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

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Chicago, Ill., [1930]

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IV. THE RELATION OF THE REACTION TO EPINEPHRINE TO THE POTASSIUM/
CALCIUM RATIO AND TO OTHER RATIOS*

[urn:nbn:de:hbz:38m:1-145693](https://nbn-resolving.org/urn:nbn:de:hbz:38m:1-145693)

IV. THE RELATION OF THE REACTION TO EPI- NEPHRINE TO THE POTASSIUM/CALCIUM RATIO AND TO OTHER RATIOS*

During the course of investigations dealing with a correlation of skin reactions with the blood chemistry and certain cardiovascular renal reactions, we have had occasion to study the effect of subcutaneous injections of epinephrine on the blood pressure of one hundred so-called "normal" men, as well as on about fifty patients who were ill from various diseases (glaucoma, exophthalmic goiter and other conditions). It is our purpose to enter into an analysis of these correlations in this paper.

It is agreed, we believe, that the original efforts of Eppinger and Hess¹ to classify all persons into groups that were vagotonic or sympathicotonic proved unsatisfactory, indeed confusing. There is no doubt that the emphasis placed on the study of the autonomic reactions of the patient has contributed immensely to the concept of the underlying factors of a number of disease conditions, but this study has added, for the time being at least, much uncertainty as well. Some of the confusion is due to the earlier concept that the autonomic apparatus consists merely of an equilibrated nervous mechanism with antagonistic impulses; to the pharmacologic aspect which has probably not infrequently failed to distinguish between direct protoplasmic action and selective action of the so-called autonomic drugs; to the fact that the cardiovascular response to epinephrine, for instance, need not be a criterion of its effect on other tissues. The great dependence of the reaction of individual organs or tissues on their state of activity when the autonomic impulse might become operative; the importance of the endocrine and humoral ionic milieu has been almost wholly disregarded. We seem warranted in believing at present that the original idea of Eppinger and Hess as to a one-sided preponderance of either the vagus or sympathetic nerve is incorrect; indeed, that when alterations do occur in the autonomic apparatus, both vagus and sympathetic nerves are involved; that when an apparent overbalance exists, overcorrection is usually apparent either in the organ or in remote regions; and that we deal not merely with an autonomic apparatus as such, but with more fundamental

* Article by Petersen, W. F.; Levinson, S. A., and Arquin, S., reprinted from Arch. Int. Med. **42**:256 (Aug.) 1928.

1. Eppinger, H., and Hess, L.: Ztschr. f. klin. Med. **68**:205, 230, 1909.

alterations in the cells of the organs, changes intimately associated with stimulation or rest, fatigue or even death.²

Partly as a result of the indefinite clinical observations which have been associated with the so-called vegetative neuroses, clinicians in general make little use of the tests designed to elucidate the preponderance of either vagus or sympathetic influence, except in the study of the cardiac reactions. But in recent years the study of the electrolytes of the body, originating with Loeb and carried out in clinical directions particularly by the Kraus school³ (Zondek, Arnoldi, Wollheim, Dresel, Kylin) and others, has indicated the intimate connection between the presumptive autonomic reactions, the electrolyte balance and the hormones. Kylin, in particular, has devoted considerable time to the correlation of these alterations in the blood chemistry in asthma, hyperpiesis, diabetes and other conditions to the reaction of epinephrine.⁴

As stated in the foregoing paragraphs, our material consisted, first, of a group of one hundred normal persons. Of these, about twenty were laboratory workers, the rest were men sent to us from an employment bureau. They were normal in the sense that they were not patients, and that they gave a cross-section of a male working population of varying ages. On closer analysis, however, the great majority were by no means absolutely normal. Of the total number, twenty-six were apparently normal in every sense; thirteen were apparently normal, but a well defined healed parenchymal tuberculosis was revealed by roentgen-ray examination. Then there were those cases in which active pulmonary tuberculosis was made probable by the roentgenogram, the cases with a positive Wassermann reaction, the markedly nervous persons, and a large group of persons who revealed cardiovascular-renal alterations, as shown by the blood pressure, roentgen-ray examination of the heart and large vessels, observations on the urine, microscopic examination of the capillaries of the skin, etc.

2. Because of the confusion resulting from the conflicts between anatomic nomenclature and classification of the autonomic nervous apparatus and the pharmacologic methods of analysis, Müller and one of us (W. F. P.) (*Arch. Int. Med.* **40**:575 [Nov.] 1927) have used the term sympathetic status to denote organ activity associated with contracted vessels (i. e., usually tissue rest), while we have used the term parasympathetic status to denote tissue activity when the vascular channels are dilated (i. e., with stimulation of an organ). This is, of course, a purely functional point of view, but one which we believe avoids certain of the present difficulties.

