	−0.6
G	C											
M	C	125	−1	−610	−28	−25	−0.03	−11.6	−6.1	−6.4	−4.4	−8.2
Total tests:												
G			12	12	12	12	12		11	11		
M			28	28	28	28	28		26	26		
Tests showing an increase after morphine.			14	9	18	20	9		14	17		
Tests showing a decrease after morphine.			21	31	22	20	21		23	20		
Tests showing no changes			5	0	0	0	10		0	0		

TABLE 3.—*Blood changes found 1½ hours after a dose of morphine.* (*Results are per 100 cc. blood, plasma, or serum*)

Name	Period of study	Cell volume (percent)	Hemoglobin (gm.)	Specific gravity		Water		Sodium (mg.)	Potassium (mg.)	Calcium (mg.)	Chlorides (mg.)	Carbon dioxide content (mg.)	Phosphorous (mg.)	Plasma protein (gm.)	Viscosity time relative to 71.2 for 0.90 percent NaCl (seconds)	Plasma pH
				Whole blood	Plasma	Whole blood (gm.)	Plasma (gm.)									
	Period II															
G	1 per week	[1] −0.5	0.0	[2] +0.001	−0.003	−0.01		0	+0.7		+14	−0.5	−0.02	+0.62	+1.8	+0.02
M	1 per week	0.0	+0.67	+0.003	−0.002	0.0	−0.03	+20	+3.1		−2	−1.6	+0.08			−0.01
G	2-3 per week	0.0	−0.20	+0.011	0.0	−0.4	−0.1	−11	+1.9		−3	+1.3	+0.31	−0.20	+2.2	−0.08
G	2-3 per week	+1.5	+0.45	+0.006	+0.001	−0.3	−0.4	−13	−0.9	+0.33	+6	−2.5	−0.65	+0.25	+3.4	0.0
M	2-3 per week	0.0	−0.31	−0.001	−0.002	−0.4	0.0	+13	+1.9		+2	−0.7	+0.12	−0.06	+0.2	+0.03
M	2-3 per week	+0.3	+0.20	+0.002	+0.001	0.0	+0.1	−3	+0.7	+0.71	+4	−0.2	+0.22	+0.37	+1.8	+0.04
G	Daily	+0.4	+0.23	+0.005	−0.002	+0.4	−0.5	+3	+2.1		−8	−0.4	−0.19	+0.18	+1.4	+0.07
M	Daily	+0.8	+0.12	−0.002		−0.5	+0.3	−4	+1.9	+0.42	−8	+3.1	−0.36	+1.06	+4.3	+0.12
	Period IV															
G	A	−0.3	+0.12	+0.003		+0.1		−8	+3.1	−0.33	−1	+1.5	−0.43	+0.74	+1.1	+0.03
M	B	+0.2	0.0	0.0	0.0	−0.3	0.0	−1	−1.7	+0.08	−3	+0.8	−0.70	0.0	+1.9	+0.01
M	B	+0.7	−0.10	+0.001	+0.003	−0.6	+0.2									
M	B	+3.3	+0.85	−0.002	0.0	−0.8	−0.2	+2	−1.2	+0.16	+29	+2.8	−0.21	+0.07	+1.3	0.0
M	C	+0.5	+0.12	−0.004	0.0	−0.6	+0.1	−3	+0.5	+0.08	+1	−2.3	−0.35	0.0	+1.2	0.0
M	C	−2.0	−0.27	−0.007		−0.8		−20	0.0	−0.16	+7	+0.5	+0.24	−0.33	−0.4	−0.01
M	C	−0.5	−0.19	−0.003		−0.4	+0.4									
Tests showing an increase after morphine		8	8	8	3	2	5	4	9	6	7	6	5	7	11	7
Tests showing a decrease after morphine		4	5	6	4	11	5	8	3	2	6	7	8	3	1	3
Tests showing no changes		3	2	1	4	2	2	1	1					2		3

[1] −indicates decrease.
[2] +indicates increase.

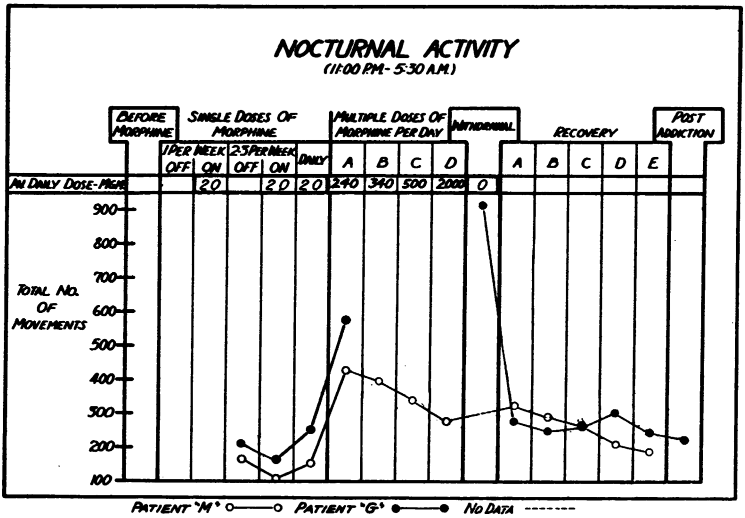

FIGURE 4

When the drug was administered daily, the activity was greater than that following single injections given two to three times per week. In period IV, the activity was increased immediately. This was followed by a general decrease, indicating development of tolerance to this effect.

Tolerance to effect on nocturnal activity.—Because of this suggested development of tolerance the data for M were more completely analyzed than is possible on the basis of periods. It was found that there was a marked increase with the beginning of multiple injections. The patient was on 300 mg. of morphine daily for a period of 73 days. For the first part of this period his activity was about 450 movements per night, whereas, during the last part it was about 275 movements. The dosage was then raised to 400 mg. per day, for 37 days. No records were made except during the last week, at which time he showed an activity of 500 movements. The dosage was then raised to 500 mg. per day, for 46 days. During this period the activity was about 330 movements. Following this the dosage was rapidly increased, but the nocturnal activity did not increase with the dosage. It may be concluded from these data that the initial effect of daily doses of morphine or of increasing amounts of morphine (within limits) is an increase in nocturnal activity and that a partial tolerance is developed.

Water Studies

The water of oxidation is largely related to the type of food in the metabolic mixture and was used in calculating total water intake. The values were irregular, varying between 123 and 380 gm. per day.

Although actual results on total water intake and output are not shown in either table or graph form, no significant difference was noted

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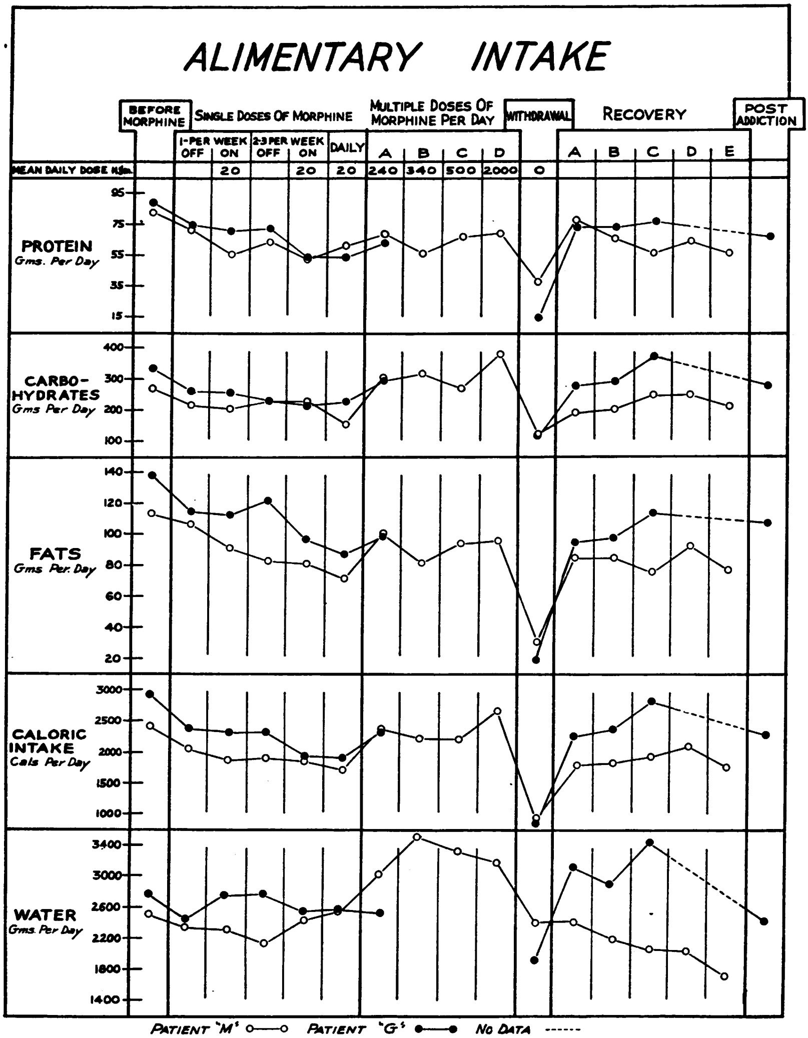

