

interfered with by the effects of the depression of the vasomotor center. That the center extends for some distance in the bulb is rendered probable by the fact that a marked rise of temperature may still be observed when the section is close to or at the junction of the pons and bulb. In several experiments in which the lobes cerebellum or the cerebellar peduncles were cut, no temperature changes were in any case noted which were at all comparable to those caused by pontine section.

Not only do the mean rises in temperature vary in degree in accordance with the region affected, but the temperature curves exhibit distinct characteristics, and such as to indicate the organ involved. Thus, after section of the caudate nuclei, the temperature tends to increase for approximately three hours on an average and then subside. In the sections of the crura cerebri the mean maximum rise is reached in about the same time, but the temperature curve rises only half as rapidly. In the pontine experiments the rise is not quite

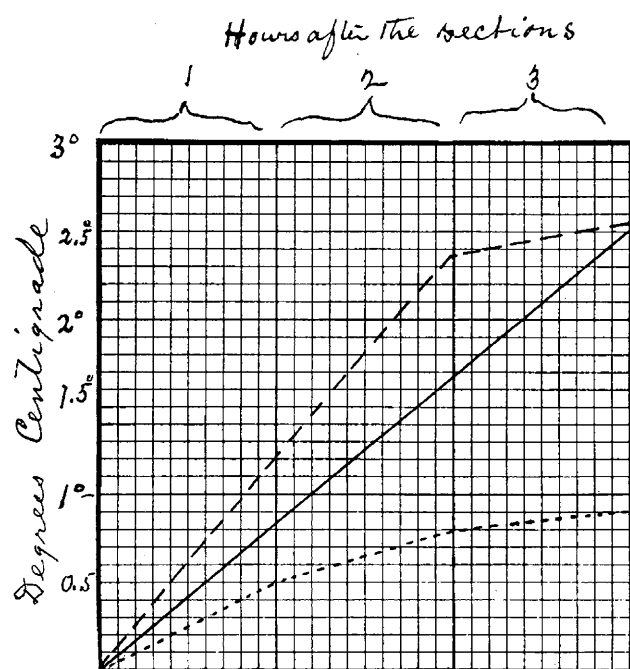


Chart of temperature curves during first three hours after the sections. The broken line is the temperature curve of the caudate series; the unbroken line of the pontine series; and the dotted line of the crural series.

so rapid as in the caudate series, but there is a marked tendency to a steady increase for from 6 to 7 hours or more, or until fatal hyperpyrexia is established. These differences can be better appreciated by a glance at the accompanying chart in which are exhibited composite temperature curves of the caudate, crural and pontine experiments. The marked differences in the mean temperature curves of the caudate and pontine sections indicate that the thermo-accelerator centers in these structures differ at least in power—the latter being the stronger—if not in other important features. That they are functionally different has been shown conclusively in experiments in which I have injected powerful pyretics and antipyretics in large doses after the sections. For instance, after section of the caudate nuclei, and after section of the crura cerebri, the administration of cocain and morphin has no effect upon the temperature changes caused by the section: cocain neither increases the rise nor hinders the fall; nor does morphin hinder the rise or hasten the fall, unless given in such quantities as to seriously affect the circulation, etc. It seems

from this that the direct action of both cocain and morphin upon the heat mechanism is upon the thermo-accelerator center in the caudate nuclei. This subject has, however, so important a bearing upon febrile processes, and is of such scope, that a further consideration must be left for a special article.

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DISCUSSION.

DR. R. O. BEARD, Minneapolis—Referring to Dr. Reichert's conclusions I would suggest a possible source of error in his sections arising from the stimulation incident to section of afferent as well as efferent fibers related to the thermotaxic centers. The fillet from the ascending lateral tract of Gowers, which is believed to carry impressions of temperature to these centers, passing upward through the bulb and pons, might easily be involved in Dr. Reichert's pontine and bulbar sections; while lying in the lateral fillet, beyond the pons, it might escape in his sections of the crura. Section has always been a doubtful method of localizing centers.

PERNICIOUS ANEMIA—THE STATISTICS OF A SERIES OF FORTY CASES.*

THOMAS McCRAE, M.B., M.R.C.P.

