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Geniculocalcarine Pathways

Insulin Binding Antibodies

Chronic Osteomyelitis

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Staff Meeting Report

The Geniculocalcarine Pathway in the Temporal Lobe*†

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and
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The purpose of this paper is to clarify certain controversial concepts regarding the geniculocalcarine pathway in man and to emphasize the importance of visual field changes in temporal lobe lesions.

Anatomy

A brief review of certain concepts regarding the postchiasmal visual pathway is in order.

The shape of the optic tracts may be compared to that of a wishbone, with the open end representing the lateral geniculate bodies and the other end the chiasm. The beginning of the tract lies free on all sides except the inner, where it is attached to the outer wall of the third ventricle by a narrow band. It is five to ten millimeters above the posterior part of the pituitary body. Between the two tracts anteriorly lie the tuber cinereum and the mammillary bodies. Posteriorly, as the tracts diverge, they enclose between them the lateral surfaces of the peduncles and lie in direct apposition to the lateral surfaces of the peduncles. As each tract continues posteriorly, in a somewhat upward direction, it lies against the lateral and inferior surface of the internal capsule which, in this location, contains fibers continued directly from the cerebral peduncles. Thus, we see that medially the optic tract is in relation anteriorly with

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†Sincere appreciation is extended to Dr. Lyle A. French, Professor of Neurosurgery, University of Minnesota Medical School, for his cooperation in this study.

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structures of the hypothalamus and posteriorly with the great motor outflow from the cortex contained in the internal capsule and cerebral peduncles. Almost directly above the tract, in its posterior portion, is the lentiform nucleus, a portion of the basal ganglia.

Laterally and below, as the tract approaches the cerebral peduncle, it becomes covered by the temporal lobe of the brain; more specifically by the uncus, amygdaloid nucleus, the hippocampal gyrus, and the inferior horn of the lateral ventricle. It has been hypothesized that still more laterally in the substance of the temporal lobe lies Meyer's loop of the geniculocalcarine tract.* Thus, the posterior part of the optic tract and anterior part of the radiations are in relatively close proximity to each other.

The tract ends in the lateral geniculate body, which lies on the ventrolateral aspect of the pulvinar; in the lateral geniculate body the geniculocalcarine tract begins. From here, the fibers pass outward into the sublenticular portion of the internal capsule, fanning out into the temporal lobe while sweeping around the inferior and posterior horns of the lateral ventricles. Some of the fibers from the inferior quadrants of the two retinas arch forward into the temporal lobe forming Meyer's loop. After completing the forward loop, these fibers join the remainder of the tract, which, in the posterior part of the temporal lobe, forms a narrow vertical bundle approximately ten millimeters in height; projected on the surface, this bundle lies at about the level of the second temporal convolution. The bundle composes the external saggital stratum and is separated from the posterior horn of the lateral ventricle by the internal saggital stratum containing corticocollicular and corticothalamic fibers. The dorsal portion of the bundle extends into the lower portion of the parietal lobe and contains fibers from the upper quadrants of the retinas. The macular fibers occupy the center of the bundle, whereas its ventral portion contains fibers from the lower quadrants of the retina. This arrangement is of considerable importance in determining the type of field defects seen in tumors of the parietal and temporal lobes.

As for the blood supply of the postchiasmal pathway, the optic tract is intimately related to the branches of the circle of Willis. Anterior to the tract are the internal carotid and middle cerebral arteries; just below are the posterior communicating, anterior choroidal, and posterior cerebral arteries. Since branches

*The presence of Meyer's loop is debated. For further discussion and our findings, see pages 485, 489 ff.

to the tract are derived from all these vessels, it has a very rich blood supply. The external geniculate body is supplied by the anterior choroidal and posterior cerebral arteries. The geniculocalcarine tract receives its blood from the anterior choroidal, the calcarine branch of the posterior cerebral, and the middle cerebral arteries.