3. Kraus, F. in Zondek, S. G.: *Elektrolyte, Ihre Bedeutung für Physiologie, Pathologie und Therapie*, Berlin, Julius Springer, 1927.

4. Kylin, E.: *Acta med. Scandinav.* **66**:197-206, 1927.

To this so-called normal material, there has been added a group of forty-nine patients from the wards of the Research Hospital. As so constituted there were:

Normal persons	26
Normal, with healed parenchymal tuberculosis.....	13
	—
	39
Cardiovascular renal abnormalities	68
Among these were: 7 with glaucoma	
5 with active tuberculosis	
2 who were nervous	
1 with syphilis	
1 with urticaria	
1 with angioneurotic edema	
Nervous or neurasthenic	9
Angioneurotic edema	1
Syphilitic	5
Tuberculous	5
Exophthalmic goiter	7
Eczema	2
Epilepsy	1
Scleroderma	1
Myasthenia gravis	1
Urticaria	1
Heart disease	1
Epidemic encephalitis	1
Cancer of the thyroid	1
Glaucoma	2
Bronchitis	1
Feminine type young male.....	1
Dwarf	1
Tumor of the brain	1
	—
Total	149

With some unavoidable degree of arbitrariness, we have divided these persons into ten groups according to the reaction of the systolic blood pressure following the subcutaneous injection of 0.5 cc. of a 1:1,000 dilution of epinephrine. In the individual curves which are presented, the systolic blood pressure curve for one hour after the injection is shown.

The first five groups can be regarded as sympathetic in character. Seventy-six persons are represented in these groups.

The second series can be classified as parasympathetic, in that either the reaction was negative, or showed a depressor action, either primary or permanent. There were seventy-three in these groups.

In examining the charts and tables, it may be of interest to note that so-called normal persons are found in both the sympathetic and the parasympathetic groups, but there are more in the sympathetic groups. No normal person has responded with a marked or persistent fall in blood pressure. It may also be of interest to note that twice as many of the extuberculous persons (as shown by roentgen-ray examination) are to be found in the sympathetic groups.

In table 3 are presented the averages of results of the observations in the ten groups for the various examinations that were made on the persons examined.

TABLE 1.—*Group of Persons Who Give Sympathetic Reactions*

Group	Number in Group	Type of Reaction	Normal	Ex. Tuberculosis	Cardiovascular Renal Disease
I	16	Immediate and sustained increase	1	3	9
II	19	Immediate increase, not sustained	3	0	8
III	15	Slow, sustained increase.....	3	3	6
IV	10	Slow rise, not sustained.....	2	1	7
V	16	Slight increase	6	2	6
Total...	76		15	9	36

TABLE 2.—*Group of Persons Who Give Parasympathetic Reactions*

Group	Number in Group	Type of Reaction	Normal	Ex. Tuberculosis	Cardiovascular Renal Disease
VI	24	Slight decrease	4	1	11
VII	14	More marked, slow decrease.....	0	0	8
VIII	14	First reaction down, recovery.....	3	0	4
IX	11	Similar to VIII.....	3	2	5
X	10	More marked primary drop, recovery	1	1	4
Total...	73		11	4	32

In table 4 A, the averages for the sympathetic groups (I-V) and the parasympathetic groups (VI to X) are shown. In these summaries, it will be noted that: (1) the amount of serum calcium and potassium is increased in the sympathetic group, but the ratio remains unchanged; (2) the albumin-globulin ratio is lower in the sympathetic group; (3) the Kromayer time is somewhat prolonged; (4) the electrical resistance of the skin is higher; (5) the reactions to epinephrine (as computed mathematically) are, of course, higher in the sympathetic group; (6) the subjects are proportionally lighter in weight.

As there are relatively many nonreactive persons in each group, we have narrowed the selection of the material to the groups more strikingly different, and for this purpose have taken groups I, II and III for the sympathetic and groups VII and X for the parasympathetic types. These groups contain fifty and twenty-four persons, respectively.

