

## **ZB MED - Informationszentrum Lebenswissenschaften**

### **The skin reactions, blood chemistry and physical status of 'normal' men and of clinical patients**

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#### **X. DISCUSSION AND DEDUCTION**

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## X. DISCUSSION AND DEDUCTION

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### GENERAL CONSIDERATIONS

In the preceding group of papers, an effort has been made to correlate a number of measurable biologic reactions observed in normal persons and in patients, with each other, with clinical symptoms and with resistance to an infectious disease, i.e., tuberculosis.

In making the tests, we have sought to employ such as might presumably give information concerning the vegetative status of the individual, more particularly the status of the vascular system and the

epidermis. We have sought, furthermore, to determine whether such a vegetative or autonomic status is related to the genotype or whether it is conditional (paratype, and therefore modified by preexisting and latent infection).

Incidentally, we have sought to determine what alterations in the tests that we have employed are indicative of increased or decreased resistance to tuberculosis and what therapeutic deductions might be drawn from such indications.

In view of these particular interests, we cannot avoid a preliminary discussion of certain concepts concerning the vegetative status of the organism and the relation to the constitution in its widest sense.

*Study of the Individual Constitution.*—It is perhaps a natural swing of the cycle that is bringing medical interest back to an analysis of constitution and conditional reactivity. The triumph of the "era of specific etiology" had completely overwhelmed every thought of constitutional differences in reactivity. Obvious clinical experience was discredited and discarded when in conflict with experimental results from the animal laboratory. Correction has followed, however, because of the obvious fallacy of the underlying method. Precise clinical observation and animal experimentation brought incontrovertible evidence that neither in man nor in animals do like reactions necessarily follow like insults. Even the physiologists and the pharmacologists have recognized that normal animals in deep anesthesia offer a test object totally different from sick patients.

Recognition of the importance of differences in the host has come from the epidemiologist, as well. Thus there are differences in reactivity of the skin and the mucous membranes, respiratory, as well as gastro-intestinal, which determine in a large measure one's liability to infection, as Arnold<sup>1</sup> has recently pointed out.

The scientific study of the individual constitution has been under way from two important nonmedical sides. The earlier anthropologist sought to formulate and define racial groups. More recent studies have been broader and have sought to establish general types irrespective of racial grouping. To this comes an added impulse through the modern study of heredity.

Naturally, physicians have sought to make use of these two lines of approach and have applied them particularly to noninfectious diseases—in which "heredity" and "constitution" have never quite been denied. But emphasis on anthropologic and genetic phases savors too much of predetermination to be wholly acceptable to the medical observer. The conditional factors of environment, of tissue experience,

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1. Arnold, Lloyd: J. Hyg. **29**:82, 1929.

of preceding infection, of food, of light, of autonomic training (particularly of the skin), of climate—these must be of equal importance in variable susceptibility to infection, and resistance to one already established. However, many fruitful clinical observations and correlations have taken origin from these two sources. The literature is too large to be discussed, but a recent paper of Draper<sup>2</sup> and his co-workers is illustrative.

*Views of Kraus, Bauer, Verschuer, and Others.*—"Constitution" as a factor in the disposition to disease means different things to different investigators, depending on their particular interests.

We may, for instance, with Leo Loeb regard constitution as a synthesis and vital unification—the "individuality differential"—a view held by Martins and his school, as well; or go to the opposite extreme with Draper and examine everything from a purely anthropometric point of view. Bauer,<sup>3</sup> on the other hand, discounted the value of the various anthropometric "indices" of this school, but nevertheless limited the term to the "genotype." Pfaundler stressed the importance of environmental (conditional) forces, i. e., the "paratype."

Many physicians have sought to group persons according to the presumptive reactivity of their glands of internal secretion and speak of the "hypophyseal," the "thyroid," or the "adrenal," type. Stern worked out a rather elaborate "glandular formula" and Pende<sup>4</sup> theorized considerably in this direction. Of course, such a classification is attractive because it makes more easy the correlation of genotype and phenotype, the endocrine glands acting, presumably, in the modification of the inherited structure. With definite evidence of nervous control of the suprarenal (Cannon) and thyroid glands (Ascher<sup>5</sup>), the circles of biologic control become ever more intricate.

Kraus<sup>6</sup> and his school, primarily clinical in orientation, stressed the idea of "personality," the term "Syzygiologie" having been coined for the new field.

The novelty of this point of view lies in the fact that it emphasizes the periphery of the organism, the region in which the metabolic processes are going on, and particularly the exchange between the cell and its environment, i. e., the membrane of the cell. As components of this system are to be regarded all factors that play into this intricate

2. Draper, G.; Allen, Grace, and Spock, Jane: *Studies in Human Constitution*, *Clinical Genetics*, J. A. M. A. **92**:2149 (June 29) 1929.

3. Bauer, J.: *Klin. Wchnschr.* **8**:145, 1929; *Ann. Int. Med.* **2**:127, 1928.

4. Pende, Nicola: *Constitutional Inadequacies*, Philadelphia, Lea & Febiger, 1928.

5. Asher, L., and Pfluger, O.: *Klin. Wchnschr.* **6**:1614, 1927.

6. Kraus, F.: *Allgemeine und spezielle Pathologie der Person*, Leipzig, Georg Thieme, 1926, pt. 1.

exchange, either accelerating or inhibiting it, as for instance, water, the colloid electrolytes, salts, combinations of cations, the buffer system, hormones, definite endogenous and exogenous irritants and poisons, as well as the catalysts.

The local and transient balance of this intricate mechanism is not determined only by the degree, the direction and the rapidity of the specific cell functions, but also by the degree and directions of the vegetative nervous irritability. The vegetative nervous system has the function of regulation—regulation in the sense that it determines to a large degree the distribution of the electrolyte reserves from one place to another.

In the logical development of this idea, Kraus came to the conception of a phylogenetically long established "Tiefen-person," that individualism of the most vital and most profound sort, a vital component of the constitutionally and primarily ordained protoplasm. This fundamental individualism is to be placed in contrast with the centrally organized and much younger cortical personality.

One of the great advances which lies in this concept of the constitution is, we believe, the fact that it emphasizes the impossibility of trying to coordinate isolated observations on both nervous systems (vegetative and central) without a proper regard for all the other factors of the vegetative apparatus. On the other hand, it is of use in the proper evaluation of the vegetative nervous system for all of our clinical problems. We shall refer repeatedly to the general idea.

Daniélopou<sup>7</sup> also stressed the importance of the periphery, i. e., the terminal organ as the site at which the basic orientation of the individual is determined.

Perhaps, the simplest and most useful of medical points of view of constitution is that of von Verschuer,<sup>8</sup> who defined it merely as "the relative (constitutional) status in the terms of resistance," stressing, nevertheless, that constitution (= Körperverfassung of Tandler = status,) is an organically fixed condition.

Bauer emphasized the importance of constitution in differentiating a group of biologically inferior persons—extreme variants from the normal—in adaptability, in vitality and in resistance. This, too, might seem a most useful concept for the physician.

He was content for practical purposes to group persons as:

| Slender                                      | Normal      | Heavy                    |
|----------------------------------------------|-------------|--------------------------|
| (Dolicho, or asthenic type with small heart) | (Normotype) | (Brachy, or pyknic type) |

7. Daniélopou, D.: Presse méd. **31**:649, 1923.

8. Von Verschuer, O.: Klin. Wchnschr. **8**:769, 1928.

The French have always associated the first group with lessened resistance to pulmonary infections; the latter group with gout, rheumatism, diabetes and arteriosclerosis.

Sigaud made extensive use of the type terms muscular, respiratory, digestive and cerebral. Kretschmer added the study of character in relation to constitution, the conscious reactivity being obviously a part of the general constitutional makeup. To these and related classifications must be added those concerned chiefly with the functional status of the endocrine glands and finally the grouping of persons as primarily sympathetotonic or vagotonic.

While we cannot review the recent contribution of Brown<sup>9</sup> at great length, we cannot but quote the pertinent conclusions that he has drawn from an elaborate and most convincing series of animal experiments that illustrate certain phases of constitutional resistance to disease. Brown wrote:

The elementary conception of constitutional variation and its relation to disease which I have attempted to outline involves only one assumption, and that is that all functional activities of the body are either performed or controlled by organs and that the organs are provided in such numbers and amounts as are necessary for the performance of their appointed functions. One need not know the function of a single organ in order to show that persons differ from each other in respect of their organic equipment, or that they are persons and not standard machines or standard mediums for the growth of pathogenic microorganisms. It can be shown that variations in the mass and mass relations of organs are constantly occurring in response to demands made by the changing conditions of life and that these changes in organic constitution are accompanied by variations in chemical constitution, all of which may be confined within the usual limits of normal, for they are normal. It can also be shown that these differences and variations in physical and chemical constitution are associated with differences and variations in functional activity and susceptibility to disease or in the degree of natural immunity.

In studying our material, we have disregarded all anthropometric factors and have used only the grouping of slender, normal and heavy, as based on the weight/length ratio.

#### THE SLENDER (ASTHENIC) VERSUS THE HEAVY PERSON

It will be recalled that our two extremes based on such a classification showed, in general, the conditions set forth in table 1.

Does such a classification have any necessary relation to the concept of "sympathetotonic type" or "vagetonic type?"

*The Sympathetic Versus the Vagetonic Type.*—When we examine the ten persons with the extreme "sympathetotonic" reactions and the

9. Brown, Wade H.: Constitutional Variation and Susceptibility to Disease, Arch. Int. Med. 44:625 (Nov.) 1929

ten with the extreme "vagotonic" reactions to epinephrine, as determined on the basis of the systolic reaction, we find the characteristics to be as shown in table 2. While the two classifications are by no means identical, we see that in both we deal with slender persons who have a

TABLE 1.—*Characteristics of Slender Persons and Heavy Persons of Extreme Type*

|                                              | Slender *<br>(Weight/Length Ratio 1.87) | Heavy +<br>(Weight/Length Ratio 2.32) |
|----------------------------------------------|-----------------------------------------|---------------------------------------|
| Capillary permeability .....                 | 0.63 greater                            | 0.57                                  |
| K/Ca ratio .....                             | 1.81 lower                              | 2.08                                  |
| Sugar .....                                  | 69.50 lower                             | 73.80                                 |
| Basal metabolic rate.....                    | +10.00 greater                          | +7.00                                 |
| Muscle reaction .....                        | 2.38 greater irritability               | 3.48                                  |
| Epinephrine pulse pressure.....              | +12 increased effect                    | +8.00                                 |
| CO <sub>2</sub> -combining power .....       | +58.5 slightly more alkaline            | 54.4                                  |
| Cholesterol .....                            | 210 lower                               | 225                                   |
| Reactivity of skin                           |                                         |                                       |
| Resistance of skin to electric current ..... | 0.66 higher                             | 0.28                                  |
| Reaction to ice.....                         | 21 longer                               | 19                                    |
| Kromayer light erythema time..               | 2.21 longer                             | 2                                     |
| Epinephrine wheal .....                      | 18.8 smaller                            | 20                                    |
| Morphine flare .....                         | 14.8 smaller                            | 15.8                                  |
| Thyroxin wheal .....                         | 12.2 larger                             | 11                                    |
| Thyroxin flare .....                         | 4.8 larger                              | 3.2                                   |
| Caffein wheal .....                          | 19.2 larger                             | 18                                    |
| Caffein flare .....                          | 2.8 larger                              | 2.4                                   |

\* Microsplanchnic type; phthisic habitus; asthenic habitus; linear type of Stockard; Pende presupposes an increase in basal metabolism; predominantly "sympatheticotonic."

† Megalosplanchnic type; "apoplectic" constitution; pyknic type of Kretschmer; lateral type of Stockard; Pende presupposes increased cholesterol, increased potassium, relative alkalosis and chloride retention; predominantly "vagotonic."

TABLE 2.—*Characteristics of Sympatheticotonic Persons and Vagotonic Persons of Extreme Type*

|                                          | Sympatheticotonic Group | Vagotonic Group |
|------------------------------------------|-------------------------|-----------------|
| Capillary permeability * .....           | 69.1 increased          | 64.5            |
| K/Ca ratio * .....                       | 1.74 lower              | 2.04            |
| Basal metabolic rate.....                | +10.4 equal             | +10.9           |
| Muscle reaction .....                    | 4 increased             | 2.3             |
| Epinephrine pulse pressure *.....        | +21.4 higher            | -1.3            |
| CO <sub>2</sub> -combining power .....   | 54.6 lower              | 57.7            |
| Cholesterol * .....                      | 209 lower               | 218             |
| Reactivity of skin                       |                         |                 |
| Resistance of skin to electric current.. | 0.41 equal              | 0.43            |
| Reaction to ice.....                     | 23 longer               | 20              |
| Kromayer light erythema time.....        | 1.72 shorter            | 1.95            |
| Epinephrine wheal * .....                | 19.4 smaller            | 20              |
| Epinephrine flare .....                  | 9.4 larger              | 8.3             |
| Thyroxin wheal * .....                   | 12 larger               | 11.4            |
| Thyroxin flare * .....                   | 4 larger                | 3.2             |
| Caffein wheal * .....                    | 21 larger               | 19.2            |
| Caffein flare * .....                    | 2.6 larger              | 2.4             |

\* The reactions indicated by (\*) are identical in direction in both the "slender" and the "sympatheticotonic" groups.

low K/Ca ratio, an increased vascular reaction to epinephrine, lower cholesterol, somewhat less reaction of the skin to epinephrine, and a greater reaction of the skin to thyroxin and caffein.

The "slender" person in contradistinction to the heavy person has, furthermore, an increased basal metabolic rate, a more irritable musculature with a slightly lower CO<sub>2</sub>-combining power of the serum, higher

resistance of the skin to electric current and a longer Kromayer light reaction time.

The "sympatheticotonic" person in contradistinction to the "vago-tonic" person has no difference in the basal metabolic rate, less muscular irritability and a lower  $\text{CO}_2$ -combining power, no difference in resistance of the skin to electric current and a slightly slower Kromayer light reaction time. The blood pressure is lower.

*The Thyroid Type.*—If we now compare the extreme "thyroid" type, we also have a slender person (ratio 201) with increased capillary permeability (ratio 72) and increased basal metabolic rate (+48), no change in the K/Ca ratio, but an increase in the total serum calcium and potassium; the skin blister time is shortened, the ice reaction time is rapid, the resistance of the skin to electric current is low and the epinephrine wheal is small.

Pende<sup>10</sup> assumed that the sympathetic type is characterized by a state of defense and aggression (raising of blood pressure and pulse rate, glycogenolysis, etc.) the parasympathetic type by emphasis on intestinal and reproductive phases (glycogen formation, congestion of sex organs, etc.).

Goldstein, too, stressed the general catabolism, irritability and aggressiveness of the sympatheticotonic status as contrasted with the euphoria and hypomaniacal status of the vagotonic psychopathic person.

In this country Cannon, in particular, has studied the sympathetic nervous apparatus and recently demonstrated the nonvital character of these nervous impulses. Even the medullary chromophil tissue of the suprarenal glands in contrast with the cortical portions of the glands—is apparently without vital importance. After bilateral sympathectomy, emotional excitement does not cause erection of hairs, consistent increase of blood sugar, polycythemia, relative increase in mononuclear cells or marked rise of arterial blood pressure. Sympathectomized animals are sensitive to cold, and having lost the means of conserving heat, they lose heat more rapidly than normal animals. The basal metabolism usually falls somewhat after sympathectomy, especially after the cervical portion is excised. Though seemingly unessential under "normal conditions," it is of great service at times of critical emergencies when it adjusts the internal organs of the body for the use of the mechanisms responding to external exigencies.