FIGURE 5.

for either measure in the various periods, except during the withdrawal period when the output exceeded the intake by about 600 cc. per day.

The studies of insensible water loss per 24 hours did not show any significant change in any period which could be attributed with certainty to drug effect or to addiction.

Insensible water determined under basal conditions was irregular and varied between 23.0 and 34.1 gm. per hour. No significant trends were noted in any of the periods studied.

Blood Studies

The data on blood concentration, blood volume, and extracellular water are shown in figures 9, 10, and 11. The values for sodium, chloride, calcium, viscosity, inorganic phosphorus, potassium, protein, and CO_2 content were such that no conclusion could be drawn. Plans are being made to reinvestigate acid-base balance.

Erythrocyte sedimentation rate was increased in both patients as follows:

Patient	Period I	Period II	Period III	Period IV	Period V	Period VI	Period VII
	mm.	*mm.*		*mm.*	*mm.*	*mm.*	*mm.*
G	4	7	----------	----------	----------	5	3
M	26	28	----------	39	42	22	----------

The fact that the changes in period II are small and that M had an unexplained abnormally high value in period I justifies reference to unpublished data: Two patients on large doses of morphine for a period of 5 months had average readings of 4, 8, 23, 20, 21 and 12, 13, 20, 35, and 35 mm. at 60 min., respectively for the first, second, third, fourth, and fifth months of medication.

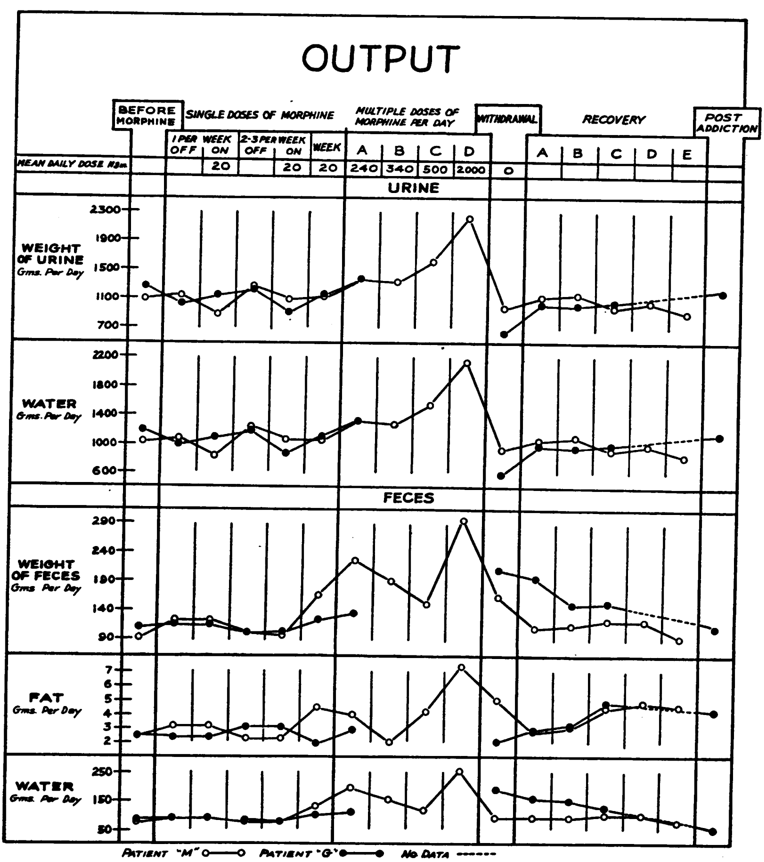

FIGURE 6.

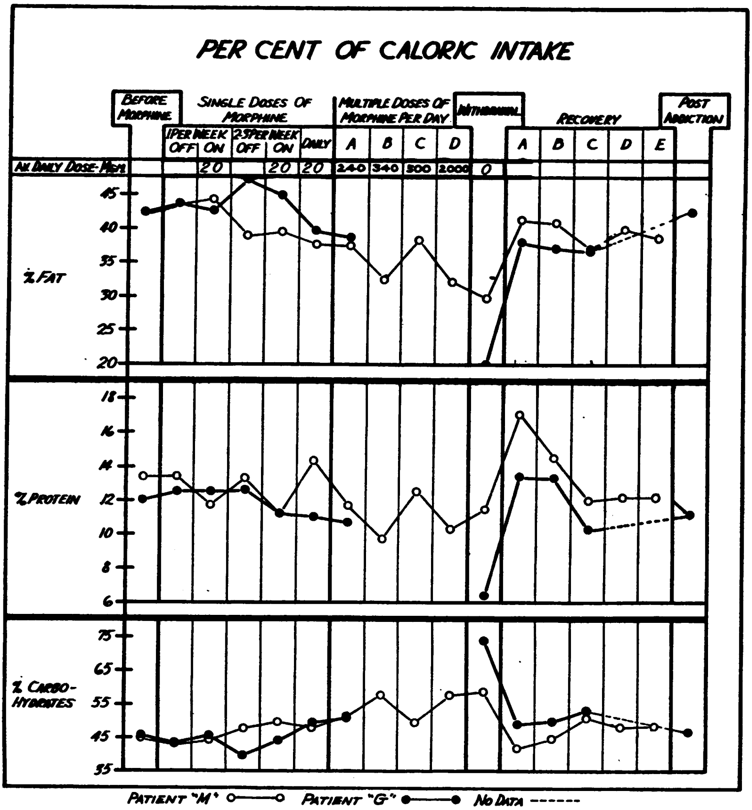

FIGURE 7.

Studies Before and After a Dose of Morphine

Is the effect of morphine the same in the tolerant as in the non-tolerant individual? In an attempt to shed some light on this question certain determinations were made before and 30 to 120 minutes after injections during periods II and IV.

Metabolism

Average changes in respiratory gaseous exchange and in insensible water loss under basal conditions 30 to 60 minutes after a dose of morphine are shown in table 2. Of 274 tests 158 showed a decrease after morphine. When the data were arranged as period averages, 48 of 72 averages showed a decrease. There was no evidence of change in the effect of morphine after dependence had developed.