TABLE 3.—Average Results of Examinations Made on Individuals in Ten Groups*

Number in Group	Group	Blister Time (a)	Permeability (a)	Inflammatory Index (a)	Calcium	Potassium	Potassium-Calcium Ratio	Sugar	Albumin/Globulin (b)	Kromayer Time (c)	Basal Metabolism	Skin Resistance (d)	Muscle Reaction (e)	Blood Pressure	Pulse Rate	Reaction to Epinephrine, P. P. (f)	Reaction to Epinephrine, P. P. x P. R. (g)	Carbon Dioxide	Reaction to Ice (h)	Age	Wt. / Lt. (i)	Cholesterol	(j)								
																							Epinephrine, White	Epinephrine, Red	Morphine, White	Morphine, Red	Thyroxin, White	Thyroxin, Red	Caffeine, White	Caffeine, Red	
16	1	9.1	67	8.7	10.6	18.8	1.8	74	2.1	1.8	8.6	0.43	4	120/70	78	22	25.5	55.5	21	45.5	194	202	20	10	11.6	10.8	14	4	21	2	
19	2	8.8	63	8.3	9.7	20.2	2.08	72	1.9	2.3	7.3	0.55	4.8	127/63	78	14	25	57.7	18	42	206	216	19.2	8.6	11.4	13.4	11.6	3.6	18.4	1.8	
15	3	7.3	66	9	10.2	22.7	2.22	77	1.5	2	8	0.39	2.5	122/67	76	25	36	57.8	19	41	215	223	20	8.8	10.8	16	13.2	5.4	16.6	2.4	
10	4	8.3	61.5	8.4	9.98	17.4	1.74	67	2.25	2.3	12.1	0.61	1.5	113/67	76	20	31.2	58.1	15	47.9	207	203	19.6	9.4	11.8	14.2	13	6.4	19.2	2.4	
16	5	7	65	10.1	10.5	20.5	1.97	71	2.4	1.75	13	0.72	3.4	125/66	75	12	19	57.4	19	37.5	193	220	20	8.8	11	16	11.4	4.6	16	2.8	
Sympathetic Group																Parasympathetic Group															
24	6	7.3	64	9.5	10.3	20	1.97	73	2.2	1.83	9.5	0.46	2.3	110/67	78	5	6	58	21	40	217	204	19.2	8.6	11	14	12.4	4.4	18.8	3.4	
14	7	7.8	63	9	10	19.6	1.99	73	2.1	1.75	9.7	0.46	2.4	133/66	77	5	6	57	22	47.7	227	204	20	8.8	10.2	13.6	9.4	3.2	19.2	1.8	
14	8	8.1	63	8.6	9.5	18.8	1.86	76	2.5	1.96	9.6	0.46	3.6	120/70	76	7.5	19	57.3	14	42	206	226	19.6	9.6	12.8	12.4	10.8	5.2	16.8	3.4	
11	9	6.5	64	10	10.1	19.9	1.97	74	2.4	1.76	11	0.25	4.6	130/75	74	12.4	23	56.4	16	42.4	230	240	20	8.6	12.4	16.4	11.2	4.8	16.4	4	
10	10	9.1	58	7.4	9.3	19.6	2.08	71	2.2	1.58	19	0.25	4	134/74	69	9.6	15.5	59.7	16	55.7	213	227	18	8.6	10.68	9.4	13.6	2.52	23.2	1	

* a, blister time—time in hours for formation of blister on forearm following cantharides plaster; permeability—ratio of protein in blister to protein in capillary blood; inflammatory index—permeability divided by blister time in hours, Petersen, Wm. F., and Willis, D. A.; Arch. Int. Med. 38: 653 (Nov.) 1926. b, method of Rohrer (Deutsches Arch. f. klin. Med. 121: 221, 1916). c, time in hours of first appearance of erythema following a 30-second exposure of the forearm to Kromayer lamp. d, resistance of skin of the forearm to passage of electrical current. e, muscle reaction (cathodal closing contraction) in milliamperes. f, average increase or decrease in pulse pressure (in percentage of preinjection level) for one hour after injection. g, average increase or decrease in pulse pressure times pulse rate (in percentage of preinjection level) for one hour after injection. h, appearance time of erythema (in seconds) following transient application of ice to the chest wall. i, weight in pounds divided by length in inches. j, average side of wheal and flare (in mm.) following intracutaneous injection of epinephrine, 1:1,000,000, 1:100,000, 1:10,000, 1:1,000; morphine, 1:10,000,000, 1:1,000,000, 1:100,000, 1:10,000; caffeine, 1:100.

In table 4B, it will be noted that the sympathetic group becomes more permeable, remains high in calcium and potassium content and retains the other differences previously noted. In addition, differences make their appearance in blood pressure, in the reaction to ice and in the red flare of the skin reactions.