The experiments of Cannon<sup>11</sup> and his co-workers are of particular importance because they demonstrate that the humoral factors (particularly the chemical) of integration of vegetative phenomena, after all,

10. Pende, N.: *Riforma med.* **41**:241, 1925.

11. Cannon, W. B.: *Science* **69**:502, 1929.

represent the older and underlying mechanism and must be considered in all of our medical problems, the nervous system being merely the more recent and less essential factor. As such, however, it may be the first to become disorganized and the first to give rise to clinical symptoms.

#### AUTONOMIC EQUILIBRIUM

The original concept of Eppinger and Hess of sympathicotonic and vagotonic types has unfortunately been so impressed on the medical mind that more modern developments dealing with the autonomic status of the individual have found but slow acceptance.<sup>12</sup> It should be understood, as Ascher has so clearly stated, that the individual cells of the body are functionally distinct individuals, regulating their existence primarily through chemical means (this involves ionic, molecular, hormone and catalytic processes) and secondly, through nerve impulses, either central or vegetative.

*Daniélopou's Concept of Vegetative Tonus.*—Daniélopou<sup>13</sup> postulated three laws concerning reactions of the autonomic response which have an important bearing on the sympathicotonic and vagotonic conception.

In the first place, substances that influence one factor also influence the other; i. e., they are amphotropic. The evidence for this has been accumulating for many years, and the literature has been reviewed repeatedly.<sup>14</sup>

With eye pressure, Daniélopou demonstrated that the impulses proceed along two pathways, along the parasympathetic to the heart and along the sympathetic to the gastro-intestinal tract. Daniélopou concluded that the vegetative tonus is maintained by amphotropic factors: one, peripheral and humoral, the other centrifugal, from the sympathetic and parasympathetic centers. When the tonus of one side is increased, the other automatically follows.

In clinical medicine, we frequently see, however, an apparent overbalance of the one system. Daniélopou believed that the preponderance depends on the intensity of the impulses. In pharmacologic experiments, we know the importance of the size of the dose of the autonomic drugs. The effect on an organ depends on the general vegetative status of the entire organism, i. e., a minimal dose of epinephrine, which in the normal person results in parasympathetic stimulation (i. e., slowing heart rhythm and lowering of the blood pressure) causes increased blood pressure and pulse rate in the sympathicotonic person; on the other

12. Editorial, Constitutional Vagotonia, J. A. M. A. **93**:1387 (Nov. 2) 1929.

13. Daniélopou, D.: Klin. Wchnschr. **7**:1748, 1928.

14. Pick, E. P.: Arch. f. Physiol. **79**:183, 1920; Deutsche Ztschr. f. Nervenhe. **106**:238, 1928. Sollman, Torald: Physiol. Rev. **2**:479, 1922.

hand, the dose which in the normal person causes increased blood pressure and pulse elicits a parasympathetic effect in the vagotonic person. These so-called paradoxical or inverted effects are, of course, well known. Finally, Danielopolu postulated a circular mechanism, the diagrammatic presentation of which we have reproduced.

*Autonomic Equilibration and Increasing Amplitude of Response.*—

At this point, we should like to illustrate another fundamental phenomenon constantly met with in the study of autonomic regulation: first, the constant manifestation of the effort of the cell and the organ and the organism as a whole to maintain an equilibrium, disturbances of the balance being always followed by rhythmic and wavelike fluctuations in a direction opposite to the original change in status; second, the frequent manifestation of a progressive increase in amplitude in such rhythmic fluctuations following single impulses. We give charts for three typical experiments. The first shows the peripheral leukocytic fluctuations following bulbus pressure in the dog; the second, following irradiation of the skin. The third shows chemical fluctuations following a bacterial insult.

In a normal dog, a lymph fistula was made under local anesthesia. After reaction, bulbus pressure was maintained for seven minutes at the time indicated in chart 2. Peripheral leukocyte counts were made at frequent intervals, with determinations of lymph concentration, sugar, calcium and erepsin. The leukocyte count which reveals the fluctuations in the peripheral tonus (dilatation of vessels—leukocytosis; contraction, stasis, leukopenia) clearly indicates the rhythmic fluctuations of increasing amplitude initiated by this stimulus.

An almost identical picture is illustrated in chart 3. This dog had an exposure for seven and a half minutes to ultraviolet light applied over the abdomen, following recovery from incannulation of the thoracic duct under local anesthesia. It will be observed that the leukocyte curves show minor oscillations of increasing amplitude, with three chief periods of leukocytosis, the first 30 minutes, the second 75 minutes and the third 130 minutes, after the exposure. Calcium diminution occurs at approximately the same intervals.

In chart 4 we are able to illustrate an even more convincing picture with corresponding calcium fluctuations. In this case we deal with a bacterial insult. A pregnant dog was operated on under local anesthesia and an incannulation of the thoracic duct was made. After a period of observation following the operation, the continuous intravenous injection of a dilute suspension of *Bacillus coli* in saline solution commenced at 11:25 (first arrow on chart).

The curves at the top of the chart indicate the sugar level and the double line the K/Ca ratio (calcium level in black columns; potassium, in white columns).

The second group of curves indicate the rectal temperature and the volume of urine; the third, the lymph protein volume, the globulin per cent (in black) and the leukocyte curve. Inasmuch as the volume was sufficient to permit chemical analysis in five-minute samples, the actual fluctuation in the K/Ca ratio more accurately reflects the changes that occur in the tissues than has been possible in most of our other experiments.

It will be observed that the initial reaction was a slight increase in the calcium. A second and larger increase followed, reaching a maximum approximately sixty

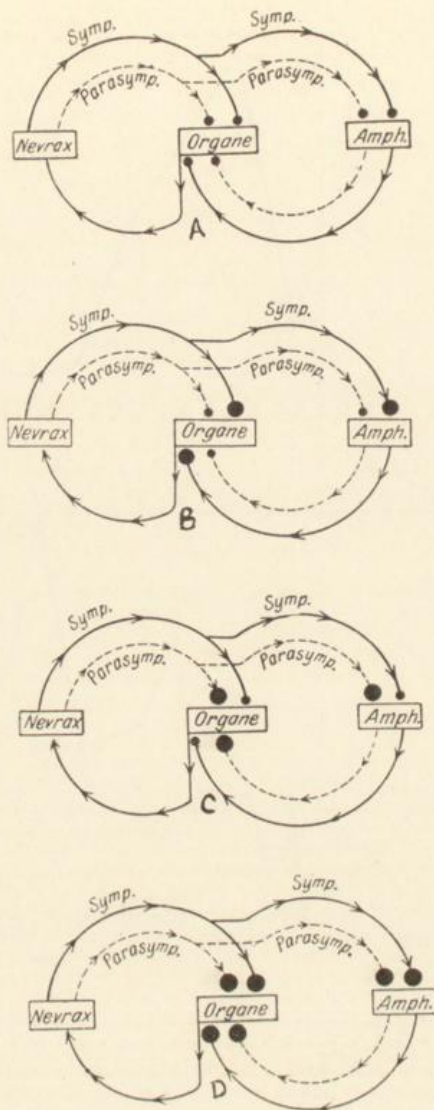


Chart 1.—Amphotropic circular mechanism of the autonomic tonus and its variations (from Danielopolu, D.: *Klin. Wehnschr.* **7**:1748, 1928). Diagram *A* indicates the normal status, i. e., equal sympathetic and parasympathetic amphotropism indicated by the equal size of the black dots.

Two factors are outlined: the peripheral amphotropic humoral factor (involving calcium, potassium, epinephrine, choline, pituitrin, cholesterol, etc.) keeping the sympathetic and parasympathetic nerve endings in a state of normal tone and maintaining a constant equilibrium. The organ itself, through the centripetal connections, acts to maintain the proper tonus of the vegetative sympathetic and parasympathetic centers. These centers again send centrifugal impulses via the sympathetic and parasympathetic tracts, which also act in maintaining tone in receptors. This forms the primary circle; a secondary one is associated. The glands of internal secretion, such as the suprarenal glands, which secrete amphotropic substances, have a dual vegetative innervation. We also know from Loewi's work that the organs give off amphotropic substances during functional activity. Grouped together, they may be called amphotropic secretory organs; in the charts they have been designated as "Amph." The impulses coming from the centers maintain a variable rate of activity in them, and this in turn regulates the peripheral factor.

*B*, sympathetic status, the sympathetic dot is heavier.

*C*, parasympathetic status, the parasympathetic dot is heavier.

*D*, amphotonic status, both dots are heavier.



Chart 2 (exper. 18).—Rhythmic tonus waves (leukocyte curve) of increasing amplitude following bulbus pressure in dog.

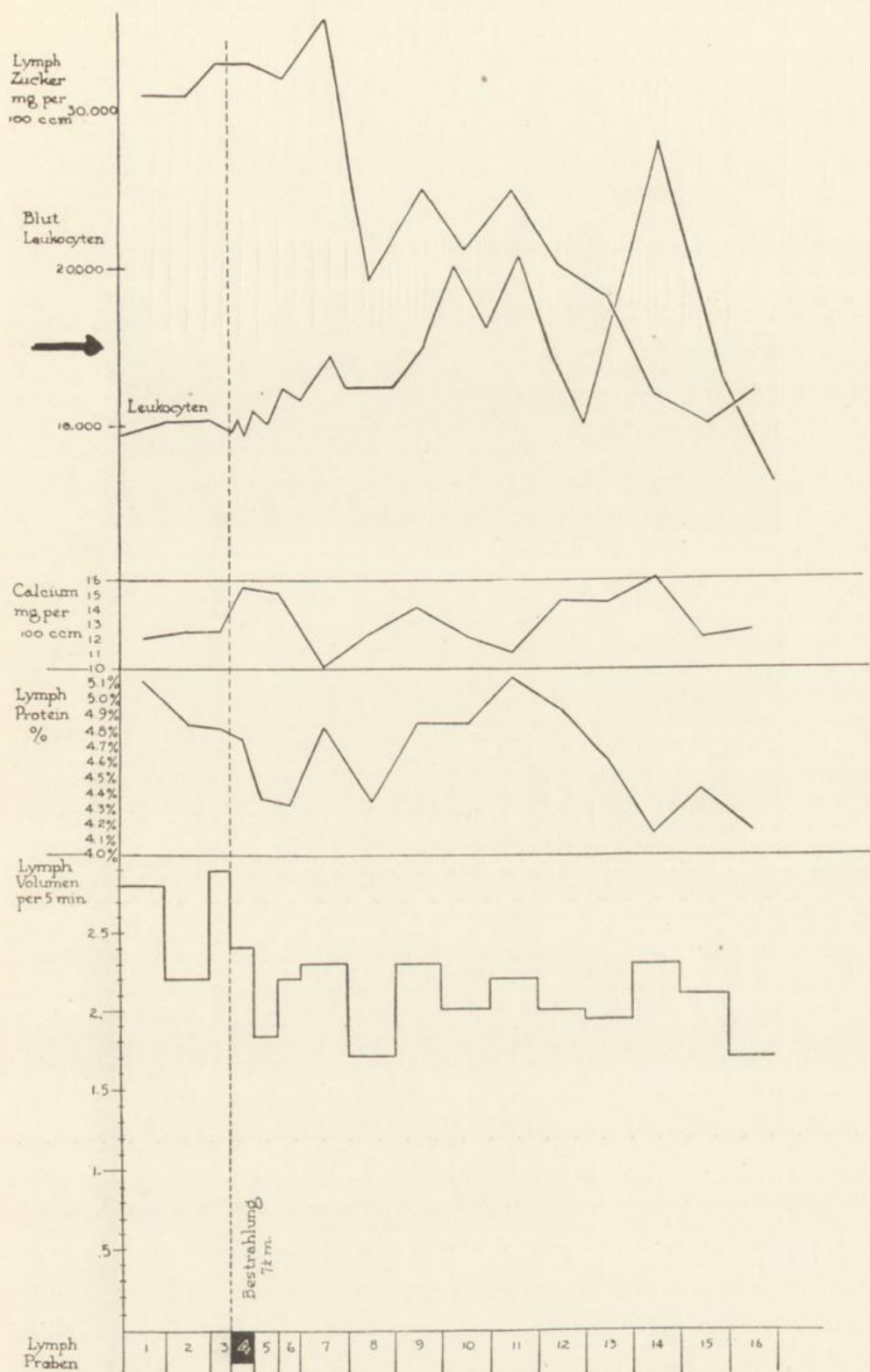


Chart 3 (exper. 2).—Rhythmic tonus waves of increasing amplitude following ultraviolet irradiation (from Petersen, W. F., and Von Oettingen, W. F.: Veränderungen der Lymphe beim Hunde nach Quarzlichtbestrahlungen, Arch. f. exper. Path. u. Pharmacol. **128**:160, 1927).

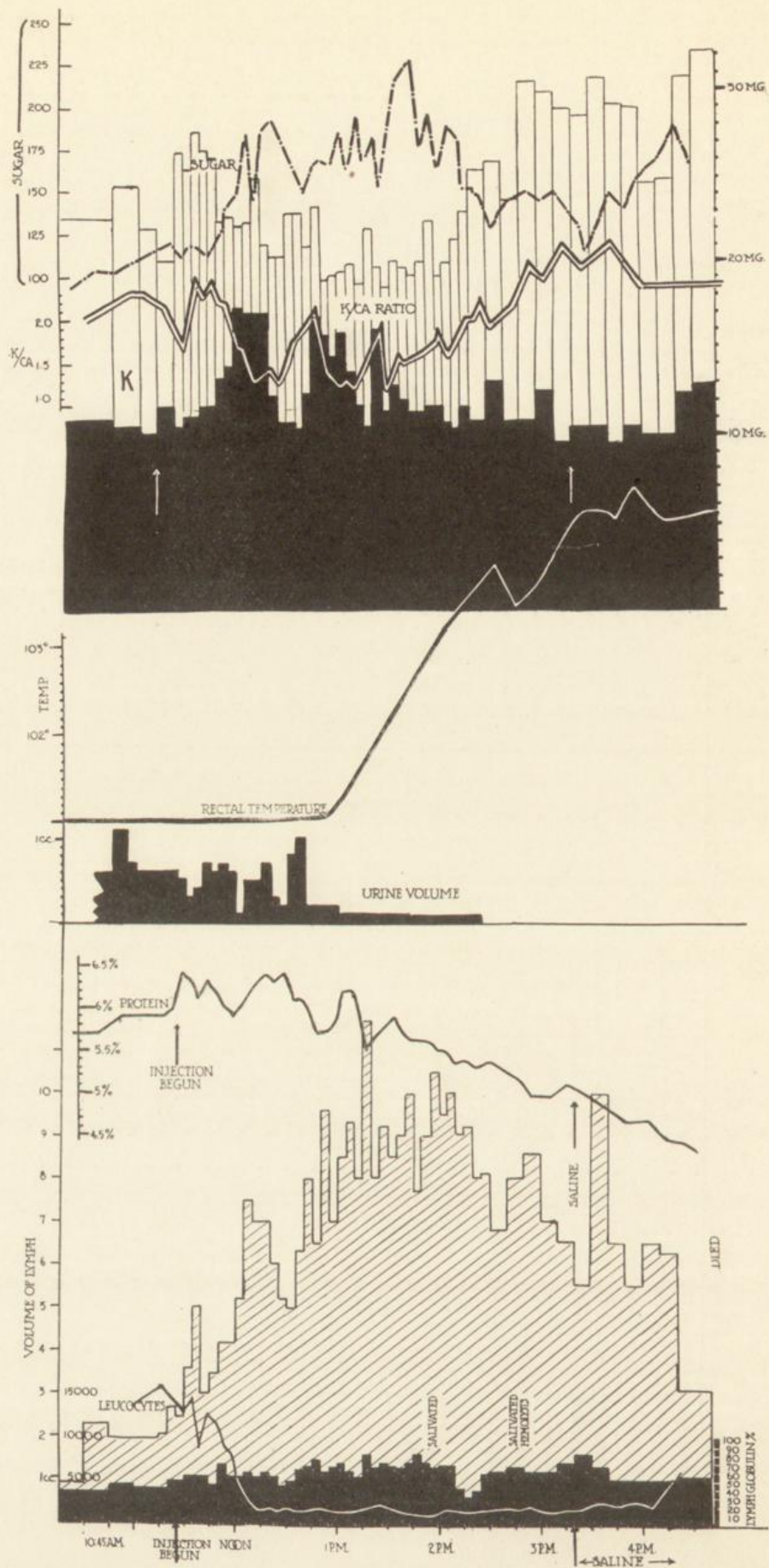


Chart 4 (exper. 18).—Typical fluctuations in the calcium and the potassium of the lymph with continuous injection of *Bacillus coli* (from Petersen, W. F.; Milles, G., and Müller, E. F.: *Ztschr. f. d. ges. exper. Med.* **60**:336, 1928).

minutes after the beginning of the injection, another after two hours and the fourth after two and a half hours. After that, the effects were effaced by a large amount of potassium coming from the injured red blood corpuscles. These chemical changes find their counterpart in the sugar curve, the lymph volume and the concentration of lymph protein. In this particular experiment, the leukocytes do not show a corresponding fluctuation, because the upset of the normal vascular splanchnoperipheral balance is so great that the peripheral region becomes fixed in a sympathetic status.