Blood Changes 1½ Hours After Morphine

Although the data do not reveal any statistically significant changes there appears to be a tendency toward an increase in: Hemoglobin, cell volume, serum protein, viscosity of serum, plasma pH, serum potassium, and serum calcium; and a decrease in: Serum sodium and

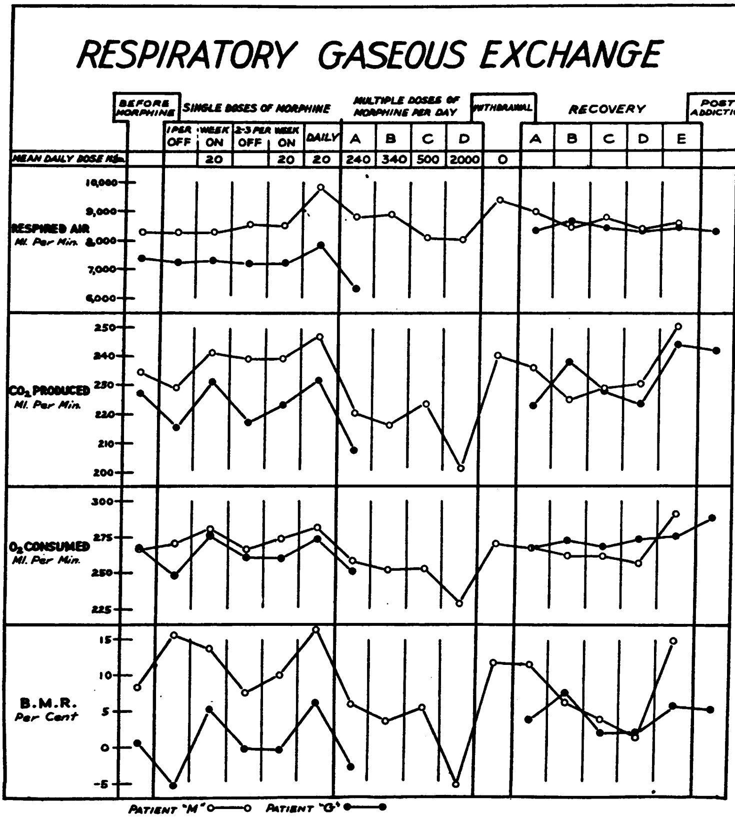

FIGURE 8.

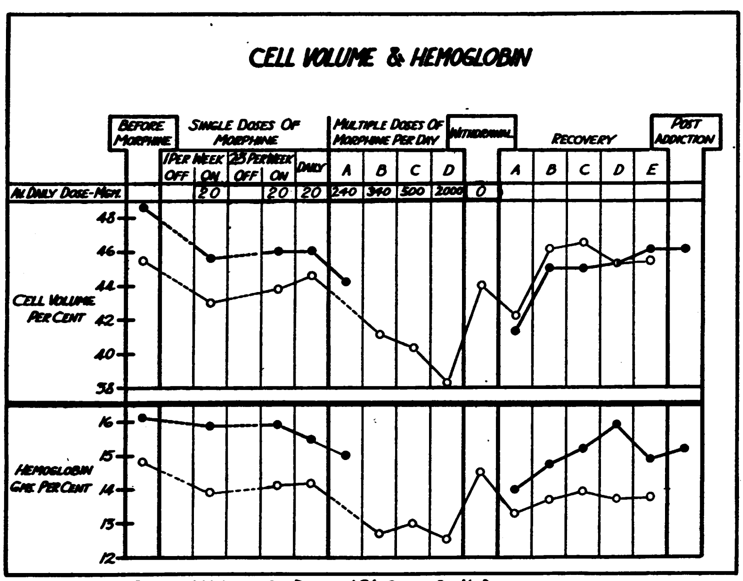

FIGURE 9.

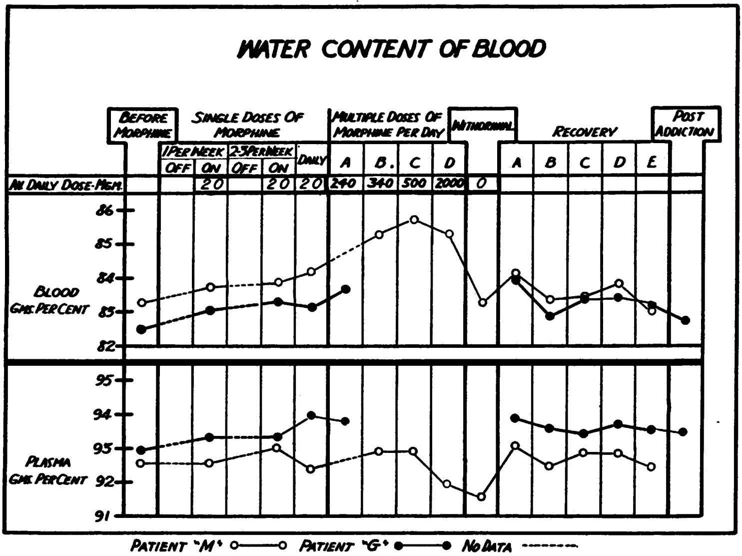

FIGURE 10.

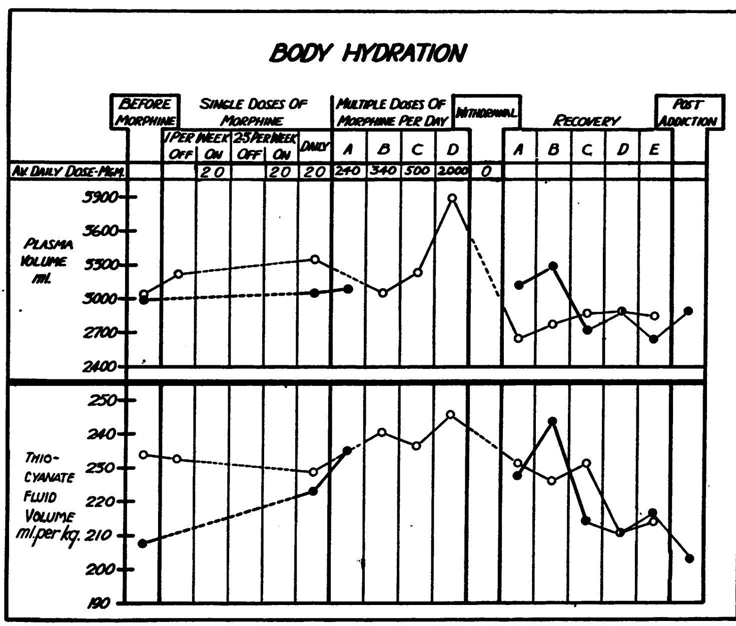

FIGURE 11.

water content of whole blood. No trends were noted in the other blood constituents analyzed. It is concluded that there is a tendency for blood to become slightly concentrated after a single dose of morphine, whether or not the subject is addicted.

NOTE: For purposes of completion, reference is made to two other studies which were made on these patients and which have been published. Excretion studies were reported by Oberst (*20*). Andrews (*21*) studied changes in cortical potentials and found that, before morphine, M regularly had an alpha index greater than 95 percent, whereas G had an index always below 10 percent. On morphine, M showed a decrease in alpha frequency and index. Tolerance to this effect was developed. G, on the other hand, showed an increase in both alpha index and frequency. On the assumption that G had a cortical excitatory state too great for alpha production (*22*) and that the excitatory state for M was almost optimum for alpha wave production, it was concluded that morphine addiction is associated with a depression in the cortical excitatory state (allowing alpha production in G and preventing it in M) and that tolerance to this effect can be developed. These effects appeared to be quite reversible, since records taken after withdrawal and recovery were practically identical with those of period I. This does not necessarily mean that the first cycle of addiction is accompanied by reversible changes.

DISCUSSION

This study represents a general survey rather than an intensive study on any particular aspect of addiction. The findings of apparent and significant changes in such a cycle of morphine addiction may serve as leads for more intensive studies.