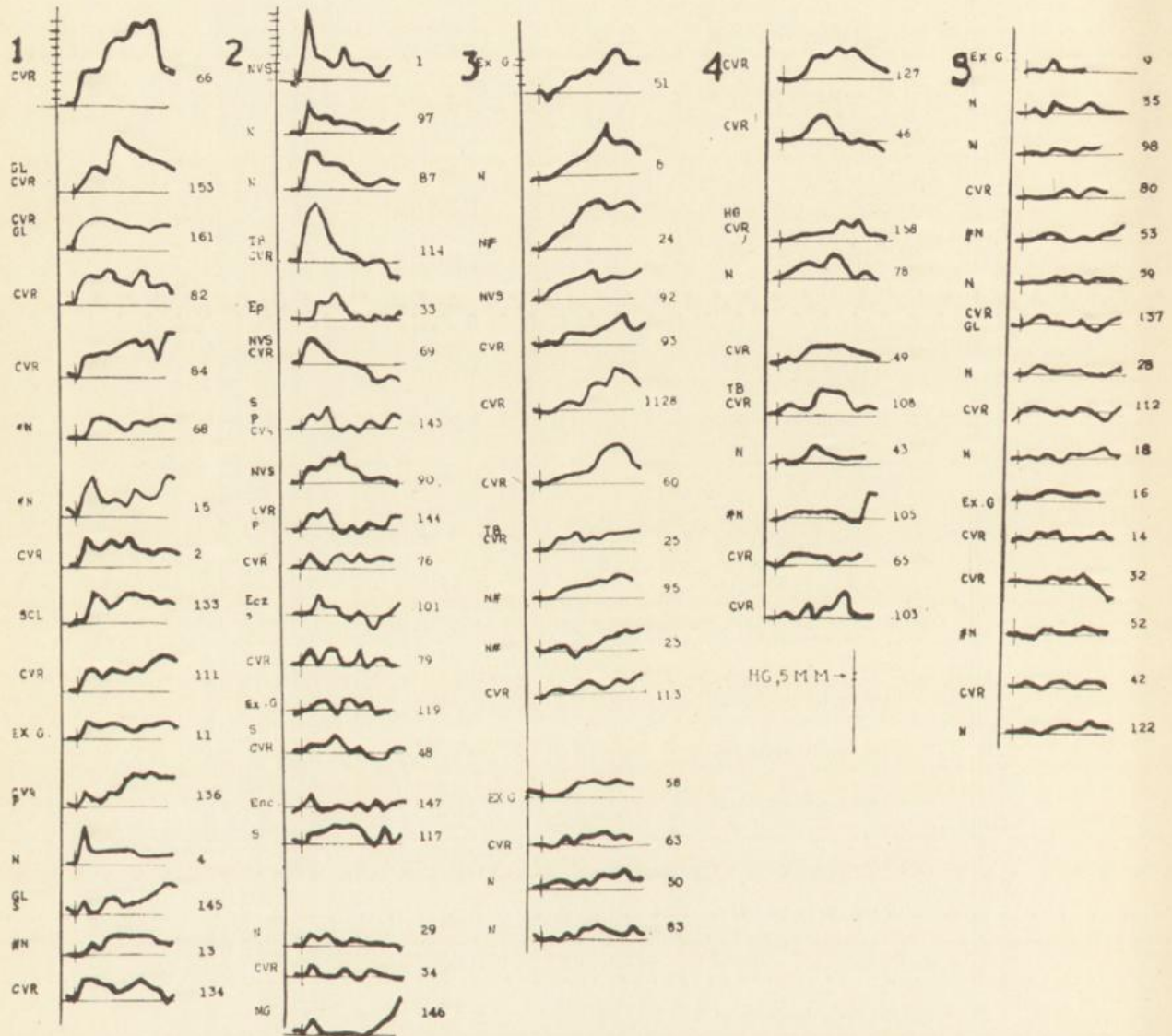


Fig. 1.—Graphic records of systolic blood pressure of sympathetic groups. Numbers at the right indicate the patient's number. The abbreviations at the left indicating diagnosis, represent the following: *N*, normal; *#N*, normal but roentgen-ray evidence of healed parenchymal tuberculosis; *C.V.R.*, cardiovascular renal complication; *Gl*, glaucoma; *Scl.*, scleroderma; *Ex.G.*, exophthalmic goiter; *P.*, pellagra; *S.*, syphilis; *N.V.S.*, nervous neuropsychasthenia; *T.B.*, tuberculosis; *Ep.*, epilepsy; *Ecz.*, eczema; *Enc.*, encephalitis; *M.G.*, myasthenia gravis; *HG*, Hodgkin's disease; *Urt.*, urticaria; *Ang. Neu. Ed.*, angioneurotic edema; *H. D.*, heart disease; *N. S.*, normal, sensitized; *G.*, glandular, feminine type; *Ca Thy.*, carcinoma thyroid; *D.*, dwarf; *F.*, fever, bronchitis.

We can go one step farther and select ten of the outstanding cases of each series and examine their averages. The cases selected include the first ten of group I and the last ten of group VII. The average are recorded in table 4.