These fluctuations of alternating periods of stimulation and inhibition which find their expression in changes in the K/Ca ratio, in the sugar level, in lymph volume and in protein alterations, etc., form part of the splanchnoperipheral balance which Müller and one of us have discussed in various papers.<sup>15</sup>

In view of the foregoing observations, it is to be remembered that not only the general and local autonomic tonus is to be taken into consideration when the reaction of tissue is studied, but that one is dealing with a constantly fluctuating, labile condition and therefore the time element and the particular phase will always modify the response of the tissue.

Obviously, stimuli reaching a cell or organ when on the up or down grade, or at the peak, as contrasted with the trough, of a wave, may bring about diametrically opposite physiologic reactions. Tinel, Santenoise and Laurent<sup>16</sup> have made analogous observations in anaphylactic shock. They found that such shock always accelerates the preceding condition (status); and that then a reversal sets in. "Vagotonic" persons, for instance, have first increased excitability of the vagus; then a reversal sets in during which no further shock can occur. In the "sympatheticotonic," on the other hand, vagotonia is secondary, during which the patient is in a condition receptive to a new shock and to the continued effect of any circulating antigenic substance. With such a mechanism, one can more readily understand this reciprocal action of the autonomic tonus on shock and of shock on tonus.

*Schilf's View of Autonomic Antagonists.*—Before leaving the more general aspects of this subject, we shall have to review briefly the views of Schilf.<sup>17</sup> In line with the work of the Cannon school, Schilf pointed out that the older idea of a balanced nervous mechanism in the sense of a sympathetic-parasympathetic central antagonism, does not hold true for all tissues, there being a number in which only a sympathetic or only a parasympathetic innervation can be demonstrated. In the skin, for instance, we know of only sympathetic nerves for the sweat glands. Of greater importance for our problem, we know only of sympathetic nerves for the blood vessels. In only a limited region can parasympathetic (dilator) innervation be demonstrated, and the assump-

15. Müller, E. F., and Petersen, W. F.: *Klin. Wchnschr.* **5**:53, 1926.

16. Tinel, J.; Santenoise, D., and Laurent, O.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:471, 1923.

17. Schilf, E.: *Klin. Wchnschr.* **6**:29, 1927.

tion that, because sympathetic fibers are vasoconstricting, vasodilatation must be accomplished by parasympathetic fibers, is at the least, not established, indeed is probably fallacious. Schilf frankly stated that this problem of nerve control of vascular dilatation is still an unsolved problem, an opinion which is apparently shared by Stöhr.<sup>17a</sup> He emphasized that the organs predetermine their own course of action, and that we should stress organ reactions rather than attempt to force through a rigidly conceived idea of a vasomotor mechanism which actually is controverted by experimental facts. Particularly, the pharmacologic interpretation has done much to confuse the picture rather than to clarify it. The effect of a nerve impulse to an organ depends on the state of the organ to which that impulse is delivered. Schilf emphasized this, in particular, because "sick" organs react differently from normal organs.

Schilf's real contribution is his analysis of the fact that apparently antagonistic autonomic reactions (sphincterbladder mechanisms, for instance) can occur without nervous control and that such reactions are, from a broader point of view, not antagonistic but synergistic. So, too, for example, the control of temperature regulation, which, according to Cannon<sup>18</sup> is largely sympathetic. Here, again we are dealing with an apparent balance of sympathetic and parasympathetic impulses; apparently antagonistic, actually synergistic.<sup>19</sup>

A number of Russian physiologists and clinicians have reached conclusions similar to ours, among them Platoff.<sup>20</sup>

To this comes a more recent possibility that the sympathetic nerves are not only efferent, but also afferent, and may play a considerable rôle in periodic differences in the sensitivity to impulses;<sup>21</sup> and the contention of Viale<sup>22</sup> that the increase in the heart rate that follows cutting the vagi, is really due not to the deletion of inhibitory impulses, but to the increased secretion of epinephrine that follows. The correctness of such experiments must, of course, be first determined.

The discussion up to this point has, we believe, shown that we cannot arbitrarily select any one of the numerous factors that are involved in tissue activity and make it alone responsible for the clinical alterations that we see in every day practice. We are seldom justified in trying to establish purely endocrine imbalances; much less are we

17a. Stöhr, Philip, Jr.: *Mikroskopische Anatomie des vegetativen Nervensystems*, Berlin, Julius Springer, 1928.

18. Cannon, W. B.: *Tr. A. Am. Phys.* **44**:41, 1929.

19. Petersen, W. F., and Müller, E. F.: *The Splanchnoperipheral Balance During Chill and Fever*, *Arch. Int. Med.* **40**:575 (Nov.) 1927.

20. Platoff: *Russk. Klin.* **5**:3, 1926.

21. Förster: *Schless. Gesellsch. f. väterland. Kultur*, Breslau, *abst. Klin. Wchnschr.*, Feb. 1, 1929.

22. Viale, G.: *Boll. d. Soc. ital. di biol. sper.* **2**:54, 1927. Smirnow, A. J., and Schinoky, W. F.: *Ztschr. f. exper. Med.* **55**:24, 1927.

justified in trying to establish a purely nervous imbalance. We might do best by following Bergmann and speaking of certain groups of patients as "vegetatively stigmatized," and we should definitely discontinue regarding only the readily observable smooth muscle reactions as criteria of systemic autonomic change. The smooth muscle, with its tonus, represents primitive contraction; the twitch of the voluntary muscle appears much later. But this tonus requires little oxygen; it is a vegetative phenomenon regulated by the bio-electric (ionic) means. Later, we superimpose vegetative and voluntary nerves, as well as the specialized amines and vegetative poisons, epinephrine, histamine, choline, etc., which can obviously act, as Langley suggested, directly on the cell membranes by changing colloidal structure, not necessarily on the nerve endings.

And if, in clinical parlance, we continue to use the term "sympatheticotonic" or "vagotonic" in lieu of the broader one of "autonomic dysfunction" or "vegetative stigmatism," we should have clearly in mind the many reservations which we have indicated.

The entire field of the "autonomic nervous system" has been thoroughly reviewed by Kuntz;<sup>23</sup> or one may consult the older book of Müller.<sup>24</sup> The more clinical "Vagotonies, Sympathicotones and Neuritonies" by Guillaume<sup>25</sup> also offers much detailed information.

#### THE CHEMICAL EQUILIBRIUM

In the preceding discussion, we have traced the changes which have taken place from the original concept of functionally antagonistic sympathetic and vagus centers with resulting sympatheticotonia and vagotonia, to the present view with its emphasis on the autonomic status of the periphery. In the peripheral organ, we have already seen the presumptive influence of its milieu, its hormone content, its chemical equilibrium, etc., in determining local autonomic tonus and have also made note of the possibility of the effect of remote organs on such local tonus.

*Rôle of Calcium and Potassium and the H-Ion Concentration.*—The interest in the chemical phase goes back to the work of Jacques Loeb, who first emphasized the importance of the ions, particularly of calcium and potassium ions, in the control of cellular functions. The more recent and intensive cultivation of the field, particularly the application to clinical problems, comes from the school of Krause. Thus, Zondek,<sup>26</sup>

23. Kuntz, Albert: *The Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1929.

24. Müller, L. R.: *Die Lebensnerven*, ed. 2, Berlin, Julius Springer, 1924.

25. Guillaume, A. C.: *Vagotonies, Sympathicotones and Neurotonies*, ed. 2, Paris, Masson & Cie, 1928.

26. Zondek, S. G.: *Klin. Wchnschr.* **2**:382, 1923; **3**:707, 1924; **4**:905, 1925; *Die Electrolyte*, Berlin, Julius Springer, 1927.

after calling attention to the activity of ions on colloids in influencing their dispersion, hydration, etc., stressed the fact that two balances are of greatest physiologic importance, the H-ion concentration and the K/Ca ratio.

In general, we may accept the following:

With cellular activity, the calcium concentration of the cell membrane is diminished. Calcium leaves the cell, and there is a relative increase in potassium in the cell. The cell is more permeable, the protein becomes hydrated.<sup>27</sup>

From this stage of activity, as one pole, the opposite extreme, of rest, is reached, with apparently a relative increase of calcium at the cell surface, relative impermeability, dehydration, etc. Calcium and potassium concentrations are therefore indicative of the swing of the pendulum of cellular activity (Osterhout; <sup>28</sup> Lillie <sup>29</sup>).

These changes are cellular changes. They may be initiated by external impulses, a nerve impulse, for instance; the tone, however, will depend on a mechanism such as Danielopolu described. The concentration of either calcium or potassium in the serum may mirror the cellular change; but it must be clear that the serum levels do not necessarily change the reactions of the cells. The alteration of ionic concentration may ultimately bring about an abnormal vegetative reaction, but we may, and frequently do, find unipotential autonomic reactions without a corresponding consistent blood chemical picture.

The temptation is great to associate certain effects brought about by the increase of ionic concentration with definite autonomic nerve tonus; for instance, calcium with sympathetic effects, and potassium with vagus effects.

This association has been an outcome largely of clinical observations with injections of epinephrine hydrochloride. In the analysis which we present of our material on the basis of the epinephrine reaction, we have clearly shown that, while our outstanding "sympatheticotonic" persons had a lower K/Ca ratio (i. e., have relatively less potassium) than the outstanding "vagotonic" persons, there are many exceptions to the rule. But the fact that we find many exceptions to the rule, as did Brems,<sup>30</sup> and the fact that Jendrassik and Czike<sup>31</sup> could find no constant correlation at all between the reaction to epinephrine and the K/Ca ratio do not for a moment vitiate the importance of the ion balance for these autonomic alterations. We must not forget that the epinephrine

27. Zondek, S. G.: *Biochem. Ztschr.* **132**:362, 1922.

28. Osterhout, W. J. V.: *Injury, Recovery and Death in Relation to Conductivity and Permeability*, Philadelphia, J. B. Lippincott Company, 1922.

29. Lillie, Ralph: *Protoplasmic Action and Nerve Actions*, Chicago, University of Chicago Press, 1923.

30. Brems, A.: *Acta med. Scandinav.* **66**:207, 1927.

31. Jendrassik, L., and Czike, A.: *Klin. Wehnschr.* **6**:1521, 1927.

acts on the cell membrane—peripherally; the reaction of the cell depends on its status, tonus; i. e., on the ionic condition of its surface membrane. The relative ionic concentration of calcium and potassium in the adjacent cell fluids, quite apart from the blood, is only of secondary importance. Furthermore, all of our results and those of numerous others are estimated as total calcium and probably give a picture far different from the actual ionic calcium available.

*Confusion of the Terminology Involved.*—We must keep in mind, furthermore, that cell membranes are interposed between the cell protoplasm and the blood stream.

With a Donnan equilibrium here established, the amount of non-dialyzable ions combined with protein on both sides of the membrane and the total amount of protein becomes of greatest importance.<sup>32</sup> We have shown by actual experiments (see chart 4) that with cell stimulation, calcium is liberated from the cell protoplasm and potassium there increased—corresponding to the time of vascular dilatation of the organ and therefore to a presumptive vagotonic status of the capillaries and tissues. This would mean that if we now use the term “vagotonia” as denoting a condition of tissue activity with capillary dilatation and increased permeability, then the blood stream should contain more calcium and relatively less potassium.

Actually, Kylin<sup>33</sup> found the “vagotonic” person, as clinically defined, to have more potassium and less calcium (higher K/Ca Ratio), and we, too, in using this clinical classification, can but confirm this.

Dresel<sup>34</sup> assumed that the blood of the “vagotonic” person is more alkaline and contrasts the resulting ionic states as follows:

| <i>Vagotonic Status</i>                                                      | <i>Sympatheticotonic Status</i>                                        |
|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Tissues alkaline: little calcium-colloid, much potassium-colloid             | Tissues acid: much calcium-colloid, little potassium-colloid           |
| Blood alkaline: little ionized calcium, much bound calcium, little potassium | Blood acid: much ionized calcium, little bound calcium, much potassium |

Accordingly, the “vagotonic” person should have a low K/Ca ratio, the physiologic effects being modified, however, by differences in ionization.

What we are actually facing here is merely a difference in definition. The clinical grouping of “vagotonic” does not define a person whose metabolism is increased and whose capillaries are permeable and dilated. This we should expect if in the vasomotor definition “dilatation” is synonymous with the “vagus effect.” On the contrary, the clinically

32. The capillary endothelium is permeable for proteins when stimulated.

33. Kylin, E.: *Deutsches Arch. f. klin. Med.* **149**:354, 1925; *Die Hypertoniekrankheiten*, Berlin, Julius Springer, 1926.

34. Dresel, K.: *Klin. Wchnschr.* **1**:1601, 1922; *Klin. Wchnschr.* **3**:311, 1924.

"vagotonic" person has a lower rate of metabolism and less permeable capillaries. Dresel was correct in theory, Kylin in practice. We can illustrate this further in the chemical changes of sleep.<sup>35</sup>

Here we deal with a "vagotonia," even in decerebrate animals. There can be no doubt about the general condition of tissue rest; during this time, calcium diminishes in the blood and increases in the tissues and the potassium values show the reverse. The greater frequency of attacks of asthma and angina pectoris, the occurrence of pavor nocturnus, Pende ascribed to the vagus preponderance at night.

*Clinical Grouping of Vagotonic and Sympatheticotonic Persons.*—We have discussed this at some length to bring out the fallacy of our present classification of "sympatheticotonic" and "vagotonic." It should be given up, unless we are clearly cognizant of the various implications.