General Considerations of Temporal Lobe Lesions

Temporal lobe optic radiation lesions are caused by: tumor, abscess from otitic inflammation, demyelinating disease, encephalitis, vascular accident, and trauma. By far the commonest cause is tumor. Papilledema is more common in temporal lobe tumors than in any tumor affecting the visual pathways, the tumor often being well advanced before the patient consults a physician. Vascular accidents are relatively infrequent in the optic radiations in the temporal lobe, owing to its rich blood supply. Occlusions of the anterior choroidal artery, or the middle cerebral artery or its branches may result in a homonomous hemianopsia due to optic radiation involvement. The sudden onset of vascular lesions is, of course, the most reliable guide to the cause of the defect.

Opinion differs as to whether temporal lobe lesions affect solely the radiations or the tract or both. For general orientation, it may be stated that the visual field defects in temporal lobe lesions produce—most commonly in the early stages—homonomous upper quadrant field defects. At first, the macula may be spared, but as the defect progresses, it too is affected. A sharp horizontal boundary to the field defect may arise. As temporal lobe lesions progress, the lower quadrant of the field becomes invaded, and eventually a complete homonomous hemianopsia results. Until the hemianopsia is complete, the upper quadrant is usually more affected than the lower quadrant, and this has definite localizing value. Temporal lobe lesions have often resulted in incongruous field defects, a condition in which the field defects in the two eyes, although homonomous, are somewhat dissimilar in outline and can be caused only by anatomic separation of visual fibers from corresponding retinal points.

It is known that in the optic tract, fibers from corresponding retinal points are separated from each other; therefore, a lesion affecting the tract will produce incongruous field defects. But until the relatively recent advent of temporal lobectomy in patients with idiopathic epilepsy, no satisfactory method existed for studying the architecture of the geniculocalcarine pathway in man. Thus, the mechanism of production of the visual field defects in temporal lobe tumors, the presence or absence of

Meyer's loop, and the degree of approximation of fibers from corresponding retinal points in the anterior portion of the optic radiations have been points of controversy almost since the initial description by Meyer[1] of the loop that bears his name.

Many have found incongruous field defects in temporal lobe tumors, but the explanations of these defects have been diverse. Traquair[2] expressed the belief that since the defects were incongruous, the optic tract must be affected. He postulated that from the lateral geniculate body on, the fibers from corresponding retinal points were in close approximation, and that if the radiations were affected congruous defects must result. Clinically, he found nothing to support the presence of Meyer's loop, although he did not deny its existence. Krevitz[3] shared his view. Spalding,[4] in discussing gunshot injuries of the radiations, demonstrated congruous defects in lesions of the anterior radiations.

Hughes[5] questioned the unproved assumption that looping forward of fibers in the temporal lobe was accompanied by dissociation of fibers from corresponding retinal points; he noted further that in nearly all cases in which involvement of the optic radiations has occurred, the field defects are congruous.

An opposite view was advanced by Harrington,[6] who expressed the opinion that homologous visual fibers in the anterior portion of the radiations were indeed separated from each other, and that the incongruity of the fields in temporal lobe lesions was, in fact, the result of radiation damage—not of optic tract involvement as Traquair had proposed. Duke-Elder[7] echoed this view.

Henschen's[8] classical description of the geniculocalcarine pathway contained no mention of Meyer's loop, but Cushing[9] accepted its presence. Falconer and Wilson[10] found congruous defects in temporal lobectomy patients, whereas Van Buren and Baldwin,[11] in a similar study, found both congruous and incongruous defects.

We believe that the present study sheds light on some of the problems indicated by the diversity of opinions above and enables us accurately to state the relationship existing among fibers from corresponding retinal points in the anterior portion of the geniculocalcarine path. Implications resulting from our findings will be discussed.

Material and Method

The subjects in this study consisted of 24 patients who had undergone temporal lobectomy between 1952 and 1960 for treatment of seizures. Visual field determinations were carried out by the two authors on all these patients. Neurosurgery was

performed at the University of Minnesota Hospitals by Dr. Lyle A. French, Professor of Neurosurgery. Dr. French's surgical technique was essentially similar in all cases and consisted of excising a varying but measured amount of temporal lobe tissue; the incision line was at right angles to the long axis of the temporal lobe and always entered the inferior horn of the lateral ventricle.