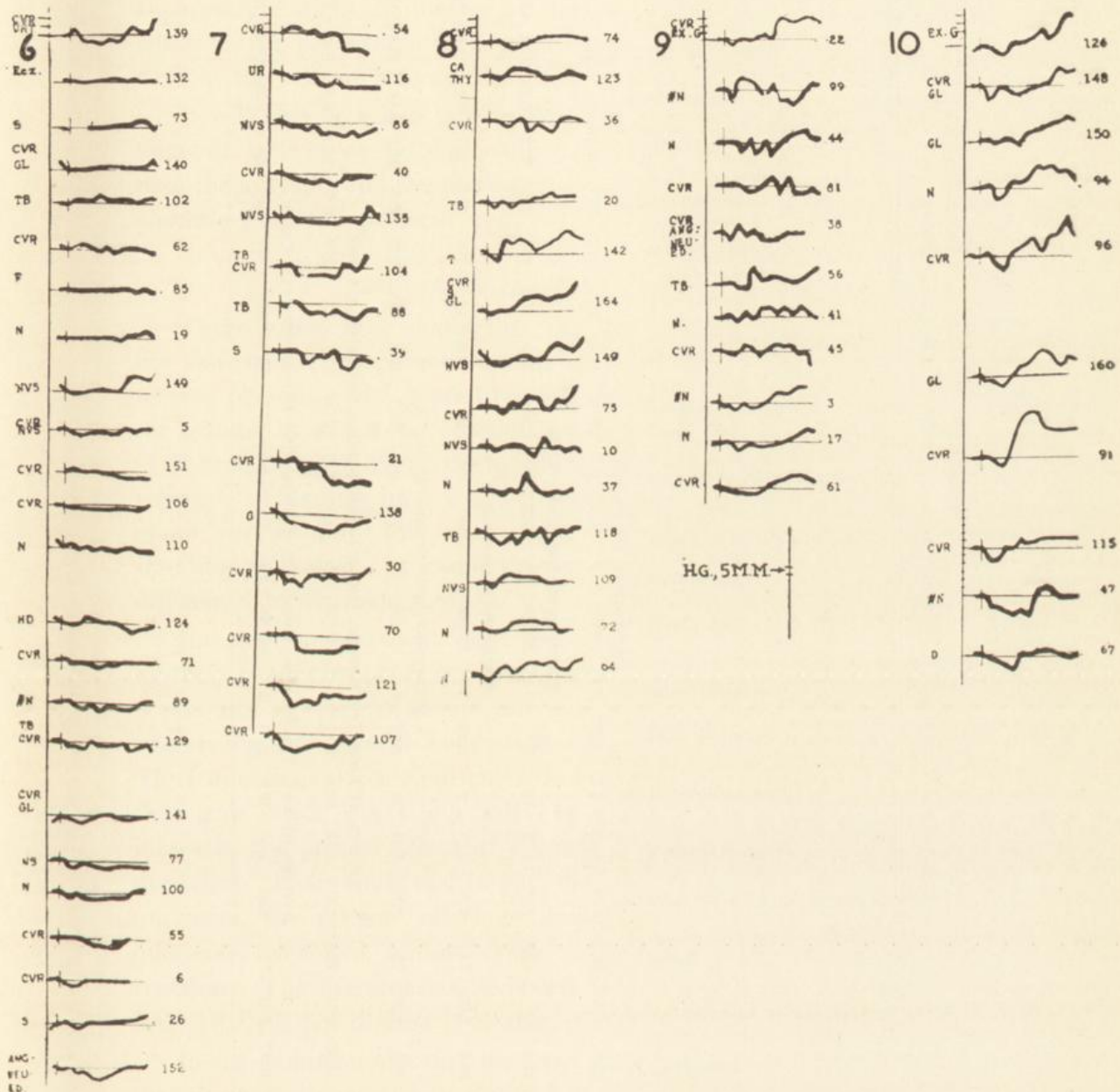


Fig. 2.—Graphic records of systolic blood pressure of "parasympathetic groups."

We now have the outstanding group of contrasting persons and can note that the sympathetic group is characterized by: (1) more permeable skin capillaries; (2) a higher amount of calcium, but a lower potassium calcium ratio; (3) a smaller proportion of albumin in the

TABLE 4.—Averages for Sympathetic and Parasympathetic Groups

[illegible]

serum; (4) a more rapid reaction to the Kromayer lamp; (5) a more sluggish muscle reaction; (6) a lower blood pressure; (7) a lower carbon dioxide combining power; (8) a slightly longer time before reaction to ice occurs; (9) a lower weight-length ratio, and (10) apparently a slight diminution of the size of the morphine and thyroxin wheal in the parasympathetic groups and a somewhat less marked red flare in the reactions to epinephrine, morphine and thyroxin.

It will also be noted that in the more outstanding cases (in sympathetic as well as in the parasympathetic group), the subjects are older than the average, and the pulse rate is higher; in neither group are there absolutely normal persons.