When we have spoken of the sympathetic status, we have always indicated the state of tissue rest: contracted vessels, calcium accumulation, dehydration.<sup>36</sup> When we have spoken of the parasympathetic status, we have indicated the state of the tissue with dilated capillaries, tissue activation, calcium dissimulation, hydration. When we have used the terms "sympatheticotonic" and "vagotonic," we have designated the clinical states as commonly interpreted.

And this brings up another apparent inconsistency. When smooth muscle contracts, the obvious inference is that the muscle tissue is active (it may contract, of course, with either sympathetic or parasympathetic stimulation), but actually during contraction the capillaries are also contracted, their endothelium is less permeable, metabolic processes are slowed, less energy is supplied. With relaxation comes dilatation of the vascular bed and increased permeability. Relaxation must, therefore, if we wish to be consistent, be the period of metabolic activity, i. e., the parasympathetic status in the sense that we have used it.

Now, it happens that when epinephrine is injected in small doses, the blood vessels dilate and the endothelium becomes more permeable. It is a true parasympathetic status of the tissues. With larger doses, the vascular musculature contracts, and the endothelium becomes less permeable. These are direct cellular effects and take place presumably without nervous mediation. This is a true sympathetic effect. But the many other effects initiated at the same time by the large dose of epinephrine result in a most complex picture.

35. Fischer, H.: *Biochem. Ztschr.* **193**:169, 1928.

36. If the sympathetic status with contracted vessels occurs for a long period of time with a resulting stasis in the capillaries, it is possible that the cellular metabolism of the region will show a condition far different from "rest," i. e., rather an asphyxial stimulation. Such states may presumably occur in the peripheral tissues during a chill.

Of course, Zondek<sup>37</sup> was careful to state that the vagus effect is like the potassium effect; he never insisted that the two are identical, although, in general, it is assumed that the nerve impulse makes use of the ions in upsetting the membrane equilibrium. With this consideration, one can understand why in certain clinical conditions—urticaria, for example—the calcium level may be normal and yet the administration of calcium be, at times, useful, at other times, without effect. We can understand why the level may be constant—and it is one of the most firmly held of the balances, as Kroetz<sup>38</sup> has shown, with a negative balance; i. e., cells may be losing calcium, but the level remains the same, as Aub<sup>39</sup> and his associates have so clearly demonstrated in exophthalmic goiter. And we can understand why the level may be low in the blood, while the relation in the cell membranes is at its proper level.

*Rôle of Cholesterol.*—There seems to be some basis for the belief that cholesterol is involved as an intermediary in the ionic autonomic mechanism that we have been discussing,<sup>40</sup> and here again we are dealing with a confusion resulting from the presumable effects of cholesterol as a component of the cell membrane and cholesterol free in the blood stream. It is, of course, possible that an increase in the cell membrane can be present at the same time that we have an increase in the blood stream. The possibility also exists that with an active exchange going on between the two, high membrane content may be associated with low plasma content and vice versa. Just as with the ionic balance, the membrane relations present great complexity, with innumerable physical and chemical differences, free and saponifiable forms and the ability of the blood proteins to form protective colloids all influencing the ultimate balance. Mjassnikow<sup>41</sup> definitely associated the increase in blood cholesterol with hyperasthenia, not only in the apparently normal condition, but in the associated diseases, of this constitutional type, i. e., gout, obesity, hypertonia, asthma, hay fever, gallstones, etc. This cholesterol increase appears to be true for our "heavy" group, as well.

But Dresel and Sternheimer<sup>42</sup> definitely placed cholesterol in the sympatheticotonic group, counterbalanced by lecithin as a parasymp-

37. Zondek, S. G.: *Klin. Wchnschr.* **6**:1951, 1927; footnote 26, second reference.

38. Kroetz, C.: *Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong.* **40**:91, 1928.

39. Aub, J. C.; Bauer, W.; Heath, C., and Roper, M.: *J. Clin. Investigation* **11**:97, 1929.

40. Westphal, K.: *Ztschr. f. klin. Med.* **101**:545, 566, 584 and 603, 1925.

41. Mjassnikow, A. L.: *Ztschr. f. klin. Med.* **105**:228, 1927.

42. Dresel, K., and Sternheimer, R.: *Klin. Wchnschr.* **4**:816, 1925.

pathetic agent. Glaser<sup>43</sup> discussed some of the relations in arteriosclerosis and found, as had Wacker and Hueck,<sup>44</sup> that the injection of epinephrine hydrochloride increases the amount of cholesterol in the serum. A complete discussion of the literature would be superfluous at this time. We merely mention the probable rôle of these lipoids in the chemical and physical equilibrium that is involved in the autonomic background.

#### THE SKIN

*Its Autonomic Importance.*—Among the vegetative organs concerned with our immediate relation and adjustment to the outside world, none is of greater importance than the skin; it is unfortunate that it has been largely ignored by the physiologist, perhaps, because in his preoccupation with the experimental animal, he has failed to realize how far different the human skin is in its reactivity from that of any of the lower animals; perhaps because he has regarded the skin merely as a protective mechanism—the “overcoat” with which Engman has chided the dermatologists for their narrow point of view.

As a matter of fact, the skin is the reactive membrane for the whole organism, just as the cell membrane is for the individual cell, and with almost as many important and sensitive receptors and reactive possibilities. Clinical observation has always recognized the interrelation of the skin and the deeper tissues. The so-called antagonism of visceral and skin tuberculosis and syphilis is one example. So, too, is the protective immunity established by the exanthems; and the tradition that a good reaction of the skin protects against internal complications in the same group of infections is established folklore. More recently, the rôle of the skin in allergy and the therapeutic possibilities incidental to stimulation of the skin have raised the clinical interest and aroused considerable investigative curiosity. Müller and Delbanco<sup>45</sup> developed the idea of the skin as a vegetative sense organ and in line with von Groer<sup>46</sup> emphasized the skin as a mediator of autonomic regulations by virtue of both its chemical and its physical potentialities.

As is well known, the latitude of the adaptability of the skin to an insult or to a change in environment is great, must of necessity be great, because on it depends the life of the whole organism.

We should therefore like to develop the subject of the importance of the skin and its autonomic tonus in more detail and shall use bacterial invasion as an example of the effect of an abnormal external insult.

*Local Resistance.*—The sum total of the processes involved may vary from the normal physiologic responses, or what may be termed

43. Glaser, F.: *Klin. Wchnschr.* **6**:2377, 1927.

44. Wacker, L., and Hueck, W.: *München. med. Wchnschr.* **60**:2097, 1913.

45. Müller, E. F., and Delbanco, E.: *Dermat. Wchnschr.* **87**:1348, 1928.

46. von Groer, F.: *Klin. Wchnschr.* **6**:96, 1927.

"local tissue resistance," all the way to the severe inflammatory reactions elicited when certain organisms or biologically active toxic substances penetrate the superficial layers. The human skin, as we have pointed out, is much more reactive both specifically and nonspecifically than the skin of other animals.

The inflammatory reaction differs in degree from the normal physiologic response, the direction of the change is apparently uniform at the onset in both cases. Both the "local resistance" of the normal and undamaged tissue and the inflammatory resistance depend to a marked degree on the preexisting vegetative status of the tissues.

In order to maintain local resistance of the tissue an unaltered function of the cellular elements is the prime requisite; the second is an undisturbed replacement of the energy requirements during the course of normal metabolic processes. This involves a definite orientation of the autonomic apparatus of the involved tissue, so that the full development of tissue function and energy supply can be maintained.

Certain cells, particularly those that are to some extent free from cell complexes and organs (reticulo-endothelium and the resting wandering cells of Maximow), are more independent in their adaptability to changes in the environment in so far as they seem less subject to the influences which are operative when cell groups are involved.

On the other hand, in the organized tissues, every reaction of one organ involves more or less directly certain fundamental correlations with all the other organs and tissues. Brown's<sup>9</sup> work makes this interrelation evident. Remote organs, under conditions of stimulation, may then act either as accelerators or inhibitors of the function of other organs, whereby the adaptability of a remote zone may be enhanced or retarded.

The law of Dastre and Morat and our own experiments with the splanchnoperipheral balance of the organs show this clearly. If, for any reason, we observe a sudden increase of activity of the abdominal organs with increased vascularity of the region, there is not only a diminished amount of blood in the peripheral vascular bed, but also a diminution in the functional capacity of the peripheral organs associated with synchronous contraction of the vessels.<sup>47</sup>

We have already touched on the autonomic vascular mechanism involved, in connection with the paper of Schilf. We shall here limit ourselves to the question how far such alterations (which are constantly occurring under physiologic conditions) influence the organs and tissues

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47. Fremont-Smith, F.; Morrison, L. R., and Makepiece, A.: *Proc. Am. Soc. Clin. Investigation*, May 6, 1929; abstr., *J. Clin. Investigation* 7:489, 1929. Smith, Morrison and Makepiece have recently made observations on the capillaries during chill and find a complete stasis in all visible capillaries due to the constriction of the terminal arterioles.

with a possible loss of the local resistance of the tissue and predisposition to disease.

*Herpes and Splanchnoperipheral Balance.*—On the skin, in the nasal mucous membrane, and in the gastro-intestinal mucous membrane, pathogenic organisms live without further penetration, that is, until at some time a slight trauma, a "cold" or some other indisposition leads to local infection. With mechanical injury and its obvious disturbance, the lowering of the resistance of the tissue is easily understood. It is much more difficult to understand the other types of susceptibility, the appearance of a labial herpes for instance, with a sudden onset of fever. We know its pathognomonic interest and the enormous spread occasionally seen in association with the chill of an infection with *Bacillus coli*; we also know the nasoparasitic character of herpes virus.

The ubiquitous virus previously present in the adjacent surface of the skin suddenly penetrates the superficial layers and, from the clinical point of view, becomes virulent at the time of systemic reaction incidental to the generalized disease. The virus, having once penetrated, meets with further resistance in the form of local inflammation, the intensity of which is usually sufficient to check the further spread.

This picture is a typical example of the transition of a previously latent organism to full virulency as the result of the failure of local resistance of tissue. The question as to the cause of such failure with the onset of the chill and high temperature is of far greater interest than that involved in the mechanism of the infection of the pelvis or uterus with *B. coli* in septic abortion. Other herpetiform invasions are apparently related to similar processes: the herpes infection of the skin in certain periods of the menstrual cycle, and in certain persons during acute indigestion, etc.

The cause is always the same. A sudden and intense increase of activity in the splanchnic region involving marked increase in the vascular bed and increase of the secretory function reflexly involves a change in the peripheral tissues. The change includes a diminution in the size of the vascular bed and a reduction of cellular activity. The periphery becomes less capable of reaction to external stimuli for the reason that reactions which under normal conditions are associated with increased vascularity and increased metabolic cell processes are either diminished or do not make their appearance.

A second possibility must be considered. The stasis of the peripheral capillaries may be of sufficient duration to bring about injury of the more superficial epithelial cells—cells that normally are undergoing necrobiosis. This dysfunction incident to the stasis may be sufficient to account for the penetration.

Such alteration of the distribution of the blood takes place in all conditions associated with fever. A similar redistribution in the vascular

bed together with an increase of the secretory function of the stomach and other large glands of the abdominal region occurs in varying intensity during the menstrual cycle, during migraine and even during digestion, more evident in certain persons, when we see it as part of the "Widal hemoclastic crisis."

The cause of this abdominal splanchnic dilatation may vary in individual cases, but the reaction of the organs and the vessels in the splanchnic region is fundamentally the same. It is unidirectional, and it is associated with peripheral constriction made apparent in the pallor of the skin, with headache, with nausea, etc. In the chill of an infection with *B. coli*, one can observe the most intense form of this splanchno-peripheral change. The enormous increase in activity of the liver which results from the systemic invasions is associated with a decreased flow of blood at the periphery and a diminution of all peripheral cellular function. It is this latter change which is of the greatest practical importance.

Heat radiation and sweat formation are clinically familiar to us. Their inhibition, even if transient, is part of the mechanism that causes fever, because the dissipation of heat produced by the increased activity of the splanchnic organs is thereby checked. Only when, with gradually diminishing activity of the liver, the correlated inhibition of the autonomic functions of the skin is lessened, does the temperature begin to fall. During the menstrual cycle, similar conditions may prevail even though the clinical symptoms are less apparent. Here, too, one finds minor fluctuations of temperature that have the same physiologic basis, though here without infection.

Local tissue resistance, which is most impressive in the skin, is subject to the same inhibitory influences. Reactions of the skin associated with increased resistance to infection are hard to recognize. It is true that our clinical experience indicates that a skin or a mucous membrane with good circulation is less apt to become infected, and that healing takes place more rapidly under such conditions. This might be apparent, too, from the relative freedom of the exophthalmic patient from infections of the skin.

Inhibitory influences on the skin, with diminution of its autonomic adaptability, also become apparent only when every day demands are not met in the normal fashion, for example, when one has a virus present and finds that with lowering of the local tissue resistance, the virus is enabled to penetrate into the deeper tissues.

It is of secondary importance whether such an inhibition takes place primarily through nerve impulses, through alteration of the metabolism or through endocrine alterations which secondarily lower the resistance toward the infections.

We <sup>48</sup> have previously noted definite autonomic influences on the skin of women during the menstrual cycle. In the absence of a potential virus on the skin, these alterations are clinically innocuous because, practically, one is dealing only with a susceptibility toward infection. Only when one is dealing with a potential infection, as in persons harboring the herpes virus, does the periodic depression of resistance become apparent.

*Respiratory Tract.*—In the nasopharynx, similar autonomic influences become apparent. In chill and in high fever, the mucous membranes of the mouth and the nose are dry because the cell functions of the mucous membranes are definitely depressed or inhibited. The coated tongue is a manifestation of the same influences.

Glands and mucous membranes are in themselves uninjured; it is only their functions which are diminished during the time of fever. Despite urgent need and mechanical stimulation through chewing and sucking and contact with food, the formation of saliva is inhibited because of the vegetative contraction of blood vessels, as well as the vegetative inhibition of the cell functions. The same condition holds true for the hunger sense. The diminution of contractions that we <sup>49</sup> have demonstrated for the stomach during this time is part of the picture of diminished appetite (the opposite vegetative orientations of salivary glands, mucous membranes and tongue, on the one hand, and of stomach, liver, etc., on the other, are particularly marked in these cases, as we have shown previously). The stomach during this time is under a condition of stimulation which leads to a considerable secretion of a strongly acid stomach juice.

Other infections of the mucous membranes besides herpes are well known during fever, for instance, the inflammatory reaction of the upper part of the respiratory tract, as well as of the conjunctiva. Such inflammatory reactions are by no means to be regarded as part of the primary infection, but are merely manifestations that these tissues for the time being have lost their resistance either partially or entirely, resistance which under normal conditions would be more than able to cope with every day irritations. Here, for instance, could be mentioned the conjunctivitis occasionally seen with the flare-up of a localized pulmonary tuberculosis, so characteristic that it may be regarded as a distinct symptom of activation.

We shall show later on that the exanthems of the acute exanthematous infections (scarlet fever, measles) only become possible because

48. Petersen, W. F., and Milles, George: Relation of Menstruation to Permeability of Skin Capillaries and the Autonomic Tonus of Skin Vessels, *Arch. Int. Med.* **38**:730 (Dec.) 1926.

