

matters little, but the plan of the department should be broad enough to care for the problems of clinical medicine, and for this reason the word "medicine" should appear in the title rather than the word "pathology." Such a department should keep in close touch with the department of clinical medicine, and should supplement the facilities of the various hospital laboratories, but, nevertheless, should also work in cooperation with the fundamental laboratory sciences in order to insure a realization of the greatest good to the school. The head of the department should be a man familiar with the problems of clinical medicine trained preferably as a pathologist, and with sufficient knowledge of the possibilities of physiology and chemistry to apply the methods of these subjects to clinical problems. I say preferably a pathologist because the pathologist is more apt to combine clinical training with a knowledge of pathology, bacteriology and the principles of immunity than is the physiologist, chemist or pharmacologist, though any one of the latter might well head such a department.

The work of this department should be the investigation of clinical problems, and not of academic problems of pathology, chemistry, physiology, etc. The latter can still be carried on in the departmental laboratories which have always followed academic lines, and, in truth, are forcing, through their neglect of clinical problems, the establishment of the type of department described. General practitioners, clinical assistants in the school, and even those at the head of clinical departments are constantly meeting problems which demand solution but find no adequate opportunity to investigate them in departments as now constituted.

Another function of this department should be undergraduate instruction to fourth-year men taking research work in clinical medicine as an elective, and also postgraduate instruction for those desiring training in the methods of experimental medicine as the basis for a career as teacher or investigator.

The practice of medicine has developed out of empiricism by the application of the methods of its tributary sciences and whatever is definitely known and understood in medicine can be traced to the application of the experimental method.

In recommending to you that, as practitioners, you keep always the point of view of the investigator, I realize fully that as you go out among so-called "practical" doctors you will find many who sneer at what they term the "scientific" doctor. This view, of which we hear less and less each year, is a survival of the opinion commonly held prior to the development of the sciences of bacteriology and physiologic chemistry, which sciences, by their practical applications to every-day medicine, have perhaps done more to dispel it than is usually realized.

I have read recently an address by President MacLaurin in which he discusses some of the factors which in the course of fifty years have placed the Massachusetts Institute of Technology in its present commanding position. Two of these factors are worthy of the earnest consideration of the trustees and teachers of our medical schools. The first President MacLaurin presents as follows: "There has never been any uncertainty or indefiniteness as to what the institute is aiming at in its scheme of education;" the second, embodies the idea that the success of the educational policy of the institute has been due to the fact that the emphasis has been laid on the "method" and *spirit* of science rather than on *subject*, and that the "learning by doing" or

"do it yourself" idea has been systematically applied. We need, in medicine, a greater appreciation of both these factors by our trustees as well as by our teachers; of educational policy by the former, of educational method by the latter.

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THE RELATION OF THE INTOXICATING DOSE OF HORSE-SERUM TO THE PROTECTIVE DOSE OF ATROPIN IN ANAPHYLAXIS IN THE GUINEA-PIG *

HOWARD T. KARSNER, M.D.

Assistant Professor of Pathology, Harvard Medical School
BOSTON

AND

JOHN B. NUTT, M.D.

PHILADELPHIA

Within the past two years Auer and Lewis¹ and Auer² have shown that atropin sulphate has a distinct protective action against the asphyxia of immediate or acute anaphylaxis in the guinea-pig, and their observations have been repeatedly confirmed.³ Inasmuch as most of these studies have had for their purpose the determination of the physiology of anaphylaxis, no attempt has been made to determine the quantitative relation, if

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* From the McManes Laboratory of Pathology, University of Pennsylvania, aided by a grant from the Committee on Scientific Investigation of the American Medical Association.

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such exists, between the intoxicating dose of the serum and the dose of atropin sufficient to protect the animal from death. The study presented in this paper had for its object the determination of this point.

The problem was attacked from two sides. First, with a minimum fatal dose of horse-serum as a standard, the minimum protective dose of atropin was determined; the toxic dose of serum was then increased and the minimum protective dose of atropin again determined, this procedure being repeated until the dose of atropin became so large as to be markedly toxic for the animal. Second, a maximum dose of atropin, just short of the lethal dose for the animal, was administered and a

All animals were closely observed in their cages and autopsies performed on those that died. It was found in the latter that the lungs were somewhat more congested than is the rule with typical anaphylaxis; the myocardium often showed punctate hemorrhages, and the abdominal viscera were much congested but free from macroscopic hemorrhage.

The first phase of the study occupied about a month. For this reason the second injection of serum with its corresponding dose of atropin was given from twenty-five to fifty-five days after sensitization, the larger doses being given in the later periods. In the second series, however, the work progressed more rapidly, the time of

sensitization being from seven-
teen to eighteen
days; further-
more, the order
of experiment
was reversed in
the second series,
the larger doses
being adminis-
tered first. Any
objection that
might be raised
on account of
the varying time
of sensitization
in the first series
is certainly over-
come by the
method of the
second.