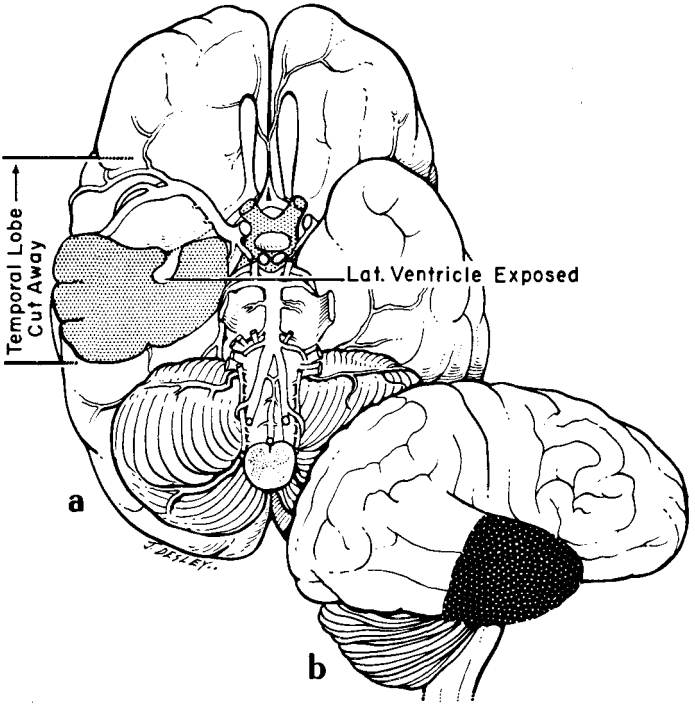

Fig. 1. Type of temporal lobectomy performed in this series of cases

This group of 24 patients represents a select group, since it did not include patients who had had temporal lobectomies for gross lesions such as neoplasms, abcesses, and hemorrhages owing to possible distortion of their fields. Optic tract damage caused by an expanding lesion was thus ruled out. The subjects fell within the diagnostic group labeled idiopathic epilepsy. They were remarkably cooperative and consistent in their re-

sponses, and all of them, when interviewed, appeared alert and active. All noted improvement—in most cases pronounced improvement—of their seizures.

Central field determinations were performed at one meter in all patients, and perimetry was carried out in 16 cases. Half the subjects were tested with four white targets ranging in size from 1 to 30 millimeters; the remainder were tested with at least two white targets. Each field determination took approximately one and one-half to two hours and was done with the utmost consistency and care.

Results

All the visual field defects in this study were remarkably congruous with all targets used. The slopes of the defects were extremely steep in all but two cases, and even these were relatively steep. Contrary to the findings of Van Buren and Baldwin[11] (as can be seen from observed congruity of the fields), no relationship was found between the side of the cerebrum operated on and the eye having the large field defect. The characteristic defect was pie-shaped, with its apex extending toward the fixation point and with one of its sides formed by the vertical meridian (Fig. 2). Some correlation was noted between the size of the pie-shaped sector and the extent of the lobectomy (Table 1). In general, the larger the lobectomized area, the greater the defect, but this relationship varied considerably. The sides of the field defects were all radial in their slopes except for three instances in which they approached a more horizontal slope.