49. Müller, E. F., and Petersen, W. F.: *München. med. Wehnschr.* **74**:531, 1927.

the skin and the mucous membranes have a diminished resistance toward the circulating toxin. Müller, Metz and Myers<sup>50</sup> demonstrated such a pathogenicity for one exanthematous disease due to a known toxin, namely, the arsenical dermatitis following arsphenamine.

Even the occurrence of halitosis in severe infections is due to the lessening of cell activity in the mucous membrane of the mouth, with diminution of the bactericidal power. The idea that the fetor is of stomachic origin is incorrect, for the growth of bacteria in the stomach is not increased during fever, though the bacterial flora may ascend to the higher levels of the gastro-intestinal tract, as has been demonstrated by Arnold and Brody.<sup>51</sup> As a matter of fact, the stomach contents, when removed, have no such fetid odor. Soor paradentosis, caries and the pityriasis versicolor of the cachectic patient have a similar origin in so far as the loss of the resistance of the tissue makes possible the infections named. The loss of hair and the impairment of the growth of the nails give further evidence of the peripheral vascular disturbances.

Before we enter into a discussion of similar changes in the other organs, we must discuss for a moment those reactions which serve for the protection of tissue when toxic substances or a virus have entered the skin and the mucous membrane. We characterize them as inflammatory. Intensity of change, and this in relation to the protection of tissue means the effectiveness of change, also depends on vegetative orientation of the tissue as such. Examples of such influences are well known. With the onset of fever—let us say the sudden onset of an angina—the exudate of a gonorrheal infection ceases for a time. The formation of pus in a sterile turpentine abscess during a fever starts after defervescence; all evidences that an autonomic influence is of paramount importance in local inflammatory processes.

The work of Kauffmann<sup>52</sup> and of Petersen<sup>53</sup> presents further examples. Particularly, the work of Kauffmann with cantharides blister during the course of lobar pneumonia seems to us of particular significance, because Kauffmann carried out his experiments without considering the autonomic orientation in its influence on the metabolism and reactivity of the tissues. During the course of the febrile stage of pneumonia, he observed a decided impairment of reaction. He said:

The exudates are peculiarly poor in the cellular elements. Among the cells present lympho-histiocytic elements are completely absent, as are also eosinophile cells, so that the exudate consists practically of neutrophile leukocytes. But even

50. Müller, E. F.; Metz, G. P., and Myers, C. N.: Arsenic Lesions of the Skin, *Arch. Dermat. & Syph.* **15**:186 (Feb.) 1927.

51. Arnold, L., and Brody, L.: *Am. J. Hyg.* **6**:672, 1926.

52. Kauffmann, F.: *Krankheitsforschung* **2**:372, 1926.

53. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch. Int. Med.* **38**:663 (Nov.) 1926.

the immigrative cell elements so represented are increasingly diminished in the more severe disease processes. It is only with the crisis—when the inhibitory influences on the skin have disappeared, that inflammatory irritability and particularly the intensity of the cellular processes again increase.

In this work with the cantharides blister, Kauffmann therefore described the dependence of the inflammatory reaction on the vegetative orientation. Some years ago, Müller<sup>54</sup> pointed out that every collection of leukocytes was associated with a dilatation of vessels. Such dilatation is inhibited during a period of general reaction to infection. Herein, just as in the inhibition or diminution of the mobilization of tissue cells in the inflammatory exudate, we can recognize the negation of this phase of tissue protection of the skin at times when the center of metabolic activity of the body has been transposed to the internal organs.

*Gastro-Intestinal Tract and Change of Temperature.*—The reversal of such vegetative orientation can also be established. Arnold<sup>1</sup> showed that when the blood vessels of the skin and the peripheral tissues are active, the bactericidal properties (that is the self-protection of the tissues) in the gastro-intestinal tract, particularly of the duodenum and the upper jejunum, are diminished. Man, as well as animals, exposed to heat and high humidity show, not only a coincident diminution in the secretion of the gastro-intestinal fluids, but a diminution in the normal response of the gastro-intestinal tract to food. If one examines dogs in superheated rooms, bacteria are found passing the stomach and duodenum practically in 100 per cent of the cases, whereas in the animals kept under normal conditions of temperature the bacteria are killed. If one feeds such overheated animals meat poisoned with enteritis toxin, the animals die, whereas animals kept at normal temperature or a cool temperature survive. If one measures the organic function of these animals in terms of stomach and bile secretion, following ingestion of poisoned meat, then one observes a marked and occasionally a total inhibition in the animals kept too warm and an enormous reaction in the control animals. In the human being, we also have observed this diminution with external heat as contrasted with normal temperature and a correspondingly increased reaction at the time of actual chill. The susceptibility to gastro-intestinal infection increases notably at times of increased external temperature. This is not only the case when infected food or pathogenic organisms pass in fully virulent form through the stomach to the gastro-intestinal tract. Even the normal gastro-intestinal parasitic flora is no longer indifferent under these conditions. Thus, Arnold<sup>55</sup> showed that with increasing

54. Müller, E. F.: München. med. Wchnschr. **69**:1506, 1922.

55. Arnold, L.: Am. J. Hyg. **8**:604, 1928.

external temperature the flora changes its character, as well as its range. Characteristically, the lower gastro-intestinal flora invades the upper region of the gastro-intestinal tract. Similar conditions underly the manifestations of gastro-intestinal morbidity in populations at the beginning of the warmer periods of the year or in persons who go from cold to tropical climates. With the associated increased activity of the periphery of the body, the functional capacity of the abdominal organs is diminished.

This, too, is not necessarily dependent on the actual height of the external temperature, but rather on the reactivity of the skin and the lungs at the time, and on the autonomic impulses that under those conditions leave the periphery and influence the gastro-intestinal tract and the abdominal group of organs, in general. The decrease of resistance of the gastro-intestinal wall—in other words, the increase of susceptibility—in warm climates and in the hot summer is therefore most apparent in the unacclimated persons, that is, with sudden and unaccustomed changes, rather than in persons who gradually accustom themselves to higher temperatures. This point is of epidemiologic importance for a variety of gastro-intestinal infections, as well as for tropical diseases.

In the liver, too, the local immunity of the parenchyma is clearly dependent on the autonomic orientation of the tissues and is only effective when inhibitory impulses are not predominant.

The normal increase in activity of the liver in chill and fever has been previously described in some detail.<sup>56</sup> Secretion of lymph and bile increases tremendously and with it vascularization, function and cell permeability. The marked increase of the permeability of the cells and tissues, in general, does not involve a necessary penetrability for all substances present in the blood. Despite continuous intravenous injection of living *B. coli* in the animal over experimental periods lasting for hours, the lymph of the thoracic duct remains free from bacteria. That is, the sterility of the lymph is constant as the function of the liver increases. On the other hand, bacteria are being constantly excreted into the bile passages. If such an experimental injection of *B. coli* is continued long enough (for ten, fifteen or twenty hours), one arrives at a time when the function of the liver is apparently rapidly diminished. At this time, the peripheral constriction of the vascular bed is also broken, and the animals show a peripheral hyperemia. In the liver, the vessels contract, the permeability of cell and tissue is diminished, as is the production of lymph and bile. At the time of this injury, red blood corpuscles appear in the lymph stream, proteolytic

56. Petersen, W. F.; Müller, E. F., and Boikan, W.: J. Infect Dis. **41**:405, 1927.

enzymes are markedly increased, the temperature falls, and some of the bacteria make their way into the lymph stream. Later this picture may be reversed.

Here, too, we see that the characteristic balance between the skin and the mucous membranes of the mouth, on the one hand, and the mucous membranes of the gastro-intestinal tract, on the other, may also influence the local resistance of tissue in other organs by means of a supererogated vegetative control.

These observations seem of certain importance in various directions, not only for the understanding of such processes as herpes, the infections of the mucous membranes of the mouth with parasitic invaders previously latent, and the catarrhal conditions of mucous membranes, in general, during infectious diseases and following chilling of the body surfaces, but for the understanding of gastro-intestinal manifestations in persons in unaccustomed warm climates, and of the status of the liver in the course of septic infections. From them we may be permitted to make certain deductions concerning the susceptibility of organs and tissues, in general.

The protection of normal tissues against an infection does not depend to any great degree on immune powers of the serum, but is, as every other function of the body, due to the cellular activity of the tissues and therefore is closely associated with the vegetative impulses and the vegetative status as particularly manifest in vascular alteration. One realizes, too, that the cellular tissue functions, on which local resistance depends, are controlled (as are all other functions of cells and tissues) in their responses and activity not only by the anatomic and functional activity of the individual elements as single cell organisms might be, but by certain limitations of their potential possibilities placed on them by more remote organic processes that directly influence the intensity of the vegetative orientation not only of the entire body, but of the local organs and tissues. It is possible, therefore, that with complete anatomic and physiologic integrity of the tissues, and despite the manifest danger due to the local infection, the local resistance of tissue may fail because it is inhibited through influences which, originating in remote regions, influence the local functional status. How this inhibition of functional response in the tissues may be brought about is clinically and practically unessential. At least two possibilities exist. Primarily, the diminution of function may be secondary to vascular dysfunction with an associated diminution of energy resources. Secondly, it may be directly imposed by the vegetative nervous impulses, or by chemical or hormone alterations acting on the blood vessels, as well as on the individual cells, either immediately or mediately.

The only fact that is of practical importance is that the local protection of the tissues, particularly those that have come in contact with

the surrounding world, is associated with and dependent on a super-imposed vegetative orientation. Important is the knowledge that influences which may change the vitality of tissues, the functional capacity of the tissue and therefore the self-protective mechanism may remain objectively unnoticed, since they can be measured only in the end-result. In terms of relative resistance, they are perceptible only indirectly, that is, when functional inhibition has gone so far that the infection actually takes place.

It is not the mechanical integrity of the skin that offers the most effective protection, it is the vegetative condition of the tissue during which the adaptability of the cells can be developed to its maximum potential degree. It is seen that, on the basis of the splanchnoperipheral balance in the community of organ response, the more intense activity of the one group is balanced by a relative inhibition of the vital activity and capacity of another group, and that local resistance, as a measure of metabolic activity, as other functions, loses some of its potentiality under the influence of inhibitory forces. The local resistance of tissue is intimately bound up and dependent on local tissue elements and their functional capacity. With lowering of this functional capacity of the tissue, there occurs a lowering of the resistance of the tissue, irrespective of the origin of these inhibitory influences from without or from within, or of whether they are initiated by tangible organic changes or by psychic processes. The head cold, for instance, is not the result of a change of temperature to which one may have been exposed, but is the result of an individual difference in local resistance. Even in a severe draft with a considerable cooling, the temperature of the mouth, of the nasopharynx, of the musculature and of the joint cavities may remain approximately the same. With long continued intensive cold of the skin, of course, all the tissues and organs respond, the peripheral ones with a relative diminution of vascularity. We are therefore of the opinion (because of clinical observation) not only that articular rheumatism may be due to certain types of organisms, but that the joint membranes and the musculature have definite fluctuations of resistance against these invaders depending on the vegetative orientation of the moment. The Weber phenomenon is based on the fact that sudden displeasure or sadness leads to a diminution in the amount of blood in the periphery with a corresponding increase in the abdomen. But in psychic trauma, such as fright or fear or worry, a severe and long continued physical influence on the body can be brought about. In all of these one finds pallor of the skin, dryness of the mouth, loss of appetite, etc. One can readily see that the influences that make manifest many organic disturbances in association with psychic trauma do so because of the fundamental and underlying autonomic changes that we

have discussed in relation to the herpes virus. The organic changes depend, as this does, on the vegetative ability and adaptability of the local tissue.

#### EXOPHTHALMIC GOITER

Recently, Warthin,<sup>57</sup> in a discussion of exophthalmic goiter, reaffirmed his conviction that the underlying factor is constitutional, symptoms developing only as a result of abnormal reactions to stimuli which in a normal person would be met by physiologic adaptation. Oswald,<sup>58</sup> too, believed that the effect on the thyroid gland depends wholly on an instability of the nervous system in certain persons, an instability that Kessel, Lieb and Hyman<sup>59</sup> place in the myoneural junction. Warthin, furthermore, believed that "Graves' constitution" is associated with a "thymic-lymphatic" status and is characterized by hyperplastic primitive lymph nodes in the gland itself, which is involved in the disease only incidentally. Aschoff and Krehl both expressed similar views, and Miller<sup>60</sup> emphasized the probability of at least two active factors in the disease, one not identical with the substance that increases the basal metabolism.

There is a growing volume of clinical comment in agreement with this view.<sup>61</sup> Bram<sup>62</sup> tersely differentiated toxic adenoma by stating that here "the thyroid makes the body sick; in exophthalmic goiter (a constitutional disease) it is the body that makes the thyroid sick."

Our previous,<sup>63</sup> as well as present, series have made apparent a striking increase in capillary permeability in exophthalmic goiter, which, we believe, is basically associated with the clinical manifestations. Such an increase in permeability has been suspected as a result of the previous work of Eppinger and Hess. Gellhorn<sup>64</sup> has more recently proved the increase in permeability by direct experiments. Weil<sup>65</sup> drew the conclusion that the increase in permeability is to be correlated with, first, the increase in absorption and, second, the increased electrical conductivity of the tissues, and finally, with the increase in cell division

57. Warthin, A. S.: *Ann. Int. Med.* **2**:553, 1928.

58. Oswald, A.: *Klin. Wchnschr.* **4**:1053, 1925.

59. Kessel, L.; Lieb, E. C., and Hyman, H. T.: *A Study of Exophthalmic Goiter and the Involuntary Nervous System*, J. A. M. A. **79**:1213 (Oct. 7) 1927.

60. Miller, J. L.: *Proc. Inst. Med, Chicago* **7**:89, 1929.

61. Zondek, H., and Bansi, H. W.: *Klin. Wchnschr.* **8**:1697, 1929.

62. Bram, I.: *M. J. & Rec.* **129**:579, 1929.

63. Petersen, W. F.: *The Permeability of Skin Capillaries in Various Clinical Conditions*, *Arch. Int. Med.* **39**:19 (Jan.) 1927.

64. Gellhorn, E.: *Das Permeabilitäts Problem*, Berlin, Julius Springer, 1929, p. 341.

65. Weil, R.: *Klin. Wchnschr.* **8**:852, 1929.

observed in exophthalmic goiter. Weil found that thyroxin in small doses increases liver autolysis, which is due, presumably, to colloid chemical membrane changes with increased permeability. The clinical interest, as well as the physiologic interest, must therefore turn from the supposition that the effect is on the nerve endings as an intermediary. We are really dealing with a direct membrane change.

Dresel,<sup>66</sup> who also observed an increase in amino acids in liver autolysis following the injection of thyroxin, made use of the increased oxidation in the liver and testicle by injecting small doses of blood of the exophthalmic patient into a mouse.

The liver under these conditions becomes glycogen-free. From his experiments he concluded that the active agent circulating in the blood of the exophthalmic patient is far more active than any thyroxin preparation.

Mora<sup>67</sup> studied the shortening of the resorption time of intracutaneously injected salt solution in exophthalmic goiter, and Asher<sup>68</sup> made use of a similar dye test to demonstrate the central (sympathetic) effect on the thyroid gland.

The increase in permeability associated with increased metabolic activity should be followed by a negative calcium balance—and that it is, was recently demonstrated by Aub<sup>69</sup> and his associates, who also noted that osteoporosis may appear during the course of the disease.