Effects Produced by Repeated Doses of Morphine

The question was raised as to whether physical dependence would develop in patients receiving only single doses of morphine at regular intervals; first one per week, then two per week, three per week, and finally one per day. The 3-day withdrawal period following period II was designed to answer this question. Observations made during these 3 days (period III) were compared with the average values during daily single injections of period II. Many of the changes, though small, were in the same direction as those found during withdrawal in bona fide addicts. In addition to these, it was noted that the patients were unhappy, irritable, had a "let-down" feeling, and some rhinorrhea, lacrimation, and yawning. Scoring these observations by the point system of Himmelsbach (*3*) would yield very few or no points, yet it seems clearly evident that morphine had produced a low degree of physical dependence. It is believed that physical dependence effects occurred very early. It was noted that when the patients had been receiving two doses per week for about 3 weeks, they began to be irritable, showed increased psychomotor activity, yawned frequently, had slight rhinorrhea, and lacrimation the day before the next injection. They complained of being depressed, and pleaded that the drug be given more frequently. After they were on three doses per week for several weeks, the same disturbance recurred until daily doses were instituted. These phenomena are being studied further.

This study adds little to our knowledge of tolerance. The question of increased nocturnal activity and development of tolerance thereto is being investigated further. Some tolerance was developed to the effects on cortical potentials (see note on page 21). After daily multiple doses were started it was only a matter of a few days before both patients were receiving 300 mg. of morphine per day without ill effects. After about 4½ months on 300 to 500 mg. per day, the dosage in one patient was increased to 4,440 mg. per day in the course of about 2 weeks. He was kept on the high dosage for only a few days because of the inconvenience of injecting such large quantities of fluid (12.7 cc., 5-percent solution, seven times daily). He was reasonably happy, carried on his usual routine activities, and ate and slept well. Five days before withdrawal the dosage was decreased from 4,440 to 1,750 mg. for 1 day and to 640 mg. per day for 4 days. There were no abstinence symptoms during this period. His withdrawal period was not unusual. The abstinence syndrome exhibited by him was comparable to that of an addict who had been stabilized on about 200 mg. of morphine per day.

Schmidt and Livingston (*23*) (quoting Light and Torrance) state that addicts tolerant to morphine administered subcutaneously are also tolerant to large doses given intravenously. This is undoubtedly true within the limits of their experiments, but the peculiar subjective and visibly objective effects of intravenously administered morphine are still present. These phenomena are flushing of the face, a tingling or pricking sensation "all over," and, in many instances, headache. These symptoms, except the headache, are fleeting and constitute the added "kick" sought by "main-line shooters." They may be alarming to the "skin shooter" who accidentally gets some of the drug into a vein. One of our patients, M, who had been receiving morphine for 4 months, and had been receiving 500 mg. daily for 20 days, suddenly appeared in the office in great fright, stating that some of his dose had gotten into a vein. His face was flushed and his trunk pale. He complained of a terrific headache. His blood pressure was not measured. He was reassured as to the harmlessness of the accident and in a few minutes the symptoms were gone, except the headache, which persisted for several hours.

Morphine usually depresses respiration. As a rule, complete tolerance is not developed to this effect and the rate remains subnormal during addiction. On the contrary, M showed an increased respiratory rate throughout periods II and IV.

Data in the literature on blood changes during addiction are limited.

In most instances little or no change has been reported. Williams (*24*) reported that addiction was associated with a lessened concentration of the blood. In this study his findings were corroborated in the following way: Hemoglobin and hematocrit readings were usually decreased and water content of the whole blood was increased during period IV. In addition to this blood hydration, the thiocyanate fluid volume was found to be increased during addiction. Together these findings imply an increased hydration of the body in general. That this might be a protective phenomenon is suggested by the reports from the literature (*25*) that dehydrated dogs, mice, and rats were more sensitive to morphine, and water loading made mice less sensitive. The question of body hydration and weight loss is being investigated further.

The findings on basal metabolic rate in this study are variable. However, there was a tendency toward a slight decrease during addiction, especially when the dosage was high. Heat production under basal conditions as determined from insensible water loss is in agreement with this. Himmelsbach (*26*) found only a slight decrease, if any, in B. M. R. in 21 patients during addiction.

There is a general notion that addicts prefer sweet foods. Observations on these two patients confirm this. The proportion of carbohydrates in their self-chosen diets was increased during addiction, largely at the expense of fats. The total caloric intake was not appreciably changed.

Effects of Single Doses of Morphine

Reports in the literature as reviewed by Krueger, Eddy, and Sumwalt (*25*) are somewhat conflicting as to the effects of morphine on the blood. The consensus, however, is that there is an increase in the hemoglobin content of peripheral blood and in the number of erythrocytes following morphine. In this study we found the blood to be slightly concentrated following single doses of morphine whether the individual was addicted or not.

Some investigators report an increase and others a decrease in blood pH after morphine. A biphasic action affecting pH has also been reported in which pH was first decreased and later increased. Probably the variability of the results may be attributed to such factors as differences in dosage, technique, and type of animal used. In the present study, blood was found to be slightly more alkaline following morphine.

The directional changes comprising the acute effects of morphine were unaltered throughout this study. That is to say, in no instance did we find that addiction had reversed the effect of morphine. However, the alterations which accompanied addiction were, in some instances, in the opposite direction to the acute effects of morphine (single doses). For example, regardless of the state of addiction the blood was regularly slightly concentrated following a single injection, whereas during addiction it was hydrated with reference to the post-addiction values.

During withdrawal, as has been shown (*3*), caloric intake decreases especially from the second to the fourth day. Before morphine studies were started, the patients were studied for a period of 5 days during which the caloric intake was reduced by approximately the same amount as is observed during morphine withdrawal. No signs or symptoms comprising the morphine abstinence syndrome appeared during this time. It is therefore concluded that the clinical changes present during withdrawal are not due to a direct effect of reduced caloric intake.

SUMMARY

A longitudinal approach to the problem of drug addiction, using laboratory methods, was made on two post-addicts. Prior to any morphine injections, certain tests were made to establish norms for these patients. They were given 20-mg. doses of morphine sulfate subcutaneously, at weekly intervals, for a period of 2 months. During the next 6 weeks the frequency of the dosage was increased first to two, and then to three per week, after which the drug was administered daily for five weeks. It was then discontinued for 3 days and it was found that a slight but definite dependence had developed. Following this, morphine was given four times per day in increasing amounts. One patient was on this regimen for approximately 1 month and then permanently withdrawn. The other was given multiple doses of morphine daily for 6 months. The dosage was increased by arbitrary increments at intervals of 2 to 5 weeks. The highest dose was 4,440 mg. per day. The recovery period was divided into five parts to show progressive changes. The post-addiction period was arbitrarily chosen as beginning with the ninth month of abstinence.

An accurate account of carbohydrates, fat, protein, and water intake for each patient was made each day for periods of 6 days on alternate weeks. Urine and feces were analyzed for water during the corresponding periods.

Clinical observations, including temperature, blood pressure, pulse, and respiration were made three times daily. Nocturnal activity was determined by recording the number and magnitude of movements the patient made in bed from 11 p. m. to 5:30 a. m. Basal metabolism determinations were made from analyses of oxygen and carbon dioxide in expired air and from insensible weight loss.

Blood was analyzed approximately once a month for sodium, potassium, calcium, inorganic phosphorus, protein, carbon dioxide,

pH, specific gravity, water, hemoglobin, and cell volume. Body hydration was determined from plasma volume, thiocyanate fluid volume, water content of blood, hemoglobin, and packed cell volume.

The results of this study indicate that morphine addiction is accompanied by increases in: Body water, water content of blood, blood sedimentation, carbohydrate intake, and nocturnal activity; and by decreases in: Body weight, hemoglobin, packed cell volume, pulse rate, basal metabolism, and diastolic blood pressure.

In order to determine the "acute" effects of morphine, respired gaseous exchange, insensible weight loss, and blood constituents were studied before and after single doses of morphine at various times during the study. The minute volume of respired air, respiratory quotient, and insensible water loss were usually decreased after morphine, especially after large doses. Basal metabolic rate was decreased after large doses. Blood was found to be slightly more concentrated after morphine. There was no indication that addiction alters the action of the drug.