RESULTS OF EXPERIMENTAL WORK

There seems little doubt that the permeability of the capillaries of the skin in the sympathetic group is increased. The ratio for twenty normal persons (38.3 years of age) was found to be 62. The ratio in the groups in which the reaction was sympathetic increased from 64.6 to 65 and finally to 69, as the more marked cases (table 4 A, B, C) were selected. This may have a direct relation to the activity of the thyroid gland, for we find⁵ that an increase in permeability is one of the outstanding phenomena of exophthalmic cases, a feature which is promptly influenced by thyroidectomy.⁶

Interest during recent years has centered about the possible relation of the vascular response to epinephrine and the amount of calcium or potassium, or the potassium-calcium ratio. There seems little doubt concerning the general association of calcium with sympathetic effect. Thus injections of calcium chloride increase the blood sugar and make the urine acid; potassium salts have the opposite effect. Calcium increases the pressor effect of epinephrine, while potassium diminishes the effect. Kylin finds that in patients with the lower potassium-calcium quotients, the pressor effect of epinephrine is more marked. With quotients over two, almost every patient examined gave a vagotonic reaction. The literature is reviewed both by Kylin and by Zondek, so that we shall not discuss it at this time.⁷

In the examinations that we have recorded, it is first of all apparent that the entire sympathetic group has a somewhat higher calcium level,

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

6. Article V. The Patient with Exophthalmos and the Nervous Patient, p. 135.

7. Our calcium values for normal subjects are 9.7; potassium, 20.3; the potassium-calcium ratio, 2.1.

the difference between the sympathetic and parasympathetic groups increasing as the more marked cases are selected as shown in table 4:

(a) Sympathetic	10.2		
Parasympathetic	9.9	Difference	0.3
(b) Sympathetic	10.1		
Parasympathetic	9.7	Difference	0.4
(c) Sympathetic	10.8		
Parasympathetic	9.6	Difference	1.2

The corresponding potassium averages and the potassium-calcium ratios are also shown in table 4:

	Potassium	Potassium-Calcium Ratio
(a) Sympathetic	20.	1.97
Parasympathetic	19.7	2.
(b) Sympathetic	20.5	2.03
Parasympathetic	19.6	2.02
(c) Sympathetic	18.8	1.74
Parasympathetic	19.8	2.04

Only in the extreme cases of the "sympathetic" type is there an association of a low potassium-calcium ratio with the sympathetic effect, and in the individual cases there are many conflicting results. This can also be noted in the calcium, potassium and the potassium-calcium ratio for the first three groups in table 3, all of which are strongly sympathetic in reaction. Here the first group (immediate and persistent systolic rise) has a ratio of 1.8; the second group (immediate rise, followed by a fall) a ratio of 2.08, while the third group (slow but continuous rise) has a ratio of 2.22. It would be attractive to postulate that these differences in types of reaction are associated with the differences in the ionic balance, but we should be hesitant in drawing such a conclusion for the following reasons:

The calcium (and potassium) of the serum may reach an identical level under diverse physiologic states of the tissue. There may be a hypercalcemia when calcium is leaving the tissues and increasing in the serum. On the other hand, a hypercalcemia may exist when there is a current in the opposite direction, when calcium excess is being offered the body, and when both the serum and the tissues may consequently be saturated. Under such conditions the reactions of the tissue cells may be diametrically opposite, but the calcium level is the same in both instances. Similar conditions may hold for the potassium level. We have discussed the constant shifting of the calcium and potassium values as observed in previous experimental infections.⁸ We must further

8. Petersen, W. F.; Müller, E. F., and Milles, G.: *Ztschr. f. d. ges. exper. Med.* **60**:336, 1928.

keep in mind that the ionic effect of the calcium may be quite different from that indicated by the total calcium concentration.

It is curious that there is practically no difference in the levels of the sugar content of the respective groups. We might anticipate that the sugar level of the sympathetic series would be higher. This in itself is, we believe, additional proof that the concept of a uniform sympathetic orientation of the individual does not exist. These patients may have a greater response of their vascular musculature, but the hepatic sugar mechanism has not been altered.

There is evident throughout a lesser amount of globulin in the parasympathetic series. Table 4 shows the following $\frac{\text{albumin}}{\text{globulin}}$ ratio in the three series:

(a) Sympathetic	2.01
Parasympathetic	2.26
(b) Sympathetic	1.84
Parasympathetic	2.15
(c) Sympathetic	2.1
Parasympathetic	2.34

The normal ratio is around 2.22.

The averages for the appearance time of the erythema following irradiation by the Kromayer lamp are conflicting. The averages for the larger groupings, 4 A and B, indicate that the sympathetic groups are somewhat less responsive, the figures being:

(a) Sympathetic	2 hours
Parasympathetic	1.8 hours
(b) Sympathetic	2.05 hours
Parasympathetic	1.64 hours

When the most marked groups are taken into consideration, the figures are:

(c) Sympathetic	1.6 hours
Parasympathetic	1.7 hours

indicating merely that the response is in general more rapid in both groups than in the normal person.