Our observations indicate that the increased permeability determined by the blister is not necessarily related to the increased basal metabolic rate. In this respect, the results correspond with those noted in the markedly sympatheticotonic and nervous group in the members of which we observed an increased permeability without an increase in the basal rate. This fact, among others, inclines us to the view that we are dealing with two distinct factors—one, an underlying change in tissue reactivity, and another which is distinctly related to the calorigenic effect of the thyroid secretion. The question concerning the duality or multiplicity of the effect on the thyroid gland has repeatedly been raised; most recently by Csépai,<sup>70</sup> who, judging only by the effects on blood pressure, denies the probability.

The reactivity of the skin in patients with exophthalmic goiter presents a number of interesting features. The erythema after the applica-

66. Dresel, K.: *Verhandl. f. inn. Med. u. Kinderh.*, Berlin, Jan. 7, 1929; abstr., *Klin. Wchnschr.* **8**:425, 1929.

67. Mora, J. M.: *J. M. Sc.* **177**:153, 1929.

68. Asher, L., and Pfluger, O.: *Ztschr. f. Biol.* **87**:115, 1927.

69. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: *J. Clin. Investigation* **7**:97, 1929.

70. Csépai, K., and Fernbach, J.: *Arch. f. exper. Path. u. Pharmakol.* **129**:256, 1928.

tion of ice appears rapidly, and the resistance of the skin to electric current is lowered, as Richter<sup>71</sup> has previously noted.

Lueg and Grassheim<sup>72</sup> studied the capacity of the skin for polarization in thyroid disease and noted that the increase in the basal metabolic rate usually parallels the increase in capacity for polarization. Curiously enough, the upper and lower portions of the body may show considerable difference. Nothhaas,<sup>73</sup> in examining the dermographic reaction, found a longer latent period in exophthalmic goiter.

Hoke<sup>74</sup> made use of a traumatic reaction (carbolic-salt) and demonstrated an increased reaction of the skin in exophthalmic goiter and also after injections of thyroxin. Similar increases in reactivity were noted when milk or typhoid vaccine was injected.

In our preliminary discussion, we pointed out the occurrence of a dissociation of certain changes of the skin from the metabolic rate. We called attention to the fact that, following operation, the basal metabolic rate might return to normal but certain of the alterations of the skin become more pronounced. Such a dissociation of symptoms is, of course, a common observation in exophthalmic goiter and merely confirms our impression that the underlying change is dual. The treatment, too, would indicate this. Zondek<sup>75</sup> grouped the methods under three heads: (1) operative removal of the thyroid gland, (2) fixation of thyroxin in the thyroid gland (with iodine) and (3) treatment with certain of the narcotic drugs that change the surface of the cell.

König<sup>76</sup> added to this, thorough alkalization, a procedure that might seem logical from the probable effect on the membrane of the cell.

#### THE NERVOUS PATIENT

It will be recalled that our nervous patients had a relatively low level of potassium with a practically normal level of calcium in the serum, were, in general, thin, usually showed an increased permeability of the capillaries, had a high resistance of the skin to electric current and a rather delayed reaction to ice.

Glaser<sup>77</sup> reported that there were observable differences in the amount of calcium in the serum in different psychic states in the same person.

71. Richter, C. P.: Electrical Skin Resistance: Diurnal and Daily Variations in Psychopathic and Normal Persons, *Arch. Neurol. & Psychiat* **19**:488 (March) 1929.

72. Lueg, W., and Grassheim, K.: *Ztschr. f. klin. Med.* **110**:531, 1929; *Klin. Wchnschr.* **7**:647, 1928.

73. Nothhaas, R.: *Klin. Wchnschr.* **8**:820, 1929.

74. Hoke, E.: *Wien. klin. Wchnschr.* **33**:904, 1920.

75. Zondek, H.: *Verhandl. f. inn. Med. u. Kinderh., Berlin*, Jan. 7, 1929; abstr., *Klin. Wchnschr.* **8**:425, 1929.

76. König, W.: *Klin. Wchnschr.* **8**:634, 1929.

77. Glaser, F.: *Med. Klin.* **20**:1237, 1924.

Tomasson<sup>78</sup> published the most extensive work, studying the mineral metabolism of a large series of psychopathic patients. From his studies he concluded that the calcium fluctuations precede periods of mental instability and that they are inversely proportional to the mood of the patient. In the maniacal periods of maniac depressive insanity, the calcium in the serum is increased and he did not find any low values. Movement in itself is not responsible for this, although under hypnosis there is some lowering of the level. Alterations of the mineral equilibrium of the serum which Tomasson described would be indicative of a loss of calcium from tissues with a coincident penetration by potassium. With it, he found a slight alkalosis.

Hoff and Werner's<sup>79</sup> experiments indicate that in the neurotic patient one is dealing primarily with a lowering of the threshold between the vegetative and psychic centers, leading to obvious instabilities.

Kraus<sup>80</sup> definitely grouped "neurasthenia" as a vegetative disturbance, i. e., vagolability, electrolytic alterations not only being associated with the vegetative-neurotic stimulation but determining the type of the reaction.

Regarding the vegetative status as the fundamental background of all reactions, reproductive, developmental—irritability, in general—he conceived the neuroses as distinctly constitutional (as, clinically, they obviously are) with general psychic manifestations, or as organ neuroses with local vagotonic or sympatheticotonic overbalance. He assumed that it is potassium which plays the large rôle—nonionized potassium going over to ionized forms on stimulation; this would correspond with our observations. Insofar as the ultimate status of the individual (vital periodicity, reactivity) is, in its final analysis, the result of a balance between cosmic (external) and internal stimuli, we can understand that the constitutional status plus the conditioning effects influence the psychic reactions just as they would any other organ or tissue.

While there seems little doubt that we may legitimately associate changes in the permeability with functional changes in the nervous apparatus, the converse, that the nervous system may change the permeability of the capillaries is also probable; we may be dealing with a circular mechanism.

We have repeatedly stated that the stimulation of the sympathetic side of the autonomic nervous apparatus is associated with diminished

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78. Tomasson, Helgi: *Undersøgelser over nogle af blodets elektrolyter (Ca, K, Na, H) og det vegetative nervesystem saerlig hos patienter med maniodepressiv psykose*, Copenhagen, Levín & Munksgaard, 1927.

79. Hoff, Hans, and Werner, Paul: *Klin. Wchnschr.* 7:346, 1928.

80. Kraus, F.: *Klin. Wchnschr.* 6:537, 1927.

capillary permeability. Vessels that have been deprived of their sympathetic innervation are more permeable.<sup>81</sup>

The work of Gellhorn,<sup>84</sup> definitely proving the increased permeability following pilocarpine and diminution following epinephrine, is in line with related demonstrations by many observers. We would, however, call attention to the fact that these effects are probably direct effects on the cell membranes. With thyroid and sex hormones increasing permeability (the observations of Asher, Gellhorn, Fröhlich and Zak<sup>82</sup> and others are convincing) and epinephrine and pituitrin diminishing permeability, and with a regulatory effect of the nervous system in controlling the output of the glands of internal secretion made probable, we can understand that an overflow of nervous impulses to such glands in certain persons would change tissue permeability. Asher and Pfluger<sup>83</sup> demonstrated increased activity of the thyroid gland under such conditions. This would in turn increase capillary permeability in general.

There is a close parallelism between "nervousness," capillary permeability, permeability of the meningeal barrier and the K/Ca ratio. In the menstrual cycle, the nervous manifestations are clinically obvious. The related blood chemistry<sup>8</sup> has been well developed.<sup>84</sup> Heilig and Hoff<sup>85</sup> demonstrated the increased permeability of the meninges, and we have shown an increase in capillary permeability.<sup>48</sup> In our present series, the "nervous" persons have, in general, a distinct increase in permeability and with it, as a group, a low K/Ca ratio.

We have had the impression for a number of years that mental instability can result from changes in the ionic equilibrium and from changes in the capillary permeability, just as such alterations may change the reactivity of other tissues in the body. In a woman with a puerperal psychosis, for instance, we observed an unusually high capillary permeability.<sup>86</sup> In another instance, that of an individual in this series, we called attention to the fact that the patient's high capillary permeability occurred during a time of emotional stress incidental to stock market losses.

Perhaps no more striking association of mental disturbances with alteration of the vegetative system (particularly muscular abnormality) exists than in catatonia. Here we have definite evidence of the control

81. Yamamoto, J.: *Biochem. Ztschr.* **145**:201, 1924. Gabbe, E.: *Ztschr. f. d. ges. exper. Med.* **51**:728, 1926.

82. Fröhlich, A., and Zak, E.: *Klin. Wchnschr.* **8**:1540, 1929.

83. Asher, L., and Pfluger, O.: *Ztschr. f. Biol.* **87**:115, 1929.

84. Riddle, O.: *Proc. Am. Philos. Soc.* **66**:497, 1927.

85. Heilig, R., and Hoff, H.: *Klin. Wchnschr.* **3**:2049, 1924.

86. Petersen, W. F., and Lash, A. F.: *Alterations in Permeability of Skin Capillaries During Pregnancy and Puerperium*, *Arch. Int. Med.* **39**:12 (Jan.) 1927, table 3.

of the clinical picture through ionic alterations. Reese,<sup>87</sup> together with Loevenhart and Lorenz, demonstrated complete (though transient) restoration of catatonic patients to a normal condition when the latter were stimulated by means of carbon dioxide respiration. Gordonoff and Walther<sup>88</sup> also showed a marked increase in potassium in the blood and blood corpuscles of such patients.

#### GLAUCOMA

Our examinations indicate that the patient with glaucoma has a lability of the cardiovascular renal system. This seems in accord with the observations of other investigators. Sulzer's<sup>89</sup> observations led him to believe that primary glaucoma is due to a vascular disturbance. Schmidt<sup>90</sup> noted that the water balance of the body is atypical in glaucoma. Thus, in the normal person, the ingestion of water is not followed by a change in eye pressure; in the glaucomatous patient, the pressure is increased. While Schmidt does not believe that the effect is wholly osmotic, he does insist that it concerns a capillary change.

One must, of course, not forget that local anatomic changes—size of the lens, dilatation of the pupil, etc.—are probably the determining factors; the initiation of the disturbance may, however, be closely related to sudden changes in capillary permeability. Goldenburg<sup>91</sup> recently discussed this subject in some detail.

#### TUBERCULOSIS

*Constitution.*—The human body reacts fundamentally in two different ways to tuberculous infection: one resulting in a relatively benign process, developing slowly, becoming quiescent through cicatrization and proliferative; the other resulting in an exudative process with fluid effusion, relatively rapid progression and dissolution of tissues. Clinically, we meet every phase of resistance fluctuating between these two extremes, extremes which must depend on differences in irritability of the tissues. The greater the irritability the more marked is the response, the greater the tendency to an exudative process. The less the irritability the greater is the tendency to cicatrization.

With these premises granted, the problem obviously involves the autonomic status of the organism as a whole, the status of the various organs and the question of variations in the vegetative status as modified by the infection.

87. Personal communication to the authors.

88. Gordonoff, T., and Walther, F.: *Klin. Wchnschr.* **8**:1179, 1929.

89. Sulzer, F.: *München. med. Wchnschr.* **75**:768, 1928.

90. Schmidt, K.: *Med. Klin.* **24**:859, 1928.

91. Goldenburg, M.: *Illinois M. J.* **52**:474, 1927; *Am. J. Ophth.* **11**:290, 1928.

It also must be kept in mind that even the acutely exudative process may result in utter destruction, i. e., digestion and removal of the virus and the inflammatory exudate. This latter method is probably a common method of disposal of the smaller lesions, much more common, than mere clinical observation would lead one to suspect.

Of course, the relation of "constitution" to tuberculosis is involved in this problem and is one that has interested physicians since time immemorial. The difficulty has been the definition of the term "constitution." In this way the "asthenic," "phthisical," "respiratory" type of the French has always been stamped as that of the potentially tuberculous person.

Borchardt<sup>92</sup> discussed the reactivity of the tissues to tuberculous infection in relation to constitutional types. In the "Status-Irritabilis" of Wunderlich, he found more localization in the mucous membranes, the skin, the serous membranes, etc., with a relatively good prognosis and good connective tissue reactions. In the "asthenic" type (Stiller) or the lymphatic arthritic type (Pfaundler) there is apparently a lessened reaction. We are dubious concerning the value of such classifications of constitution for the reason that in the adult the genotype must be greatly modified by the conditioning factors. One of the most important of these we consider to be the probability of a relatively long established preexisting tuberculous infection dating, not infrequently, from childhood. The tuberculous adult who is finally classified as of the "asthenic" or "phthisical" type must frequently be what he is—physically, physiologically and psychically—because of this infection.

While one ordinarily thinks of constitution in its more tangible form, one forgets the possible constitutional differences in the organ reactions and tissue reactions. Thus a congenital deficiency may indeed be expressed anatomically in the structure of the elastic tissue of an organ or in a certain degree of infantilism or in the more rapid senescence that one sees commonly in the teeth or the hair or the structures of the eye in certain families.

*The Autonomic Status.*—Considerable literature has developed that deals with the autonomic nervous system and tuberculous infection. In this country, Pottenger<sup>93</sup> has for many years pioneered in studying symptomatology with particular relation to the underlying autonomic alteration. There is no uncertainty concerning this phase of the problem nor is there any question concerning the general autonomic instability as expressed in the reactions of the vasomotor, the gastro-intestinal and the mental apparatus. Redeker<sup>94</sup> has but recently reemphasized the

92. Borchardt: *Deutsche med. Wchnschr.* **47**:1159, 1921.

93. Pottenger, F. M.: *Symptoms of Visceral Disease*, St. Louis, C. V. Mosby Company, 1929.

94. Redeker, F.: *Beitr. z. Klin. Tuberk.* **70**:259, 1928.

general psychic instability as part of the reaction of the tissues to the invading organism. A most interesting histologic confirmation has come from Michejew and Pawljutschenke,<sup>95</sup> whose conclusions we shall quote at some length:

The patho-physiological explanation of the clinical findings in tuberculosis is often most conflicting, due we believe, to incomplete methods of examination. There is no doubt, however, that the tuberculous processes bring about changes in the functions of all organs, not only directly, but indirectly, through pathological alterations of the vegetative endocrine correlations. The entire "vegetative system" in the sense of Zondek-Kraus is destroyed. . . .

Our examinations show that the tuberculous processes bring about diffuse changes in the vegetative centers. It is therefore impossible to associate definite vegetative findings with strictly limited anatomical lesions. We assume furthermore that in the central nervous system, no fixed centers for every type of metabolic activity exist, but that we deal rather with the projection of certain physico-chemical processes on certain nuclei. The diffuse character of the lesions found by us lead us to suspect that in tuberculosis, certain alterations exist that accelerate the penetration of the toxin into the central nervous system.

Leaving aside the factor of predisposition or constitution, we should like to point out that one of the chief factors must be this increase in permeability of the "hematoencephalitic" or "capillary" barrier which makes possible this effect of toxin on the central nervous system. It is not necessary to dwell on the change in the concentration in calcium as one of the factors involved in this alteration.

The complexity of the balance between the individual vegetative system and the infection accounts for the multiplicity of symptoms and the variety of symptom complexes in tuberculosis.

It seems probable that the early change in the permeability of the "barrier" plays a rôle in the early appearance of certain nervous manifestations which we may regard as pre-tuberculous.

Changes in general cellular permeability apparently alter chronaxia, for Förster<sup>21</sup> has shown that it is lowered by epinephrine, calcium chloride and parathyroid, and increased with hydrochloric acid, pilocarpine, choline, thyroxin, etc., and Förster ascribed periodic fluctuations in sensitivity to impulses to alterations in chronaxia brought about by general changes in the permeability. Lapique and his co-workers<sup>96</sup> had previously demonstrated this phenomenon. Both peripheral and cerebral changes in permeability apparently directly influence the nervous response, and the dependence of the effect of the impulses on the state of the organ has been discussed previously at length.