TABLE 1.—RELATION OF MINIMUM FATAL DOSE OF SERUM TO MINIMUM PROTECTION DOSE OF ATROPIN

Number of Animal	Dose Atropin Sulphate in Gm.	Time in Minutes Between Injections	Intoxicating Dose of Horse-Serum in C.c.	Symptoms	Result
555	0.001	10	0.2	Increased respiratory rate with dyspnea.	Recovery.
556	0.001	10	0.4	Severe	Death (5 minutes).
561	0.002	5	0.4	Marked respiratory difficulty	Recovery.
563	0.001	6	0.6	Severe	Death (5 minutes).
564	0.002	7	0.6	Marked respiratory difficulty, convulsions	Recovery.
565	0.003	6	0.8	Severe	Death (5 minutes).
569	0.007	6	0.8	Moderate respiratory difficulty	Recovery.
570	0.008	6	1.0	Severe	Death (1 minute).
571	0.010	6	1.0	Severe	Death (8 minutes).
573	0.015	6	1.0	Severe	Death (5 minutes).
577	0.020	3	1.0	Severe	Death (30 minutes).
579	0.025	3	1.0	Moderate respiratory difficulty	Recovery.
580	0.030	3	1.5	Severe	Death (5 minutes).
585	0.040	5	1.5	Severe	Death (5 minutes).
...	0.040	Moderate increase of respiratory rate	Rapid recovery.
...	0.050	Rapid cessation of respiration	Death (5 minutes).

TABLE 2.—RELATION OF MAXIMUM NON-FATAL DOSE OF ATROPIN AND MAXIMUM DOSE OF SERUM AGAINST WHICH ATROPIN IS PROTECTIVE

Dose Atropin Sulphate in Gm.	Time in Minutes Between Injections	Intoxicating Dose of Horse-Serum in C.c.	Symptoms	Result
0.015	5	1.5	Severe	Death (5 minutes).
0.015	5	1.0	Marked respiratory difficulty; convulsions; coma	Recovery. (Death, 18 hours).
0.012	5	1.0	Severe	Death (5 minutes).
0.012	5	0.8	Severe	Death (5 minutes).
0.012	5	0.7	Marked respiratory difficulty, but without complete cutting off of air supply	Death (6 minutes).*
0.012	5	0.6	Moderate respiratory difficulty; slight general convulsions	Recovery.
0.010	5	0.6	Severe	Death (17 minutes).
0.010	5	0.5	Severe	Death (8 minutes).
0.010	5	0.4	Severe	Death (5 minutes).
0.010	8	0.3	Marked respiratory difficulty; convulsions	Recovery. (Death, 18 hours).
0.008	5	0.3	Marked respiratory difficulty; frothing at nose; convulsions	Death (18 minutes).
0.008	5	0.2	Same symptoms as preceding	Recovery.
0.006	5	0.2	Slight respiratory difficulty	Recovery.
0.004	5	0.2	Marked respiratory difficulty; convulsions	Recovery.
...	..	0.2	Severe	Death (3 minutes).
0.018	General convulsions; respiratory failure	Death (5 minutes).
0.015	General twitching; increased respiratory rate	Recovery.

* Apparently result of exhaustion rather than anaphylaxis.

determination made of the largest amount of horse-serum against which the dose of atropin protected the animal; the dose of atropin was then diminished and the maximum nonfatal dose of serum again determined. This procedure was continued until a point was reached where further reduction in the size of the dose of serum would in itself have failed constantly to produce death. Throughout the study a constant sensitizing dose of 0.05 c.c. of horse-serum was used. After a lapse of sufficient time for the animals to become actively hypersusceptible the dose of atropin was given into the exposed right jugular vein and the intoxicating dose of horse-serum three to ten minutes later into the same or opposite vein.

Table 1 presents the essential results of the first series of experiments. It is seen that the minimum fatal dose of horse-serum (0.2 c.c.) was insufficient to produce death when preceded by the administration of 0.001 gm. of atropin. In order to protect against 0.4 c.c. and 0.6 c.c. of horse-serum, it was necessary to increase the dose of atropin to 0.002 gm. To protect against 0.8 c.c. serum, 0.007 gm. atropin was necessary and against 1 c.c. serum, 0.025 gm. was needed. No dose sufficiently large to protect against 1.5 c.c. serum was possible, for before such a point was reached the animals succumbed to the dose of atropin. The presence of distinct symptoms of anaphylaxis in all those animals which were saved, is sufficient evidence of the fact that they were highly sensitive. It is clear then that there is a quantitative relation between the protective dose of atropin and the intoxicating dose of horse-serum.

4. Karsner, H. T.: Die Lungen in Anaphylaxie und in Anaphylaxie gleichenden Zuständen, Ztschr. f. Immunitätsforsch., in press.