Practically no differences exist in the basal metabolic rates for the two groups.

The sympathetic group has in general a higher skin resistance (electrical), but when the most marked group (C) is examined, this difference is not found.

A distinct difference seems to make its appearance in the electrical reactivity of the muscles. This is apparent if one compares the normal

reaction of the muscles—3.7 milliamperes (cathodal closing contraction) to the group averages as shown in table 4:

(a) Sympathetic	3.4 ma.
Parasympathetic	3.1 ma.
(b) Sympathetic	3.8 ma.
Parasympathetic	3 ma.
(c) Sympathetic	4 ma.
Parasympathetic	2.3 ma.

As the parasympathetic group is in general inclined toward alkalosis, the increased muscular irritability evident in the group is in accord with the difference in carbon dioxide combining power.

The blood pressure, as might be anticipated from the known effect of epinephrine on the average hypertonic case, shows a distinct increase for the parasympathetic groups, as shown in table 4:

(a) Sympathetic	123/66
Parasympathetic	122/69
(b) Sympathetic	121/66
Parasympathetic	133/69
(c) Sympathetic	123/70
Parasympathetic	140/75

The pulse rate increases in the final group, in which the most abnormal persons are included. There is no appreciable difference between the sympathetic and parasympathetic groups.

The most marked (C) group would indicate a lower carbon dioxide combining power for the sympathetic group. This is indicated in group (B) as well, while the figures for the larger series (A) reveal no differences. It is generally assumed that the sympathetic status involves acidosis.

The reactivity of the capillaries to ice seems somewhat lessened in the persons in the sympathetic group. While the response of those in the large group (A) is alike, the (B) grouping indicates a difference of 1.4 seconds, and in the (C) grouping this is increased to three seconds. The general slowing up of the reaction from A to C is probably associated with the advancing age, which increases from an average of 45 to 51 years.

The difference between the two groups apparent in the weight-length ratio begins in the A group and progresses, the differences being 0.16, 0.18 and 0.23 in the three groups. This difference seems to be quite conclusive.

It is generally assumed⁹ that cholesterol differences are of some importance in constitutional differentiation. Our figures fail to reveal any striking changes in the groups examined.

9. Mjassnikow: *Ztschr. f. klin. Med.* **105**:228, 1927.

The individual reactions of the various pharmacologic agents used for the skin reactions show considerable latitude, particularly in the case of the red flare that appears in response to thyroxin and caffeine; so the results must be interpreted with considerable caution.

COMMENT AND SUMMARY

If we now seek to interpret our observations, we must consider them in terms of the normal and perhaps compare them to observations made

TABLE 5.—*Results for Normal Persons and for Sympathetic and Parasympathetic Cases and Cases of Exophthalmic Goiter*

	Normal Persons	Parasympathetics Table 4 C	Sympathetics Table 4 C	Exophthalmic Goiter
Number in group.....	20	10	10	12
Blister time.....	6.8	7.7	7.7	5.4
Permeability.....	62	64.5	69	72
Inflammatory index.....	9.3	8.3	9	13.3
Calcium.....	9.7	9.64	10.8	10.5
Potassium.....	20.3	19.83	18.83	21.1
Potassium-calcium ratio.....	2.1	2.04	1.74	2.03
Sugar.....	72.8	71	72.6	88
Albumin-globulin ratio.....	2.22	2.34	2.1	1.79
Kromayer time (minutes).....	110	117	103	103
Basal metabolism.....	+5	10.9	10.4	48
Skin resistance.....	0.33	0.43	0.41	0.23
Muscle reaction.....	3.7	2.3	4	2.8
Carbon dioxide combining power....	57.6	57.7	54.6	54.2
Blood pressure.....	116/70	140/75	123/70	140/70
Pulse pressure.....	46	65	53	70
Pulse rate.....	68	80	80	102
Reaction to epinephrine				
P. P. in per cent.....	19.6	-1.3	21.4	19
P. P. × P. R. in per cent.....	28.6	0.6	26.7	33.7
Reaction to ice.....	14.5	20	23	10
Weight-length ratio.....	224	229	206	201
Cholesterol.....	222	218	209	203
Epinephrine wheal (mm.).....	21	20	19.4	16
Epinephrine flare (mm.).....	9.36	8.34	9.4	10.6
Morphine wheal (mm.).....	11.7	10.2	10.6	11.4
Morphine flare (mm.).....	16.3	13.2	13.2	11.6
Thyroxin wheal (mm.).....	11.6	11.4	12	10.4
Thyroxin flare (mm.).....	5.45	3.2	4	4.6
Caffeine wheal (mm.).....	17.9	19.2	21	15.2
Caffeine flare (mm.).....	3	2.4	2.6	1
Age.....	40.2	50	52	39

in a disease condition in which sympathetic overbalance has been frequently suggested, mainly that of exophthalmic goiter. We have tabulated the most important results for normal persons, for our outstandingly contrasting sympathetic and parasympathetic cases, and for cases of exophthalmic goiter.¹⁰

10. Exophthalmic goiter by no means represents a purely sympathetic overbalance; the autonomic manifestations are obviously mixed in character (Eason, J.: Exophthalmic Goiter, Edinburgh, Oliver & Boyd, 1927).