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DEATHS DURING WEEK ENDED DECEMBER 8, 1945

[From the Weekly Mortality Index, issued by the Bureau of the Census, Department of Commerce]

	Week ended Dec. 8, 1945	Corresponding week, 1944
Data for 93 large cities of the United States:		
Total deaths	9,945	9,343
Average for 3 prior years	9,752	
Total deaths, first 49 weeks of year	439,644	440,169
Deaths under 1 year of age	640	594
Average for 3 prior years	664	
Deaths under 1 year of age, first 49 weeks of year	29,714	30,302
Data from industrial insurance companies:		
Policies in force	67,264,229	66,920,488
Number of death claims	12,949	14,326
Death claims per 1,000 policies in force, annual rate	10.0	11.2
Death claims per 1,000 policies, first 49 weeks of year, annual rate	10.0	10.1

PREVALENCE OF DISEASE

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

REPORTS FROM STATES FOR WEEK ENDED DECEMBER 15, 1945

Summary

A total of 148,688 cases of influenza was reported for the week, as compared with 49,694 last week, 2,924 and 82,951, respectively, for the corresponding weeks of 1944 and 1943, and 2,995 for the median of the corresponding weeks of the years 1940–44. Increases were reported in all of the 9 geographic divisions except the East North Central. Of the current total, 89,363 cases, or 60 percent, were reported in Kentucky, where last week 15,358 cases, or about 31 percent of the total occurred. An aggregate of 143,439 cases occurred in the 10 States reporting 1,000 or more cases each, in which 44,479 cases were reported last week. These States are as follows (last week's figures in parentheses): Kentucky 89,363 (15,358), Utah 17,023 (4,241), Texas 11,259 (7,332), Kansas 11,229 (6,848), Virginia 4,691 (3,993), West Virginia 3,808 (3,395), South Carolina 2,659 (2,459), North Dakota 1,244 (277), Arizona 1,163 (323), Georgia 1,000 (253). The total reported for the year to date is 309,422, as compared with 361,685 and 209,594, respectively, for the period in 1944 and 1943, and a 5-year median of 221,737. The total since July 1 is 242,948, as compared with 26,162 and 132,013, respectively, for the same periods in 1944 and 1943, and a 5-year median for that period of 30,099. The peak of incidence in the 1943–44 epidemic was reached in the first week of January, with a total of 126,610 cases reported for the week.

A total of 92 cases of meningococcus meningitis was reported (as compared with 118 last week), a smaller number than for the corresponding week of any of the past 3 years. The total for the year to date is 7,710, as compared with 15,689 for the corresponding period last year and a 5-year median of 3,495.

Of the total of 115 cases of poliomyelitis reported for the week, 56 occurred in 4 States—New York (16), California (15), Illinois (14), and Washington (11). The cumulative total is 13,558, as compared with 19,107 and 12,319 for the corresponding periods of 1944 and 1943, respectively, and a 5-year median of 9,685.

Deaths recorded for the week in 92 large cities of the United States aggregated 10,109, as compared with 9,840 last week, 9,292 for the corresponding week last year, and a 3-year (1942–44) average of 10,175. The cumulative total is 445,641, as compared with 445,311 for the corresponding period last year.

Telegraphic morbidity reports from State health officers for the week ended December 15, 1945, and comparison with corresponding week of 1944 and 5-year median

In these tables a zero indicates a definite report, while leaders imply that although none was reported, cases may have occurred.

Division and State	Diphtheria			Influenza			Measles			Meninigitis, meningococcus		
	Week ended—		Median 1940–44	Week ended—		Median 1940–44	Week ended—		Median 1940–44	Week ended—		Median 1940 44–
	Dec. 15, 1945	Dec. 16, 1944		Dec. 15, 1945	Dec. 16, 1944		Dec. 15, 1945	Dec. 16, 1944		Dec. 15, 1945	Dec. 16, 1944	
NEW ENGLAND												
Maine	5	0	0	3	------	1	1	3	93	1	1	1
New Hampshire	0	0	0	149	------	------	34	1	2	0	0	0
Vermont	0	0	0	150	4	------	5	4	4	0	0	0
Massachusetts	10	5	5	------	------	------	152	58	245	3	7	6
Rhode Island	0	1	1	8	22	1	2	3	4	1	0	0
Connecticut	5	0	0	26	2	5	14	11	11	1	0	2
MIDDLE ATLANTIC												
New York	8	14	20	[1] 45	(1)	[1] 12	266	37	531	15	30	17
New Jersey	2	9	6	61	6	9	17	10	40	6	16	6
Pennsylvania	11	8	9	58	3	2	436	42	723	7	15	7
E. NORTH CENTRAL												
Ohio	24	9	11	86	10	13	10	12	53	4	12	3
Indiana	7	10	3	595	3	15	3	3	21	2	3	1
Illinois	8	4	16	56	5	10	214	34	83	7	13	6
Michigan [2]	11	22	6	6	1	9	229	19	86	3	9	3
Wisconsin	3	2	1	388	6	42	24	22	227	1	9	3
W. NORTH CENTRAL												
Minnesota	9	10	2	9	1	1	4	6	11	2	0	0
Iowa	10	8	3	65	------	------	6	13	44	0	0	0
Missouri	6	1	5	62	3	4	33	8	8	2	7	3
North Dakota	2	28	2	1,244	2	12	------	------	2	0	1	0
South Dakota	0	2	2	2	------	------	1	3	5	0	1	0
Nebraska	24	11	2	86	17	17	3	12	12	0	0	0
Kansas	7	10	4	11,229	4	16	41	7	59	0	2	2
SOUTH ATLANTIC												
Delaware	0	1	0	17	------	------	------	4	4	0	0	0
Maryland [2]	16	5	5	59	2	9	9	1	11	3	6	6
District of Columbia	0	0	0	22	1	2	2	3	2	0	0	0
Virginia	9	4	11	4,691	208	233	64	11	94	4	3	3
West Virginia	3	5	5	3,808	8	27	1	22	22	1	0	2
North Carolina	36	14	17	------	6	8	20	16	19	2	2	2
South Carolina	8	1	5	2,659	362	376	13	3	10	1	2	0
Georgia	19	13	13	1,000	58	80	12	21	21	0	1	1
Florida	11	4	8	8	1	11	4	3	3	0	4	1
E. SOUTH CENTRAL												
Kentucky	11	2	5	89,363	------	13	211	------	13	3	2	2
Tennessee	19	10	10	204	27	52	8	12	23	0	3	2
Alabama	25	14	17	649	53	98	2	1	35	4	1	1
Mississippi [2]	12	22	13	------	------	------	------	------	------	2	4	2
W. SOUTH CENTRAL												
Arkansas	13	5	7	644	57	150	14	5	23	3	2	1
Louisiana	22	10	9	47	3	3	7	5	4	1	1	1
Oklahoma	6	16	16	684	137	137	5	6	8	0	4	1
Texas	74	58	49	11,259	1,702	1,423	47	51	51	1	6	3
MOUNTAIN												
Montana	0	2	2	193	19	19	3	1	28	0	0	0
Idaho	0	0	0	279	1	1	73	------	3	1	0	0
Wyoming	1	0	0	66	27	27	10	4	4	0	0	0
Colorado	7	5	5	367	4	42	12	9	154	0	3	1
New Mexico	0	2	2	8	2	2	1	------	3	1	0	1
Arizona	7	2	2	1,163	109	110	2	5	21	0	2	0
Utah [2]	0	0	0	17,023	8	9	29	9	9	0	1	0
Nevada	0	0	0	------	------	------	------	1	1	0	0	0
PACIFIC												
Washington	5	35	7	------	------	12	220	34	34	1	3	3
Oregon	3	9	3	122	21	21	20	26	55	1	1	1
California	37	23	19	25	19	84	297	237	126	8	24	6
Total	496	416	393	148,688	2,924	2,995	2,581	798	4,779	92	201	108
50 weeks	17,768	13,434	14,995	309,422	361,685	221,737	123,670	600,848	587,903	7,710	15,689	3,495

[1] New York City only.
[2] Period ended earlier than Saturday.