With the recognition that the local autonomic status of the tissues is of importance in the resistance to tuberculosis, the study of that status has concerned a number of workers.

95. Michejew, W. W., and Pawljutschenke, E. M.: *Arch. f. Psychiat.* **84**:227, 1928.

96. Lapique, M.: *Soc. de biol. Paris* **74**:32, 1913. Obre', A.: *ibid.* **88**:585 1923. Florkin, M.: *ibid.* **97**:1804, 1927.

Eppinger and Hess<sup>97</sup> were the first to point out that the majority of tuberculous patients give a "vagotonic" reaction to epinephrine. Deutsch and Hoffman<sup>98</sup> reported that the patient with early tuberculosis gives a "sympatheticotonic" reaction to epinephrine. Later, the reaction is more irregular, with "vagotonia" preponderating. Dresel<sup>99</sup> confirmed this observation.

A most extensive series of observations was reported by Guth,<sup>100</sup> whose interpretation, in general, follows the line of Danielopolu. He noted that tuberculotoxin acts amphotropically, first irritating both components, later leading to a depression, with emphasis on the vagus side. In general, most of the exudative patients were found to be "vagotonic"; most of the productive types, "sympatheticotonic."

Glaser's study,<sup>77</sup> as well as Kading's<sup>101</sup> work, indicates that the chronic tuberculous person is "sympatheticotonic." Pende<sup>10</sup> came to the conclusion that if the tuberculous person is first "sympatheticotonic" and then becomes "vagotonic," the prognosis is poor, whereas if the tuberculous person is primarily "vagotonic," the process is usually relatively benign. Géza,<sup>102</sup> on the other hand, found "vagotonia" occasionally present with some productive forms.

Kamsler<sup>103</sup> studied the vascular response to epinephrine, atropine and neucisol in a group of tuberculous patients. He was careful to make the tests only in men and at the same time of the day. He found no apparent relationship between the vegetative response and the prognosis, but noted that the pyknic types responded with low blood pressure curves.

Interesting is his agreement that the vegetative response to these various pharmacologic agents is merely one of an accentuation of a pre-existing orientation and that it is dependent particularly on calcium concentration. He insisted that one should speak merely of an irritability or a depression of the vegetative system, as did Bovet.<sup>104</sup>

The autonomic status as judged on the basis of the blood pressure response to epinephrine in our series indicates a decided lessening of the reactivity of the tuberculous group as contrasted with the group of 100 normal persons. So, too, of the twenty-four patients who died, those who lived the longest had the more marked "sympatheticotonic"

97. Eppinger, H., and Hess, L.: *Die Vagotonie*, Berlin, 1910.

98. Deutsch, F., and Hoffman, O.: *Wien. klin. Wchnschr.* **26**:569, 1910.

99. Dresel, K.: *Ztschr. f. klin. Med.* **101**:70, 1924.

100. Guth, E.: *Beitr. z. Klin. d. Tuberk.* **53**:94, 1922; **54**:186, 1923; **55**:33, 1923; **60**:39, 1924. Glaser, W.: *Ibid.* **55**:390, 1923.

101. Kading, K.: *München. med. Wchnschr.* **71**:225, 1924.

102. Géza, Gali: *Gyógyászat* **62**:232, 1922; abstr. *Zentralbl. f. d. ges. Tuberc. Forschung* **19**:31, 1923; **22**:493, 1924.

103. Kamsler, A.: *Klin. Wchnschr.* **7**:110, 1928.

104. Bovet, A.: *Schweiz. med. Wchnschr.* **58**:483, 1928.

reactions to tuberculin when they were examined, and of the four patients who were losing weight at the time of examination but subsequently improved, three showed a "sympatheticotonic" reaction.

We have repeatedly expressed our reservation concerning the use of the terms "sympatheticotonic" and "vagotonic." We should much prefer to discard them entirely, resolving the term into the various components, i. e., the local status of the tissues, whether active or resting, whether with increased or diminished permeability, whether with dilatation or constriction of the vessels, whether with relative alkalosis or relative acidosis, etc. The terms "sympatheticotonic" and "vagotonic" are altogether too conflicting and too broad to be useful.

We shall examine the local reaction from this point of view. About a tuberculous focus there exists a zone of tissue stimulation (irritation) which may range from slight and transient effects that are promptly reversed by the more remote cells of the focus, through all the stages of fatigue and finally to death. In the stage of stimulation, the metabolic rate, acidity, permeability, cellular exchange and enzymatic (digestive) processes, are all increased; calcium leaves the tissue and sodium and potassium enter. A general lessening of tissue cohesion takes place. In general terms, we can regard this as an abnormal status of the vegetative balance in which the autonomic nervous system, the ionic equilibrium, the hormones and the tissue metabolites play their rôles.

Tissue changes associated with autonomic derangement are usually associated with local injury, more rarely with changes in the entire organ and sometimes with alterations in the vegetative balance involving the entire body.

1. Alterations in the nervous component of the vegetative system may originate from (a) purely psychic effects, (b) direct injury of nerves, as for instance, the pressure of enlarged mediastinal glands on the vagus, and (c) central (midbrain) injury, illustrated strikingly in some cases of postencephalitic parkinsonism and in some of the intoxications that follow bacterial or other poisoning.

2. Endocrine dysfunction plays a rôle. Diminution of the suprarenal secretion and perhaps of the pancreatic hormone would have a tendency to increase permeability, as would hyperfunction of the sex glands and of the thyroid gland. The activity is, however, conditioned to a large extent by the ion equilibrium existing at the cell surface, i. e., by the preexisting state of activity of the cell.

3. Tissue reaction is also involved. Increased acidity increases permeability, and this goes hand in hand with a release of calcium from the cells.

*The Vascular Reaction to Tuberculin.*—Given this background, let us examine the status of the tuberculous tissue and the tuberculous

person as a whole. We know, in general, that the reaction of the tuberculous tissue, as recently shown by Schade and Claussen,<sup>105</sup> is on the acid side (from  $p_H$  7 to  $p_H$  7.3) and exactly at the optimum for growth of the tubercle bacillus. We know, too, that the peripheral dilatation of blood vessels depends not on central vasomotor regulation, but on the peripheral effects of dissimilation, including primarily, increased acidity, as well as the effects of histamine and acetylcholin.

Fleisch recently added a demonstration which is most convincing.<sup>106</sup>

Tuberculin itself always causes vessels to dilate.

In preceding discussions, we have pointed out that stimulation of smooth muscle (in the metabolic and membrane sense) is associated with relaxation, i. e., lengthening of the cell. The reason for this seemingly paradoxical point of view we need not again elucidate; the physiologic observations have been generally accepted. When we extend this to the smooth muscle of the blood vessel wall, direct stimulation of cells must result in the dilatation of the vessel. Epinephrine, which makes the membrane less permeable, apparently causes contraction, irrespective of its presumable effect via the sympathetic mechanism.

Tuberculin stimulates the normal organism;<sup>107</sup> in the tuberculous animal, the stimulation may proceed to fatigue. We should expect that in the isolated vessel preparation perfusion with tuberculin would cause dilatation. Experiments of Preobraschewsky<sup>108</sup> are now available on this point. He found that tuberculin causes the normal vessels to dilate, with contraction following. In the tuberculous animal, the preliminary dilatation persists indefinitely. Buillion acts like tuberculin.

He also observed that a vessel preparation of animals with advanced tuberculosis showed a lessened reactivity to epinephrine. We believe this to be explained on the basis of the well known observation that epinephrine causes little or no contraction of vessels in irritated (inflammatory) regions. When tuberculin was injected into animals and vessel preparations were then perfused, the reaction to tuberculin (and buillion) was irregular. Similar experiments were made by Friedberger and Seidenberg.<sup>109</sup>

Here a physiologic preparation offers the counterpart of the intravital phenomena that take place when tuberculin is injected or that must obtain when tuberculin is released from a focus. The vessels are

105. Schade, H., and Claussen, F.: *Beitr. z. Klin. d. Tuberk.* **62**:300, 1925.

106. Fleisch, A.: *Klin. Wchnschr.* **8**:1315, 1929.

107. Levinson, S. A., and Petersen, W. F.: *Am. Rev. Tuberc.* **15**:681, 1927.

108. Preobraschewsky, A. M.: *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **63**:132 and 139, 1929.

109. Friedberger, E., and Seidenberg: *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:276, 1927.

directly stimulated. In place of a normal reversal occurring, the tissue is readily fatigued and reversal is delayed, i. e., dilatation persists.

Therapeutic agents that have been useful in tuberculosis are those most frequently directly active on the capillaries, and even that most specific agent, tuberculin, is effective in the therapy of tuberculosis probably not because of its immunologic properties but because of its influence on the caliber of the arterioles and the permeability of the capillaries (and tuberculous lesions), as originally supposed by Moro.

It is the vascular reaction that must always be regarded as the basis of any understanding of the tuberculous lesion. Physiologic vascular processes, which can be interpreted on the basis of stimulation, of rest or of fatigue, have been disguised by obtuse and conflicting immunologic concepts. We have come to consider resistance without reference to specific concepts, and Kalbfleisch<sup>110</sup> seems to have reached the same position when he stated that there is no room for the term "immunity" in the pathology of tuberculosis. This is quite apart from the persistent attack on the specificity of the tuberculin reaction.<sup>111</sup> We have felt justified in concluding from our experiments<sup>112</sup> that the reaction of the normal animal differs from that of the tuberculous animal only in degree. Kalbfleisch's conclusions in this connection are as follows:

There is only one thing that differentiates the effect of tubercle bacilli in tuberculous animals from the effect in the healthy animal; these are differences in the reaction of the vascular system, which, depending on susceptibility to the irritation and reactivity of the nervous elements of the vascular bed of the tuberculous animal, bring about quantitative differences from the reaction of the normal animal, and thereby bring about quantitatively altered effects in the cells and fibers of the tissue.

All the therapeutic agents of the "reactive" class, tuberculin, sodium aurothiosulphate, hetol, etc., act seemingly in a relatively simple way.<sup>113</sup> They first make the tissues more permeable, and later the tissues become less permeable for a considerable period of time.

The focal reaction, whether in the form that is obvious clinically or consisting merely of the imperceptible biologic actions following the injections of minute doses of the agents in question, is a reaction that depends on changes in permeability of the capillaries about the tuberculous focus.

110. Kalbfleisch, H. H.: *Beitr. z. Klin. Tuberk.* **70**:465, 1928.

111. Selter, H., and Bloomenberg, W.: *Beitr. z. Klin. d. Tuberk.* **66**:105, 1927. Beiling, R., and Keller, W.: *ibid.* **69**:577, 1928. Keller, W., and Dölter: *ibid.* **60**:444, 1928.

112. Petersen, W. F.; Jaffe, R. H.; Levinson, S. A., and Hughes, T. P.: *J. Immunol.* **8**:387, 1923. Petersen, W. F., and Levinson, S. A.: *Am. Rev. Tuberc.* **8**:122, 1923.

113. Levinson, S. A.; Petersen, W. F., and Milles, G.: *Am. Rev. Tuberc.* **16**:285, 1927.

Biologic processes, such as the menstrual cycle, the effects of season, etc., that are associated with an increase in capillary permeability and autonomic imbalance are apt to be associated with clinical activation.

A most enlightening condition concerns the relation of the mortality from tuberculosis to the season. The association of clinical activity with the spring goes back to Hippocrates. A recent statistical correlation is that of Herrup from the Faroe Islands.<sup>114</sup> The change in the K/Ca ratio and the seasonal changes in the size and activity of the organs made apparent in the work of Riddle<sup>115</sup> and Brown<sup>9</sup> bring us nearer a logical explanation of the clinical observations.

Clinically advancing tuberculosis is associated with increased capillary permeability; healed tuberculosis with diminished permeability. It might seem warranted to draw the conclusion that increase in capillary permeability, however produced, would unfavorably influence a tuberculous lesion, and that, conversely, diminished permeability must be associated with improvement.

We shall not endeavor to include in this summary a review of all the results of the examinations made, but shall discuss briefly only the more important phases of the work.

*Correlations Based on Clinical Classifications, Weight Curve, Clinical Prognosis and Fatalities.*—The Clinical Classifications of the National Tuberculosis Association (table 2, part VIII A, p. 168): Apart from the obvious correlations (tuberculosis fixation, Darányi reaction, basal metabolic rate, pulse rate, etc.), there are no consistent changes as we proceed from the incipient A to the far advanced C cases. We might anticipate this. The incipient A group will include patients in whom the disease may develop rapidly, may heal or may become chronic. The far advanced C group will include patients who have had chronic tuberculosis for years, with relatively high resistance. In addition, there will be many persons with febrile tuberculosis, with peripheral vasoconstriction, made evident in the prolongation of the blister time.

Weight Curve (table 3, part VIII A, p. 168): The grouping of patients by relative increase or decrease of weight at the time of examination begins to offer something more tangible. It is to be noted that the persons with healed tuberculosis (roentgen shadows only) have a permeability of 65. Persons with roentgen evidence of active tuberculosis (very chronic) have a permeability of 59. Our sanitarium group shows a progressive increase to 69.6. There is, however, no consistent relation to the blood chemistry, but the blood proteins increase, and the McClure-Aldrich test is markedly shortened.

114. Herrup: Beitr. z. Klin. d. Tuberk. **68**:739, 1928.

115. Riddle, O.: Am. Naturalist **61**:481, 1929.

Prognosis (table 9, part VIII A, p. 176): Here we begin to obtain interesting clinical and laboratory correlations. The relation to permeability and to calcium has been discussed. We note that the "vagotonic" reaction to epinephrine increases; the epinephrine flare becomes smaller while the thyroxin flare becomes larger, the cholesterol/lecithin ratio becomes smaller, the McClure-Aldrich test becomes shorter and the tuberculin reaction smaller.

Fatalities (table 10, part VIII A, p. 181): When, finally, we consider the patients who died and place them in two groups (those that lived an average of forty-five months after the onset of clinical activity and those that lived an average of sixty-five months), we find that the less resistant group had a high capillary permeability, much less calcium, less cholesterol, a higher globulin content and a shorter McClure-Aldrich time, while there were more "sympatheticotonic" persons in the group that lived longest.

*Calcium.*—We must regard the calcium metabolism as in some way closely associated with the clinical condition of the patient. In the group with low calcium, for instance, we find more deaths. We find that the persons with healed tuberculosis have higher calcium (10.3), that persons with good prognosis have higher calcium (10.7 and 10.6), that those with stationary disease have lower calcium (9.1); as we then turn to those with poor prognosis, the calcium level again rises (10.2), owing, we believe, to the probability that with a negative balance, calcium is being mobilized from the tissues. We have previously discussed some of the literature dealing with calcium in tuberculosis (part III).