Associate in Medicine, the Johns Hopkins University; Resident Physician, the Johns Hopkins Hospital.

BALTIMORE.

This paper is a report of a series of 40 cases of pernicious anemia which have occurred in the service of Dr. Osler in the Johns Hopkins Hospital. No attempt will be made to discuss in any detail the features of the disease or to give any extended notes of the histories of the patients. Cases in which there was any doubt as to the diagnosis have not been included. These 40 patients were among approximately 12,500 general medical admissions.

Incidence.—There were 32 males and 8 females, a rather unusual ratio for which no explanation can be given. The general admissions are about 5 males to 4 females. Large series show little difference in the number from each sex. As to age, the distribution was: 1 to 10 years, 1 case; 11 to 20, none; 21 to 30, 7 cases; 31 to 40, 6 cases; 41 to 50, 13 cases; 51 to 60, 7 cases; 61 to 70, 6 cases. It will be observed that four-fifths of the patients were over 30 years of age. The youngest was aged 10 and the oldest 66 years. In regard to race there were only 2 colored patients in the series, a proportion of 1 to 19, while the general ratio of admissions is about 1 colored to 7 white patients.

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Etiology.—There seemed but little of importance found in regard to this. In only one of the females did a previous confinement seem in any way connected with the onset. Mental distress and worry did not figure to any extent, there being only 3 patients who gave a history of these, although an unusual number of them were in the private wards. There was a tuberculous family history in 7 cases. Four had a history of syphilis and 14 of malaria. Previous stomach trouble had occurred in 5 and 12 had used alcohol. In one the onset followed a severe carbuncle. In the earlier cases the condition of the mouth was not noted carefully, but in the last 10 cases, carious teeth or some septic process in the mouth occurred in only 4 instances.

Complaint.—It is of interest to note the symptoms of which the patients themselves made complaint. The largest number, namely, 23, complained principally of weakness. In 11 the gastric and bowel symptoms were most marked. Four came only on account of nervous manifestations; 2 complained of the discoloration of the skin.

Onset.—The first symptom noted was weakness in 14 of the series. Weakness associated with some other condition in 9, dyspnea in 9, and digestive disturbances in 8 instances.

Symptoms.—In the histories given by the patients, of the symptoms mentioned especially, weakness was most frequent, namely, in 26 cases, change of color in 25, loss of weight in 22—a rather surprisingly large number as the usual description of the disease lays emphasis on the absence of emaciation—and shortness of breath in 16 cases. Digestive disturbances with diarrhea were present in 11 and gastric symptoms alone in 8 instances. Hemorrhages from the mucous membranes had occurred in 9 cases, and in 8 there had been some edema. Of the nervous manifestations, 4 gave a history of various sensory conditions usually tingling and numbness, one of severe pain, one of paraplegia, one of mental changes, and five of varied symptoms such as difficulty in walking, stiffness of the legs, etc.

Examination.—Of the conditions found the following were the most important. Marked emaciation was noted in 10 instances. The typical lemon-yellow color was observed in 29, and in 7 there was marked pallor without any special yellow tint. Pigmentation of the skin apart from the general discoloration was present in 8 and in 4 petechiæ were found.

In the circulatory system there was marked visible pulsation of the vessels in 16 cases. An apex systolic murmur was heard in 15, a systolic murmur everywhere over the heart in 13, and in one instance a systolic murmur was heard only in the pulmonic area. A loud systolic bruit was heard over the vessels of the neck in 12, and in 5 the complete absence of any such murmur was noted. In the examination of the abdomen, the liver was only felt in 2 instances. The spleen was felt in only 6 cases and in none of these was the enlargement at all marked, it being noted in all that "the spleen was just felt." There was marked general glandular enlargement only in 3 cases, and in 5 the majority of the glands were enlarged. Hemorrhages from the mucous membranes occurred in 8 patients during their stay in the hospital. Edema was present in 7 cases. As already noted, only in 4 out of at least 10 cases was a specially septic condition of the mouth noted.