Telegraphic morbidity reports from State health officers for the week ended December 15, 1945, and comparison with corresponding week of 1944 and 5-year median—Con.

Division and State	Poliomyelitis			Scarlet fever			Smallpox			Typhoid and paratyphoid fever [3]		
	Week ended—		Median 1940-44	Week ended—		Median 1940-44	Week ended—		Median 1940-44	Week ended—		Median 1940-44
	Dec. 15, 1945	Dec. 16, 1944		Dec. 15, 1945	Dec. 16, 1944		Dec. 15, 1945	Dec. 16, 1944		Dec. 15, 1945	Dec. 16, 1944	
NEW ENGLAND												
Maine	1	0	0	24	52	12	0	0	0	0	1	1
New Hampshire	0	0	0	0	27	5	0	0	0	0	1	0
Vermont	1	0	0	10	5	2	0	0	0	0	0	0
Massachusetts	2	0	1	121	251	251	0	0	0	1	4	4
Rhode Island	1	0	0	12	22	10	0	0	0	0	0	0
Connecticut	1	0	0	29	55	45	0	0	0	0	0	0
MIDDLE ATLANTIC												
New York	16	27	8	296	333	301	0	0	0	2	5	5
New Jersey	0	2	1	46	88	88	0	0	0	1	1	1
Pennsylvania	0	1	1	174	250	226	0	0	0	2	0	5
EAST NORTH CENTRAL												
Ohio	2	4	2	326	318	250	0	0	0	2	0	2
Indiana	0	0	0	54	76	76	0	0	1	0	0	0
Illinois	14	1	2	145	268	207	0	0	0	1	2	2
Michigan [2]	3	4	1	209	189	185	0	0	1	3	1	3
Wisconsin	3	2	0	108	128	147	0	0	0	0	0	1
WEST NORTH CENTRAL												
Minnesota	0	1	1	42	60	76	0	0	0	0	0	0
Iowa	1	1	1	24	68	55	0	0	1	0	0	1
Missouri	7	1	1	59	70	59	0	0	0	1	0	1
North Dakota	0	1	0	8	24	14	0	1	0	0	0	0
South Dakota	1	0	0	4	16	29	0	0	0	0	1	0
Nebraska	0	15	1	22	56	36	0	0	0	0	0	0
Kansas	0	1	2	78	94	70	1	2	1	0	0	0
SOUTH ATLANTIC												
Delaware	0	0	0	3	11	11	0	0	0	0	0	0
Maryland [2]	0	1	0	46	88	47	0	0	0	1	9	3
District of Columbia	0	1	0	13	49	14	0	0	0	0	2	1
Virginia	3	3	1	94	70	65	0	0	0	0	0	4
West Virginia	0	0	0	47	39	48	0	0	0	0	0	0
North Carolina	2	1	2	61	63	72	0	0	0	0	0	3
South Carolina	1	0	1	8	15	12	0	0	0	4	1	1
Georgia	0	2	0	32	32	32	0	0	0	1	5	4
Florida	3	1	1	8	8	7	0	0	0	3	1	2
EAST SOUTH CENTRAL												
Kentucky	2	2	2	65	72	72	0	1	1	1	0	4
Tennessee	0	0	0	35	89	60	0	0	0	0	2	2
Alabama	2	0	0	30	20	21	2	0	0	1	0	1
Mississippi [2]	3	0	1	35	23	11	1	0	0	1	2	1
WEST SOUTH CENTRAL												
Arkansas	0	2	1	18	17	11	0	0	0	3	1	1
Louisiana	8	0	0	23	21	7	0	2	1	5	3	3
Oklahoma	0	0	1	18	26	26	2	0	0	3	1	1
Texas	4	2	2	105	118	55	0	0	2	9	7	6
MOUNTAIN												
Montana	2	0	0	9	19	19	0	0	0	0	0	0
Idaho	0	0	0	13	27	15	0	0	0	1	0	1
Wyoming	0	1	0	7	12	8	0	0	0	0	0	0
Colorado	0	0	0	43	53	31	0	0	0	0	0	1
New Mexico	0	0	0	17	26	8	0	0	0	0	1	1
Arizona	1	0	1	15	7	7	0	0	0	1	2	1
Utah [2]	0	1	1	29	32	32	0	0	0	2	1	0
Nevada	0	0	0	0	5	1	0	0	0	0	0	0
PACIFIC												
Washington	11	4	3	38	87	37	0	0	0	1	0	0
Oregon	5	0	0	34	38	19	0	0	0	0	0	0
California	15	4	4	245	343	136	0	0	0	3	2	4
Total	115	86	85	2,882	3,860	3,100	6	6	11	53	56	72
50 weeks	13,558	19,107	9,685	167,781	183,195	134,742	339	377	764	4,773	5,302	6,603

[2] Period ended earlier than Saturday.

[3] Including paratyphoid fever reported separately, as follows: Massachusetts 1; South Carolina 2; Texas 1; California 3.

Telegraphic morbidity reports from State health officers for the week ended December 15, 1945, and comparison with corresponding week of 1944 and 5-year median—Con.

Division and State	Whooping cough: Week ended— Dec. 15, 1945	Whooping cough: Week ended— Dec. 16, 1944	Whooping cough: Median 1940–44	Week ended Dec. 15, 1945: Dysentery, Amebic	Dysentery, Bacillary	Dysentery, Unspecified	Encephalitis, infectious	Rocky Mt. spotted fever	Tularemia	Typhus fever, endemic	Undulant fever
NEW ENGLAND											
Maine	40	33	33								1
New Hampshire	12	11	11								
Vermont	20	30	10								1
Massachusetts	164	100	199	3	4						3
Rhode Island	24	17	17								
Connecticut	58	98	80								5
MIDDLE ATLANTIC											
New York	286	286	403	5	87		1				4
New Jersey	184	118	152	2		2					2
Pennsylvania	129	116	216						2		
EAST NORTH CENTRAL											
Ohio	119	105	205		2						4
Indiana	15	3	14								
Illinois	76	70	162	4	1				9		2
Michigan [2]	211	71	232	3	2						1
Wisconsin	93	70	177								3
WEST NORTH CENTRAL											
Minnesota	7	20	28	2			1				2
Iowa	19	11	16								
Missouri	5	14	14						5		
North Dakota	3	5	11								1
South Dakota	2		3							1	
Nebraska	1	4	12								
Kansas	19	31	33						3		8
SOUTH ATLANTIC											
Delaware	5	4	6								
Maryland [2]	42	75	75						2		1
District of Columbia	5	3	10							1	
Virginia	43	76	76			27		1	2		
West Virginia	22	4	35								
North Carolina	46	89	117	1			1			3	
South Carolina	38	22	29	4	8					2	
Georgia	9	2	9		1	1				21	5
Florida	5	11	11	1	1					3	1
EAST SOUTH CENTRAL											
Kentucky	22	10	60						8		
Tennessee	9	10	23			1			2	4	1
Alabama	21	6	15							5	
Mississippi [2]									1	2	
WEST SOUTH CENTRAL											
Arkansas	6	14	17	1	4					2	1
Louisiana	2	2	4	2					1	16	1
Oklahoma	5	8	5								
Texas	139	177	145	20	317	91	1			14	9
MOUNTAIN											
Montana		14	14								
Idaho	10	3	3				1				1
Wyoming		8	6								
Colorado	14	10	31	1							
New Mexico		1	11		1	1					
Arizona	6	10	11			42					
Utah [2]	13	10	19								
Nevada											
PACIFIC											
Washington	49	17	64								1
Oregon	7	16	16								1
California	120	108	151	1	6		2		1	2	5
Total	2,125	1,923	3,360	50	434	165	7	1	36	76	64
Same week, 1944	1,923			31	523	230	3	0	55	135	77
Average, 1942–44	2,412			24	370	106	6	[4] 0	34	[4] 80	
50 weeks: 1945	120,814			1,885	24,069	10,371	612	466	765	5,046	4,733
1944	92,499			1,798	23,874	8,894	620	453	633	5,154	3,717
Average, 1942–44	146,379		[4] 172,829	1,682	17,773	7,533	613	[4] 451	754	[4] 3,585	

[2] Period ended earlier than Saturday.
[4] 5-year median, 1940–44.