The second series is presented briefly in Table 2. Whereas the atropin used in the first series was from Smith, Kline, French & Co., that used in the second series was from Merck & Co. This fact probably accounts for the variance in absolute dosage of atropin seen in the two tables, for the animals of the two series were from the same general stock. Eighteen milligrams of atropin killed a guinea-pig within five minutes. It is seen that 0.015 gm. protects against 1 c.c. serum, 0.012 gm. against 0.3 c.c. serum, and 0.004 gm. against 0.2 c.c. serum. The minimum protective dose of atropin was not determined. The conclusion that there is a general relationship between the doses of atropin and serum is obvious. From the first series, it appeared that the curve of the dose of atropin rises much more rapidly than that of the dose of horse-serum, but this is not borne out by the results of the second series. That any such exact relationship could be demonstrated, was doubtful from the first because of slight variance in the individual susceptibility to the horse-serum. The same slight individual difference of response is seen in connection with the administration of atropin.

A STUDY OF FEVER IN TUBERCULOSIS WITH REFERENCE TO ITS CAUSATION AND TREATMENT*

FRANCIS M. POTTENGER, A.M., M.D., LL.D.
MONROVIA, CAL.

The fever which accompanies tuberculosis is a symptom poorly understood and unsatisfactorily treated. In recent years the opinion of the profession as to the chief factors in its causation has undergone several changes; and yet the most generally accepted theory at the present time is still unsatisfactory and leaves much to be explained. Since there can be no exactness in its therapy until we have formed some definite idea of its cause or causes, the importance of more study along this line is self-evident.

It must be obvious to anyone who has an opportunity to study patients suffering from advanced tuberculosis and who uses his powers of observation, that the cause of the chronic fever in tuberculosis and the factors which produce the irregularities in its course are numerous and complex. There has been an endeavor to make this subject entirely too simple and the result has been increased confusion.

The finding of bacteria of various kinds in the sputum of tuberculous patients, especially the pus-producers, has given grounds for the belief that tuberculosis, when it reaches the open stage, is a different process from that of early tuberculosis; and that the principal factors in the production of the symptoms in the later stages are the associated bacteria.

Koch¹ made the declaration that a daily temperature curve above 100.4 in a case of pulmonary tuberculosis is due to septic microorganisms and consequently unsuited to treatment with TR. This mixed infection theory was accepted by the profession generally. It called forth many such statements as these: "The tuberculous process is a dry process. If the tubercle breaks down it is because of mixed infection." "Cure the mixed infection and the tuberculosis will cure itself." "Any temperature above 100.4 is due to mixed

infection." Such statements as these were believed in spite of the fact that the débris formed in cold abscesses is moist and yet free from pus microorganisms; and in spite of the fact that patients with acute miliary tuberculosis have high temperature curves before the tubercles have reached the age of softening. See Chart 7.

In order to understand the cause of these fevers, we must take a broader view and look at the question from many standpoints. I believe that the primary causes are at least three in number: the tubercle bacillus and its toxins; associated bacteria and their toxins; and enzymes and the products resulting from their action upon the body cells. This last cause is generally disregarded in discussions on this subject; and, yet, I believe it is a factor of great importance in all cases of advanced tuberculosis of the ulcerative type. I cannot help thinking that one of the greatest dangers to the tuberculous patient arises from the absorption of the products resulting from enzyme action.

Our knowledge of the action of enzymes is as yet comparatively meagre. The writings of Hahn,² Ascoli and Bezzola,³ F. Müller,⁴ K. Meyer⁵ and Opie⁶ are very suggestive and show the value of careful study along this line.

Two factors, the tubercle bacillus and the products of autolysis, are present in all cases of advanced tuberculosis. These factors are present in varying degrees which depend somewhat on the activity of the process. I do not believe that associated bacteria are an important etiological factor in the production of all fevers which rise beyond moderate elevations in advanced tuberculosis, although they are unquestionably so in some.

We are wont to look on tuberculosis of the fibroid form as being due to a type of bacillus of low virulence, believing that the greater the amount of toxins or the more virulent the bacilli, the greater the tendency to tissue destruction. This is a favorable form from the standpoint of cure. I doubt not that the comparatively small amount of autolysis present is also a very important factor in rendering this a favorable form of the disease.

The ulcerative processes, on the other hand, are more serious. We assume that the tubercle toxins are a greater factor in them than they are in the fibroid form. We also must recognize that these forms present a greater amount of autolysis. Where the tubercle bacilli are supplemented by associated bacteria, we have the severest form of the disease; for here we have both the effects of the various bacteria and their toxins and an increased autolysis.

We have attempted with a degree of success to classify these fevers and associate certain types of temperature with certain pathologic conditions. The continuously subnormal temperature we associate with both chronic fibroid tuberculosis and chronic tuberculosis of the ulcerative type during the stage of quiescence. (See Charts 1 and 2.) Doubtless in patients suffering from these types there is a minimum amount of tubercle toxins and products of autolysis entering the blood-stream; consequently there is little or no rise in temperature. Now, if the disease becomes active, however, and the tissues begin to soften, the entire range of temperature assumes a higher level as shown in Chart 3. The morn-

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