The temperature was practically normal throughout their stay in the hospital in 10 of the series. In 27 it was more or less elevated, in 20 of these the average

elevation being about 101, while in the remaining 7 it varied from 101 to 106. Three were under observation for too short a time to obtain continued records. The urine was free from albumin in 23 cases. In the remaining 17 it was present, but only in very slight amounts. In no instance was sugar found. The reaction in 37 was acid, in one neutral and in 2 alkaline. The specific gravity in 10 was below 1010, in 24 between 1010 and 1020, and in 5 between 1020 and 1030.

While the patients were under observation the gastrointestinal symptoms were as follows: As regards the stomach, in 22 there were no disturbances of any kind; of the remaining 18 the symptoms were slight in 14 and grave in 4 instances. The bowels were normal in 16 cases, constipation was present in 14, diarrhea in 8 and alternating constipation and diarrhea in 2 instances.

Nervous manifestations were present in 10 instances. These varied from sensory disturbances alone to complete paraplegia. The cases showed so many differences that it was found impossible to classify them under any definite headings. The prevailing type was one with some sensory disturbances, especially in the extremities, associated with a more or less marked spastic condition. There was complete paraplegia in one, loss of power over the bladder in one, and marked incoördination with absence of the knee-jerks in one instance. Some degree of incoördination was frequently found. In some of the patients the nervous symptoms progressed while they were under observation, but in others some improvement was noted.

Blood.—Full counts were obtained when they first came under observation in 36 patients. The average of these was: Hemoglobin, 30 per cent. (von Fleischl); red corpuscles, 1,560,000 per c.mm.; white corpuscles, 6929 per c.mm.

Complete differential counts¹ were made in 30 of these, the average of the series being: Polymorphonuclears, 61 per cent.; small mononuclears, 31 per cent.; large mononuclears and transitionals, 4 per cent.; eosinophiles, 2 per cent. There were small numbers of myelocytes found in some of the cases, but never any marked percentage; the average was less than 1 per cent.

The average number of nucleated red cells found in counting 1000 leucocytes was 37. Of these the average of each variety was: Normoblasts, 23.4; megaloblasts, 4.7; intermediate forms, 9.4.

These figures are for the series of 30 cases. But among these there were three cases in which nucleated red cells occurred in very large numbers, namely, 262 (of which 222 were intermediate forms), 124 (of which 120 were normoblasts) and 420 (all of which were normoblasts) per 1000 leucocytes. If these three rather unusual cases be removed from the series, the average number of nucleated red cells per 1000 leucocytes for the remaining 27 cases is 12.7, and of these there were of normoblasts, 6; megaloblasts, 4.7; and intermediate forms, 2.

It is of interest to compare the differential counts in the fatal cases with those in the cases discharged improved. There were 11 of the series with a fatal termination. The relative percentages are the following:

	Death (11).	Improved (19).
Polymorphonuclears	62	61
Small mononuclears	29	31
Large do. and transitionals	4	4
Eosinophiles	2	2

1. For this as a routine, Ehrlich's triple stain was used. The classification of the leucocytes is that of Ehrlich. The fractions of percentages are not given.

The average number of nucleated cells per 1000 leucocytes along with the number of each variety was:

	Death.	Improved.
Nucleated red cells	23	47
Normoblasts	7.6	34
Megaloblasts	11	1
Intermediate forms	4	12

If, however, the three cases referred to before with the large number of nucleated red cells—all of which were discharged much improved—be subtracted from that series, we obtain very different figures, namely, an average per 1000 leucocytes of only 6.8 nucleated reds in the cases that improved, of which there were: Normoblasts, 5; megaloblasts, 7; intermediate forms, 1.

It will be noted that the average percentage of small mononuclears was lower in the fatal cases than in those that improved. This is contrary to the generally accepted view that a high percentage of these cells is of unfavorable prognostic importance. This also meant a lower absolute number of small mononuclears, as the average leucocyte count in the fatal cases was lower than in those that improved. There is also a striking difference in the average number of the nucleated red cells per 1000 leucocytes found, namely, 23 in the fatal to 7 in the non-fatal (if the three cases before mentioned be left out of the average). The variation in the relative ratios of the various forms is marked. The normoblasts comprise only 33 per cent. of all nucleated forms in the fatal and 73 per cent. in the ones that improved. The megaloblasts were 48 per cent. in the fatal and 14 per cent. in the non-fatal series. The percentage of the intermediate forms in the fatal cases is 17 per cent. to 14 per cent. in the non-fatal series. This rather suggests that as regards prognosis no special conclusion can be drawn from their occurrence.