WEEKLY REPORTS FROM CITIES

City reports for week ended December 8, 1945

This table lists the reports from 85 cities of more than 10,000 population distributed throughout the United States and represents a cross section of the current urban incidence of the diseases included in the table.

	Diphtheria cases	Encephalitis, infectious, cases	Influenza		Measles cases	Meningitis, meningococcus, cases	Pneumonia deaths	Poliomyelitis cases	Scarlet fever cases	Smallpox cases	Typhoid and paratyphoid fever cases	Whooping cough cases
			Cases	Deaths								
NEW ENGLAND												
Maine:												
Portland	0	0	------	0	------	0	0	0	2	0	0	------
New Hampshire:												
Concord	0	0	------	0	------	0	3	0	0	0	0	------
Vermont:												
Barre	0	0	------	0	------	0	0	0	0	0	0	------
Massachusetts:												
Boston	1	0	------	0	6	1	1	3	26	0	1	26
Fall River	0	0	------	0	1	0	0	0	3	0	0	1
Springfield	0	0	------	0	1	0	0	0	3	0	0	6
Worcester	0	0	------	0	4	0	7	1	6	0	0	12
Rhode Island:												
Providence	0	0	------	0	------	1	2	0	3	0	1	30
Connecticut:												
Bridgeport	0	0	------	0	1	0	3	0	2	0	0	------
Hartford	0	0	------	0	2	0	0	0	0	0	0	7
New Haven	0	0	------	0	------	0	1	0	0	0	0	5
MIDDLE ATLANTIC												
New York:												
Buffalo	3	0	------	0	1	0	5	0	14	0	0	29
New York	9	1	5	2	61	7	64	4	99	0	3	77
Rochester	0	0	------	0	------	2	0	0	8	0	0	5
Syracuse	0	0	------	0	88	0	2	0	4	0	0	1
New Jersey:												
Camden	0	0	------	0	------	0	2	0	3	0	0	2
Newark	0	0	7	0	3	0	2	0	15	0	0	21
Trenton	0	0	1	0	------	0	3	1	0	0	0	3
Pennsylvania:												
Philadelphia	3	0	21	5	38	4	29	0	45	0	0	36
Pittsburgh	1	0	2	2	2	2	14	1	22	0	1	4
Reading	0	0	------	0	2	0	1	0	1	0	0	19
EAST NORTH CENTRAL												
Ohio:												
Cincinnati	0	0	------	1	1	2	9	0	8	0	0	2
Cleveland	2	0	66	3	1	0	9	0	18	0	0	29
Columbus	3	0	1	1	1	0	1	0	10	0	0	------
Indiana:												
Fort Wayne	0	0	------	0	------	0	1	0	0	0	0	------
Indianapolis	3	0	------	2	2	1	5	0	13	0	0	11
South Bend	0	0	------	0	------	0	0	0	0	0	0	------
Terre Haute	0	0	------	0	------	0	3	0	0	0	0	------
Illinois:												
Springfield	2	0	------	0	------	0	2	0	4	0	0	------
Michigan:												
Detroit	5	0	------	0	55	1	14	0	41	0	1	99
Flint	0	0	------	0	7	0	3	0	3	0	0	4
Grand Rapids	0	0	------	0	4	0	0	0	3	0	0	5
Wisconsin:												
Kenosha	0	0	------	0	------	0	0	0	0	0	0	------
Milwaukee	0	0	------	0	1	2	10	0	28	0	0	24
Racine	0	0	------	0	------	0	0	0	1	0	0	------
Superior	0	0	------	0	1	0	0	0	0	0	0	9
WEST NORTH CENTRAL												
Minnesota:												
Duluth	0	0	------	0	------	0	3	0	2	0	0	4
Minneapolis	1	0	------	0	1	0	8	0	8	0	0	1
St. Paul	1	0	------	0	------	1	0	0	9	0	0	4
Missouri:												
Kansas City	0	0	3	0	23	0	8	0	13	0	0	1
St. Joseph	1	0	------	0	30	0	0	0	3	0	0	------
St. Louis	2	0	21	0	1	0	12	4	13	0	0	1

City reports for week ended December 8, 1945—Continued

	Diphtheria cases	Encephalitis, infectious, cases	Influenza		Measles cases	Meningitis, meningococcus, cases	Pneumonia deaths	Poliomyelitis cases	Scarlet fever cases	Smallpox cases	Typhoid and paratyphoid fever cases	Whooping cough cases
			Cases	Deaths								
WEST NORTH CENTRAL—continued												
North Dakota:												
Fargo	1	0	------	0	2	0	1	0	1	0	0	------
Nebraska:												
Omaha	0	0	------	3	2	0	1	0	13	0	0	------
Kansas:												
Topeka	1	0	------	0	2	0	0	0	4	0	0	1
Wichita	0	0	1	0	------	0	2	0	10	0	0	------
SOUTH ATLANTIC												
Delaware:												
Wilmington	0	0	------	0	1	0	1	0	0	0	0	------
Maryland:												
Baltimore	7	0	17	1	2	1	7	0	22	0	0	17
Frederick	0	0	------	0	------	0	0	0	0	0	0	------
District of Columbia:												
Washington	1	0	3	0	1	1	9	2	20	0	0	5
Virginia:												
Richmond	0	0	------	0	1	0	5	1	11	0	0	------
Roanoke	0	0	------	0	------	0	1	0	0	0	0	------
West Virginia:												
Charleston	0	0	------	0	------	0	0	0	0	0	0	------
Wheeling	0	0	------	0	------	0	1	0	0	0	0	------
North Carolina:												
Raleigh	0	0	------	0	------	0	1	0	0	0	0	------
Wilmington	1	0	------	0	------	0	0	0	3	0	0	------
Winston-Salem	1	0	------	0	------	0	4	0	1	0	0	1
South Carolina:												
Charleston	0	0	52	2	1	0	0	0	0	0	0	------
Georgia:												
Atlanta	0	0	60	2	------	0	1	0	3	0	0	------
Brunswick	0	0	------	0	------	0	0	0	1	0	0	------
Savannah	0	0	------	0	------	0	0	0	5	0	0	------
Florida:												
Tampa	1	0	------	0	------	0	2	0	4	0	0	------
EAST SOUTH CENTRAL												
Tennessee:												
Memphis	1	0	15	0	------	0	9	1	4	0	0	11
Nashville	0	0	------	2	4	0	5	0	2	0	0	------
Alabama:												
Birmingham	2	0	13	1	------	0	4	0	4	0	0	------
Mobile	0	0	2	1	------	1	2	1	1	0	0	------
WEST SOUTH CENTRAL												
Arkansas:												
Little Rock	0	0	------	0	------	0	2	0	1	0	0	------
Louisiana:												
New Orleans	4	0	3	3	1	1	3	3	10	0	0	1
Shreveport	1	0	------	0	------	0	5	1	1	0	0	------
Texas:												
Dallas	0	0	2	2	------	0	3	0	7	0	1	1
Galveston	1	0	------	0	------	0	0	0	1	0	0	------
Houston	1	0	------	0	------	0	7	0	7	0	0	------
San Antonio	2	0	1	0	------	0	2	0	1	0	0	------
MOUNTAIN												
Montana:												
Billings	0	0	------	1	------	0	0	0	0	0	0	------
Great Falls	0	0	------	0	------	1	1	0	1	0	0	------
Helena	0	0	------	0	------	0	0	0	0	0	0	------
Missoula	0	0	------	0	------	0	0	0	2	0	0	------
Idaho:												
Boise	0	0	------	0	------	0	0	0	0	0	0	------
Colorado:												
Pueblo	0	0	------	0	------	0	2	0	3	0	0	------
Utah:												
Salt Lake City	0	0	------	0	7	0	0	0	5	0	0	1