Thus it becomes apparent that the sympathetic group approaches the exophthalmic goiter in permeability, in high calcium concentration, in shortening of the Kromayer time, in relative acidity, in response to epinephrine, in weight-length ratio and in relatively low cholesterol content. This group approaches the parasympathetic group, on the other hand, in the electrical response, as well as in the higher systolic blood pressure.

Chart 3 illustrates the relative skin reactions noted in table 4.

An analysis of the reaction to epinephrine has been made on 100 so-called normal persons, as well as on about fifty patients. In contrast-

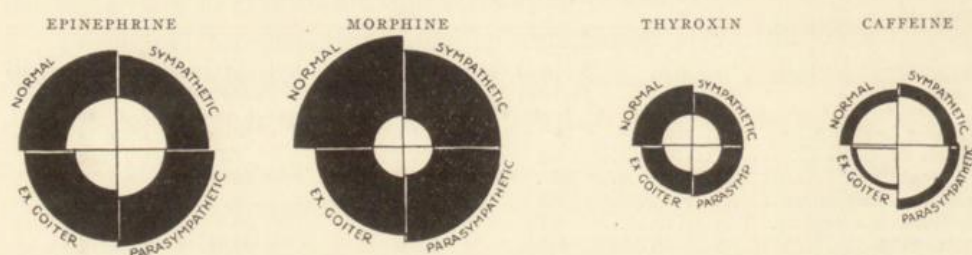


Fig. 3.—Average wheal (white) and flare (black) following intracutaneous injection of epinephrine, morphine, thyroxin and caffeine into normal persons, patients with exophthalmic goiter and the sympathetic and parasympathetic "groups" (4 C).

ing the outstanding sympathicotonic cases with the outstanding vagotonic cases, the average indicate that the sympathicotonic group differs in that the members of the group have more permeable skin capillaries, a lower potassium-calcium ratio, more globulin, a lower carbon dioxide combining power and a lessened muscular electrical reactivity. The persons weigh less and have a lower blood pressure.

Comparative data are also presented for twenty normal persons, twelve patients with exophthalmic goiter and the most marked sympathicotonic and vagotonic types.

V. THE PATIENT WITH EXOPHTHALMOS AND THE NERVOUS PATIENT*

In a previous communication, we called attention to the fact that the blister time of the patient with exophthalmos is considerably shortened, and that the permeability of the capillaries of the skin, as measured by the relative amount of protein in the blister, is markedly increased.¹

It is a well known clinical observation that the skin of the patient with exophthalmos is thinner and more transparent than that of a normal person, and vasomotor lability is plainly evidenced by the rapid flushing and pallor. The arterioles, as well as the capillaries, are dilated. The functional status of the skin is one of exaggerated activity involving both the radiation of heat and evaporation. It has recently been shown that the secretory activity of the sweat glands of the skin is controlled by a skin plexus largely independent and locally autonomic, although the sympathetic nerves are commonly regarded as the nerves having to do with secretory functions. We have used the term parasympathetic status to designate this condition of activity of the skin for reasons discussed elsewhere.²

Among our group of patients there have been twelve with typical exophthalmos, as well as one patient with hyperthyroidism associated with carcinoma of the thyroid, and one patient who was being treated with thyroid extract (basal metabolic rate + 31) following a thyroidectomy. In six of the patients, we were able to carry out a complete reexamination several months after the thyroidectomy.

CLINICAL HISTORIES OF "SYMPATHETICOTONIC" PATIENTS AND PATIENTS WITH EXOPHTHALMOS

CASE 9.—A white man, aged 36, had become ill with palpitation and tachycardia fourteen months previous to the examination. He had lost 10 pounds (4.5 Kg.). Eight months later, he had a similar attack. Occasionally, he had night sweats. He had a rather coarse tremor. On exertion he showed slight dyspnea. At the time of examination, he had the papular and pustular lesions of acne. The conjunctivae were slightly injected. A few cervical glands were palpated below the angle of the jaw, and there was a light contraction of the superclavicular fossa. The blood pressure was 132 systolic and 86 diastolic. The basal metabolic rate on December 24 was + 34, and on December 28 was + 49. There was no exophthalmos. In this case, the disease was mild.

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

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