There were 16 cases in the series with the counts of the red corpuscles below one million per cubic millimeter. Of these twelve died in the hospital. Of the remaining four, one apparently recovered completely and was admitted six years afterwards with cancer of the stomach, a second has lived for over three years and is in fairly good condition at present, while the other two can not be traced. In no one of these four cases did the red count fall below 900,000 per c.mm. In two of the fatal cases the last count before death was over one million red cells.

Results.—Death occurred in the hospital or shortly after discharge in 17 of the series. The average duration of these was practically twelve months. Eight of them, however, ran the whole course in less than six months. Fourteen were discharged improved; one of these apparently recovered completely; one was followed for four years; one is alive nearly six years afterwards, and another three years afterwards. Seven were discharged unimproved and two were not treated. The average duration of the non-fatal cases was sixteen months at the time of their admission. Twelve of these patients made substantial gains in weight. The nervous symptoms showed varying results; some progressed while under observation, and others showed gain. There was no uniformity in their course.

Treatment.—This may be alluded to briefly. It consisted generally of absolute rest in bed, fresh air, abundant good food, and arsenic. Attention was paid to the condition of the mouth, especially in the later cases. Conditions arising in the course of the disease were treated symptomatically.*

THE PHARMACOLOGY OF THE SUPRARENAL GLAND AND A METHOD OF ASSAYING ITS PRODUCTS.*

E. M. HOUGHTON, Ph.C., M.D.

Lecturer on Experimental Pharmacology, Detroit College of Medicine.

DETROIT, MICH.

Addison was the first, in 1855, to point out the great importance of the adrenals to the animal economy, showing that the disease now bearing his name was due to lesions, usually tuberculosis, of these bodies. The following year Brown-Séquard demonstrated experimentally that these glands: "1, are essential to life; 2, that they modify or destroy a substance which otherwise transforms itself into pigment; 3, that when the organs are destroyed or removed this substance collects in the blood; 4, that removal is rapidly fatal, and injection of the blood of an animal thus treated into a healthy animal leads to symptoms like those of removal." Gratiot, Phillippeaux and Harley disputed these findings, but Brown-Séquard by another series of experiments showed that his previous conclusions were correct. Brown-Séquard's conclusions were a little later confirmed by Tizzoni. Vulpian and Virchow also in 1856 showed that a reducing agent was contained in the medulla of the suprarenal bodies, which has been observed by all subsequent chemical investigators.

Arnold, in 1866, obtained a crystalline body, but this could not be confirmed in the following year by Holm. Krukenberg, in 1885, showed that the color reactions were possibly due to pyrocatechin. This was confirmed by Brunner in 1892. Marino-Zucco, about the same time, obtained considerable quantities of neurin from these bodies, while Dutto found that neurin was present in the urine of patients suffering from Addison's disease. Marino-Zucco and Guaruceri in a later series of papers were able to show more conclusively that neurin was the toxic agent present. Moore, in 1894, made an extensive chemical study of the question and showed that the blood pressure raising substance contained in these glands was likewise the chromogenic substance of Vulpian. Fraenkel, in 1896, obtained a possible pyrocatechin derivative which he names "sphygmogenin." Moore disputed his findings and concluded that the active substance was a pyridin derivative. The same year Muhlmann, however, obtained a pyrocatechin compound. Abel likewise, in 1896, published the first of a very important series of papers in which he described a number of crystalline compounds, giving their chemical and pharmacological properties, which he had succeeded in isolating from the suprarenal glands. He concluded that the active substance was of the formula $C_{17}H_{15}NO_4$ and named it "epinephrin." Von Furth isolated a substance the following year, calling it "suprarenin," which he supposed to be different from epinephrin. Takamine and Aldrich, working independently in different laboratories on the question last year, referred to me about the same time for pharmacologic examination crystalline compounds which they had obtained from these bodies, which are extremely active and are probably identical, as shown by Aldrich. The name "adrenalin" has been given to the product obtained by Takamine.

Pellacani, in 1874, reported the results of some ani-

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* The Discussion on papers on "Blood Count," was printed August 4, page 503.