City reports for week ended December 8, 1945—Continued

	Diphtheria cases	Encephalitis, infectious, cases	Influenza		Measles cases	Meningitis, meningococcus, cases	Pneumonia deaths	Poliomyelitis cases	Scarlet fever cases	Smallpox cases	Typhoid and paratyphoid fever cases	Whooping cough cases
			Cases	Deaths								
PACIFIC												
Washington:												
Spokane	0	0	------	0	10	1	0	0	1	0	0	7
Tacoma	0	0	------	0	58	0	0	1	0	0	0	11
California:												
Los Angeles	2	0	16	0	12	2	6	3	29	0	0	19
Sacramento	0	0	------	0	12	0	3	1	2	0	0	1
San Francisco	0	0	1	0	57	0	9	6	14	0	0	4
Total	64	1	313	34	511	32	326	34	627	0	8	558
Corresponding week, 1944	88	------	93	39	182	------	372	------	950	0	9	554
Average, 1940–44	71	------	1,195	[1] 64	[2] 1,025	------	[1] 467	------	791	2	14	810

[1] 3-year average, 1942–44.
[2] 5-year median, 1940–44.

Dysentery, bacillary.—Cases: Providence 1; New York 9; Charleston, S. C. 1; Los Angeles 2.
Dysentery, unspecified.—Cases: San Antonio 13.
Rocky Mountain spotted fever.– Cases: Nashville 1.
Tularemia.– Cases: St. Louis 1; Missoula 1.
Typhus fever, endemic.– Cases: Atlanta 5; Savannah 5; Tampa 1; Nashville 2; Birmingham 1; Mobile 2; New Orleans 5; Houston 3.

Rates (annual basis) per 100,000 population, by geographic groups, for the 85 cities in the preceding table (estimated population, 1934, 31,208,900)

	Diphtheria case rates	Encephalitis, infectious, case rates	Influenza		Measles case rates	Meningitis, meningococcus, case rates	Pneumonia death rates	Poliomyelitis case rates	Scarlet fever case rates	Smallpox case rates	Typhoid and paratyphoid fever case rates	Whooping cough case rates
			Case rates	Death rates								
New England	2.6	0.0	0.0	0.0	39	5.2	44.4	10.5	118	0.0	5.2	227
Middle Atlantic	7.4	0.5	16.7	4.2	90	6.9	56.5	2.8	98	0.0	1.9	91
East North Central	12.5	0.0	56.0	5.8	61	5.0	47.6	0.0	108	0.0	0.8	153
West North Central	13.9	0.0	49.7	6.0	121	2.0	69.6	8.0	151	0.0	0.0	24
South Atlantic	18.4	0.0	221.0	8.4	10	3.3	53.6	5.0	117	0.0	0.0	39
East South Central	17.7	0.0	177.1	23.6	24	5.9	118.0	11.8	65	0.0	0.0	65
West South Central	25.8	0.0	17.2	14.3	3	2.9	63.1	11.5	80	0.0	2.9	6
Mountain	0.0	0.0	0.0	16.3	114	16.3	48.8	0.0	179	0.0	0.0	16
Pacific	3.6	0.0	31.0	0.0	271	5.5	32.8	20.0	84	0.0	0.0	76
Total	10.7	0.2	52.4	5.7	86	5.4	54.6	5.7	105	0.0	1.3	93

TERRITORIES AND POSSESSIONS

Puerto Rico

Notifiable diseases—4 weeks ended December 1, 1945.—During the 4 weeks ended December 1, 1945, cases of certain notifiable diseases were reported in Puerto Rico as follows:

Disease	Cases	Disease	Cases
Bilharziasis	6	Mumps	3
Chickenpox	2	Puerperal fever	1
Diphtheria	32	Syphilis	364
Dysentery, unspecified	6	Tetanus	6
Erysipelas	4	Tetanus, infantile	1
Filariasis	2	Tuberculosis (all forms)	512
German measles	3	Typhoid and paratyphoid fever	22
Gonorrhea	162	Typhus fever (murine)	8
Influenza	305	Undulant fever	1
Malaria	580	Whooping cough	102
Measles	29		

FOREIGN REPORTS

CANADA

Provinces—Communicable diseases—Week ended November 17, 1945.—During the week ended November 17, 1945, cases of certain communicable diseases were reported by the Dominion Bureau of Statistics of Canada as follows:

Disease	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Total
Chickenpox		14	3	179	286	63	40	77	119	781
Diphtheria		3	3	59	16	4		2		87
Dysentery:										
Amebic					1					1
Bacillary				1						1
German measles				6	10		1	6	3	26
Influenza		1			11					12
Measles		1	71	235	331	1	13	6	58	716
Meningitis, meningococcus				1		1	2			4
Mumps			3	71	108	15	1	49	21	268
Poliomyelitis				2	1		1			4
Scarlet fever		15	15	168	79	11	6	15	19	328
Tuberculosis (all forms)		4	17	126	51	29	7	4	37	275
Typhoid and paratyphoid fever			2	12	9				2	25
Undulant fever				3	2			1		6
Venereal diseases:										
Gonorrhea		22	26	114	180	54	40	32	110	578
Syphilis		4	3	138	141	18	9	30	42	385
Other forms				1						1
Whooping cough		3		159	36	8	4	9		219

FINLAND

Notifiable diseases—October 1945.—During the month of October 1945, cases of certain notifiable diseases were reported in Finland as follows:

Disease	Cases	Disease	Cases
Cerebrospinal meningitis	9	Mumps	288
Chickenpox	858	Paratyphoid fever	584
Conjunctivitis	43	Pneumonia (all forms)	1,529
Diphtheria	1,823	Poliomyelitis	120
Dysentery, unspecified	31	Puerperal fever	55
Gastroenteritis	3,382	Rheumatic fever	386
Gonorrhea	2,057	Scabies	6,271
Hepatitis, epidemic	1,226	Scarlet fever	327
Influenza	586	Syphilis	618
Laryngitis	69	Typhoid fever	82
Malaria	12	Vincent's angina	54
Measles	48	Whooping cough	1,088

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

NOTE.—Except in cases of unusual incidence, only those places are included which had not previously reported any of the above-mentioned diseases, except yellow fever, during the current year. All reports of yellow fever are published currently.

A table showing the accumulated figures for these diseases for the year to date is published in the PUBLIC HEALTH REPORTS for the last Friday in each month.

Plague

Italy—Taranto.—For the week ended November 24, 1945, 2 cases of plague with 1 death were reported in Taranto, Italy.

Peru.—For the month of October 1945, plague was reported in Peru by Departments as follows: Ancash—Bolognesi Province, 3 cases, 1 death; Santa Province, 1 case; Lima—Chancay Province, 2 cases, including 1 case in the city of Huacho.

Smallpox

Belgian Congo.—For the week ended November 17, 1945, 75 cases of smallpox (alastrim) were reported in Belgian Congo.

Sudan (French).—Smallpox has been reported in French Sudan as follows: November 1–10, 1945, 26 cases; November 11–20, 1945, 83 cases.

Typhus Fever

Belgian Congo.—For the week ended November 17, 1945, 104 cases of typhus fever (murine type) were reported in Belgian Congo.

Turkey.—For the week ended December 1, 1945, 38 cases of typhus fever were reported in Turkey, including 10 cases in Istanbul and 4 cases in Izmir.

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