More and more clinical evidence is accumulating which indicates the importance of calcium in tuberculosis in regard to both the reactivity of the tissue and its influence on the disease process. Sternberg<sup>116</sup> found lower serum calcium in the most advanced cases; Schaefer,<sup>117</sup> an increase in the calcium in the lung in chronic tuberculosis. Sweany<sup>118</sup> and his associates found the calcium levels about normal, and Hoyle,<sup>119</sup> admitting the clinical impression of improvement with calcium, regarded the experimental evidence as still lacking. He found an early increase in calcium in rabbits infected with tuberculosis, with a terminal decline. The lack of experimental confirmation is, however, not necessarily a criterion of clinical value, for the reason that tuberculosis in the guinea-pig and in the rabbit, particularly, is decidedly different from tuberculosis in man. As a matter of fact, Henner<sup>120</sup> observed that when

116. Sternberg, T.: Beitr. z. Klin. d. Tuberk. **71**:737, 1927.

117. Schaefer, R.: Beitr. z. Klin. d. Tuberk. **69**:86, 1928.

118. Sweany, H. S.; Wethers, A. T., and McCluskey, K. L.: Am. Rev. Tuberc. **8**:405, 1924.

119. Hoyle, J. C.: Quart. J. Med. **22**:451, 1929; J. Pharmakol. & Exper. Therap. **34**:317, 1928.

120. Henner: Beitr. z. Klin. d. Tuberk. **51**:56, 1929.

calcium dust ( $\text{Ca}[\text{OH}_2]$ ) was used, tuberculous animals not only showed less involvement than animals exposed to other dust, but actually less than the control animals not exposed to dust. The clinical literature, as mentioned previously, is rather conflicting, and various methods have been suggested for the administration of calcium, as well as various indications. Thus Siegel<sup>121</sup> stated that he obtained improvement in 50 per cent of his cases with calcium inhalation. Becker<sup>122</sup> treated 150 patients with intravenous medications and mentioned improvements, particularly in bilateral involvements.

*Cholesterol.*—That cholesterol usually diminishes with progressive tuberculosis has been frequently noted. This, of course, is in line with the change in cholesterol metabolism apparent in other infections.<sup>123</sup> In recent work, Shope<sup>124</sup> brought experimental evidence that increasing serum cholesterol probably plays some rôle in prolonging the life of experimentally infected guinea-pigs, confirming clinical observations that date back a number of years.<sup>125</sup> Borchardt,<sup>126</sup> as well as Leupold and Bogendörfer, recently presented further experimental evidence concerning the usefulness of cholesterol in increasing resistance to infection, an increase which seems to follow specific immunization, too.<sup>127</sup> The association of a low cholesterol in tuberculosis with poor prognosis was noted by Rieter,<sup>128</sup> and is in line with the results of our observations.

It is rather interesting to note that Glaser<sup>129</sup> published clinical observations indicating that the cholesterol level of the blood may change with changes in the psychic state just as does the calcium level, while Wade<sup>130</sup> found an increase in cholesterol associated with a decrease in the serum calcium.

*Reactivity of the Skin.*—The reactivity of the skin of the tuberculous patient has been a subject of study for so many years by so many investigators that we shall make no effort to review the literature, but merely point out that there is a general recognition of the fact that, apart from the so-called "specific" factor, the degree of reactivity is dependent on the status of the skin, i. e., that the systemic factors play a decided rôle. Thus, the reactivity to tuberculin diminishes in the

121. Siegel, H.: Ztschr. f. Tuberc. **53**:256, 1929.

122. Becker, A.: Ztschr. f. Tuberc. **53**:198, 1929.

123. Heening, B. H.: J. Biol. Chem. **53**:167, 1922. Gabrila, J., and Vior, V.: Arch. d. mal. de l'app. digestif **18**:601, 1928. Heinze, V.: Ztschr. f. Tuberc. **52**:199, 1928.

124. Shope, R.: J. Exper. Med. **48**:321, 1928.

125. Valois, G.: De la cholesterinémie au cours de la tuberculose pulmonaire, Lyon and Paris, A. Maloine et fils, 1912. Farini, A.: Gazz. d. osp. **35**:993, 1914.

126. Borchardt, W.: Klin. Wchnschr. **8**:1179, 1929.

127. Barbara, M.: Arch. di pat. e clin. med. **8**:379, 1929.

128. Rieter, H.: Klin. Wchnschr. **8**:1158, 1929.

129. Glaser: Klin. Wchnschr. **6**:2377, 1927.

130. Wade, P. A.: Am. J. M. Sc. **177**:790, 1929.

terminal stages in tuberculosis, during intercurrent disease and with "desensitization" due either to tuberculin therapy or as a result of non-specific injections.

Nor is it possible to review the extensive literature concerning reactivity of the skin, in general. The monographs of Lewis,<sup>131</sup> the shorter works of Hecht,<sup>132</sup> Pulay<sup>133</sup> and Luithlen,<sup>134</sup> the reviews of von Groer<sup>46</sup> and Ebbecke<sup>135</sup> are available for this purpose.

We would, however, refer again to the work of Kauffmann.<sup>52</sup> Kauffmann observed that when he placed cantharides on the skin of a patient with pneumonia, several distinct stages of reactivity could be distinguished. First, during the febrile period, he observed a delayed or absent reaction. Second, with defervescence a marked reaction; third, after defervescence, a period of transition during the next ten days to a maximum monocytic reaction in the exudate; fourth, for a varying interval, another period of inhibition or delayed reactivity (adaphorea of von Groer, presumably not the same as local immunity in the specific sense).

As cantharides constitute a chemical irritant acting primarily on the cell membranes, specific sensitization plays no rôle, but the results are nevertheless of interest for the tuberculin reaction. Let us examine the possible correlation.

1. During the febrile stage there exists a peripheral inhibition (vasoconstriction). Cantharides can act on the cells, but little or no exudate forms. The direct injury to the cells is great because there is no dilution, and healing takes place slowly (see discussion of herpes). Applied to tuberculosis and the tuberculin reaction, it means that during the febrile stage of an intercurrent disease, the tuberculin reaction is inhibited because of the change in the status of the skin; during the terminal stages of tuberculosis itself, this factor is also operative.

2. During the period corresponding to defervescence in pneumonia when, as Meyer pointed out, vascular dilatation is accentuated, this peripheral factor is negated, and vigorous reaction takes place. Applied to the tuberculin reaction, this corresponds to the period of maximum response when sensitization (i. e., direct cellular response and vasodilatation due to the direct effect of the tuberculin) prevails at a time during which peripheral vasodilatation is compensating for the increased metabolism going on in the body, i. e., during the period of vasomotor

131. Lewis, T.: *The Blood Vessels of the Human Skin*, London, Shaw & Sons, 1927.

132. Hecht, A. F.: *Ztschr. f. d. Ges. exper. Med.* **33**:23, 1923.

133. Pulay, E.: *Stoffwechsel und Haut*, Vienna, Urban & Swartzenberg, 1923.

134. Luithlen: *Pharmakologie der Haut*, Berlin, Julius Springer, 1921.

135. Ebbecke, U.: *Deutsche med. Wchnschr.* **50**:1, 1924; *Naturwissenschaften* **14**:1131, 1926.

instability, when the tuberculotoxin has not yet stimulated the liver to the degree that the splancho-peripheral balance has become fixed. The autonomic skin function is, in other words, practically normal insofar as lability is concerned.

3. Finally, in the pneumonia patient, at varying intervals after the crisis (from three to five weeks), a period supervenes during which the skin is again nonreactive. Here we are not dealing with a peripheral vasoconstriction present during the acute febrile stage. The tissue cells have changed. The cell membranes are no longer irritated to the same degree by the same amount of the irritant. The cell membranes have become less permeable. Applied to tuberculosis we find the same picture during periods of relative quiescence of the lesions, with recovery; after a course of tuberculin treatment, or after a series of relatively bland nonspecific injections.

These are wholly nonspecific effects which influence the reactivity of the skin in general, but they are of importance for the problem of tuberculosis because the vegetative status of the skin and the vasomotor activity are underlying factors that determine the type of reaction to all toxic agents.<sup>136</sup>

That these different states of reactivity of the skin are associated with differences in the underlying physicochemical equilibrium we need not again emphasize. However, the experiments of Klauder and Brown,<sup>137</sup> which are pertinent, must be mentioned. In their experiments, a correlation of the blood and skin chemistry with the intensity of the skin reaction is made evident.

Apparently, differences exist that depend on the type of irritant; for instance, calcium seems to be much more closely related to the effect of epinephrine and to the blister time; potassium, to the effect on the skin of thyroxine and caffeine. Needless to say, there are many other modifying factors (table 1, part I).

*Leukocytic Reaction.*—Among the reactions that we have followed with particular interest has been the effect of the intracutaneous injection of a bland protein on the leukocytic curve.

136. Roeckemann: Beitr. z. Klin. d. Tuberk. **49**:301, 1922. Stutz: Schweiz. med. Wchnschr. **54**:676, 1924. Schuberth, A.: Beitr. z. Klin. d. Tuberk. **69**:273, 1928.

137. Klauder, J. V., and Brown, H.: Experimental Studies in Eczema: I. A Study of the Sensitivity of the Skin of Rabbits to Chemical Irritants Under Experimentally Induced Conditions, Arch. Dermat. & Syph. **11**:283 (March) 1925; II. A Correlation of the Chemistry with the Irritability of the Skin of Animals Under Normal and Under Experimentally Induced Conditions, *ibid.* **15**:1 (Jan.) 1927; III. The Rôle of Sympathetic Nervous Irritability in the Rabbit, *ibid.* **19**:52 (Jan.) 1929; IV. The Correlation of the Potassium-Calcium Ratio in the Serum and in the Skin of Rabbits with the Irritability of the Skin, *ibid.* **20**:326 (Sept.) 1929.

Intracutaneous injections bring about systemic effects, not only through the agency of the injected solution, but through the stimulation of the skin. Perhaps this stimulation of the skin is associated with liberation of histamine; perhaps it is due to a purely autonomic upset of the type that we have illustrated in charts 2, 3 and 4. Lewis reported experiments in which multiple areas of irritation of the skin resulted in a distinct systemic effect due, according to his hypothesis, to the actual liberation of enough histamine to bring about a general reaction.

Our composite curves indicate that when patients are classified on the basis of increasing, stationary or decreasing weight, the leukocytic reaction in the losing group is that of a rather marked primary leukopenia following the intracutaneous injection. Such a group of patients shows a coincident lowering of the blood pressure. We ascribe this to the fact that in this group the splanchnic vascular bed is more easily thrown out of balance with consequent accentuation of splanchnic stimulation and dilatation and a resulting accumulation of leukocytes in the splanchnic area. The reactions merely afford additional evidence for the supposition of an altered vegetative status with progression of the disease.

*Therapeutic Considerations.*—Granted that the tuberculous lesion can be made clinically innocuous in one of two ways—(1) by digestion and (2) by complete encapsulation—the former method would be supported therapeutically by any measures that increase vascularization, increase enzymatic processes, increase permeability or, in general terms, bring about tissue stimulation, with relative acidosis, or the so-called “parasympathetic status.”<sup>138</sup> The inherent danger lies (1) in the possibility of dissemination of the virus, (2) in the diffusion of toxic products and (3) in the possibility that stimulation may proceed to fatigue and death. We can readily understand that only sluggish lesions of the peripheral type or small lesions in the more vascular organs can be so treated with any degree of safety.

The second method, complete encapsulation, would be supported therapeutically by methods that decrease vascularization, decrease enzymatic processes, decrease capillary permeability or, in general terms, bring about rest of tissue or a “sympathetic” status,<sup>139</sup> with relative alkalosis. Here one must assume a therapeutic indication in the more extensive lesions, especially of the vascular organs.<sup>140</sup>

From the point of view of constitutional types, we can see that our heavy type should offer a general biologic status of diminished permea-

138. To be differentiated from vagotonia (see page 296).

139. To be differentiated from sympatheticonia (see page 296).

140. The vascular endothelium of the viscera—liver, kidney, spleen, gastrointestinal tract—is normally more permeable than that of the peripheral tissues.

bility, lower metabolic rate and more sluggish inflammatory reactions that would seem favorable for the development of a slowly progressive, relatively benignant lesion. Presumably, in endocrine balances we would see less effect of the thyroid gland, with probably more effect of the pituitary gland, and in some cases more secretion of epinephrine.

Our slender type should offer two possibilities: a person, who, because of intense reactivity—with relative acidosis, increased metabolic rate, increased permeability, etc.—might, under certain circumstances, succumb to the infection rapidly, especially if infected with a large dose of the virus; and another person of the same type who might readily and rapidly dispose of tubercles, with relative freedom from clinical symptoms. The latter would presumably have more thyroid secretion, more sex gland secretion and varying degrees of suprarenal and pituitary activity.

It is perfectly obvious to us that in the intricate biologic picture of inflammation presented by tuberculosis innumerable possibilities exist. We have merely delineated the extremes. We would, however, reiterate that in clinical tuberculosis, it is the vascular mechanism that must always be in the foreground of consideration.

The particular therapeutic studies that have been introduced in the final paper of the tuberculosis series (VIII C, p. 236) are to serve only to illustrate several points in connection with the theoretical deductions; they are not to be regarded as clinical evidence for another cure for tuberculosis. They indicate that:

1. Pilocarpine (case of sister A, part VIII C, p. 241), which makes the capillaries more permeable, may be followed by dissemination.
2. Epinephrine (case of sister B) which normally is not only diphasic but amphotropic, may, when it makes capillaries less permeable, diminish clinical activity; or may make the capillaries more permeable and increase clinical activity (case 2, under "Reports of Other Cases," part VIII C, p. 249).
3. Pituitrin, which apparently acts more specifically on the cell membrane in lessening permeability (even in irritated tissues) may lessen clinical activity (cases 4 and 5).
4. Alkalosis is apparently useful (case 1) and stimulation of the skin by means of a skin burn, which theoretically should result in a peripheral dilatation and a splanchnic constriction, may also be useful (case 3).

With investigators in tuberculosis becoming more and more interested in tissue activity as a factor in resistance, many therapeutic procedures will be offered and exploited. The Gerson diet has already been capitalized. Here a diet predominantly of vegetables and fruits with its tendency toward alkalization is advised with a salt-free oat-

meal diet, with its contrary tendency, and a proprietary salt mixture is added for good measure. Of course, the clinical reports are conflicting. If the Gerson diet really tends to bring about tissue acidosis, it should be useful in the sluggish peripheral types of infection, and actually the results in infection of the skin seem to be encouraging. On the other hand, there appears to be little consistent effect in the pulmonary lesions. As is the case with so many cure-alls the proponents here forget the innumerable individual features of each clinical picture and that a therapy which may be admirable for a sluggish tuberculosis of the skin is by no means necessarily useful for a visceral tuberculosis.

Practically every "cure" has met with this fate; and it must be the fate of every type of treatment that depends on tissue reactivity for its curative properties. "Stimulating" substances—tuberculin, hetol and sodium aurothiosulphate, for example—are active in sufficiently large doses by increasing permeability. And with large doses, injury almost invariably results. In small doses, they are sometimes useful because the transient stimulation and increased permeability are followed by a reversal—with a persisting impermeability. The agents that might presumably act in a contrary direction, epinephrine as originally suggested by Sargent, or calcium, may be useful when the preexisting state of the tissue is favorable. If not, one may get "paradoxical" effects with increased permeability and clinical injury. Even the physical agents, particularly heliotherapy, are followed by identical results. Sunlight may activate lesions in certain persons and may be useful in others.

We have the conviction that if we once begin to plan the therapeutic attack in tuberculosis less from the point of view of the immunologists and pharmacologists and more from that of the inflammatory reaction and its physiologic and physiochemical aspects, we shall be able to devise a more rational therapy.

What has been detailed for a chronic infection like tuberculosis has been presented merely to illustrate a point of view which we believe may be useful in other therapeutic problems.