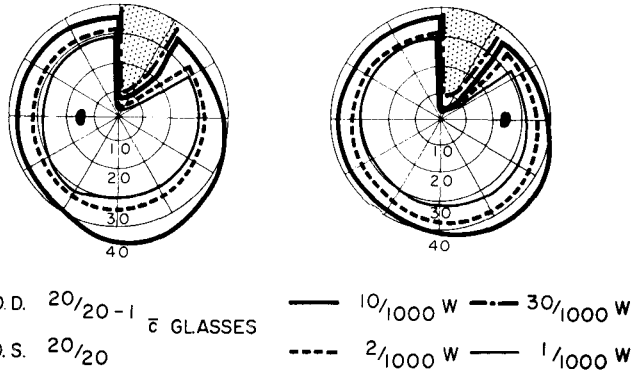

Fig. 2. Seven centimeter resection of left temporal lobe; typical pie-shaped defect

TABLE 1

Size of Field Defect in Relation to Size of Temporal Lobectomy						
Centimeters of Lobe Resected	Approximate Size of Field Defect					
	1/12	2/12	3/12	4/12	6/12	Total
5 to 7	1	3	2			6
7 to 8	2	2	4			8
8 to 9	1			1	3	5
9 to 10			1	1	2	4
Unknown					1	1
Total	4	5	7	2	6	24

Note that with increasing amounts of resection progressively severe defects occur. However, considerable individual variability is present. A defect involving more than an upper quadrant but less than a half of the field is uncommon.

In general, as progressive lobectomy was carried out, all but two patients showed the characteristic pie-shaped defect until a complete quadrantanopsia was produced, when the visual defect converted abruptly to a complete homonomous hemianopsia. Seven of the 24 patients showed a classical quadrantanopsia (Fig. 3). In the two exceptional patients the defects extended into the lower quadrants without producing complete homonomous hemianopsias. Interestingly, one of these patients was one of two examined within two weeks after surgery, while all the others were seen seven months or longer after lobectomy. This patient was also unique in that a spherical area extending into the occipital lobe was excised posterior to the usual site of temporal lobectomy. The case of the other patient whose field defect extended into the lower quadrant was extremely interesting (Fig. 4); the peculiar triangular shaped areas that were spared in this case may have interesting anatomic implications.

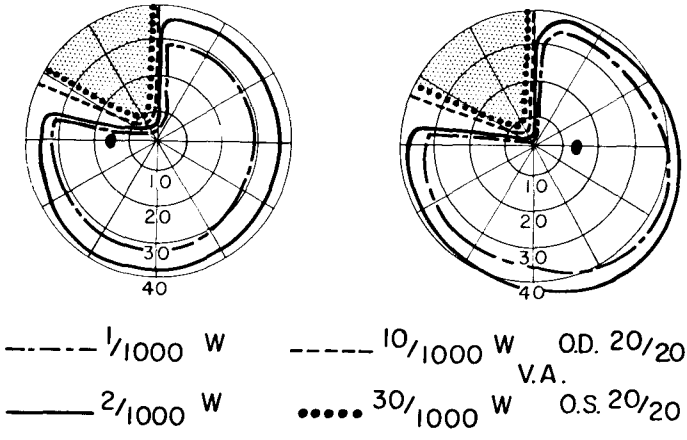

Fig. 3. Classic quadrantanopsia after 7 cm. resection of right temporal lobe

Discussion

The observed involvement of the upper homonomous quadrants of the visual fields occurring before that of the lower quadrants in progressive amputation of the temporal lobe indicates a more anterior location of fibers subserving the upper homonomous areas of the visual fields. From the lateral geniculate body fibers from the lower retinal quadrants must loop forward into the temporal lobe. The hypothesis that Meyer's loop exists is thus strongly supported. But since there is not a close correlation between the amount of amputation and the degree of field defect, a different amount of forward looping may exist in different brains. The size of the temporal lobe also differs in various individuals, however, and it is only to be expected that, in terms of centimeters, the field defect would vary for a given number of centimeters of amputation. Meyer's loop itself must also vary in size, as do all other anatomic structures of the human body.

Further examination of the visual fields reveals that nine had varying degrees of upper quadrant defect, seven each had a complete upper quadrant defect with a sharp horizontal margin, two had involvement of all the upper quadrant and a portion of the lower quadrant, and six had complete hemianopsias. Likewise, the area of the upper quadrants first involved always lay next to the vertical meridian. These findings indicate: 1) that the horizontal meridian is the dividing line with respect

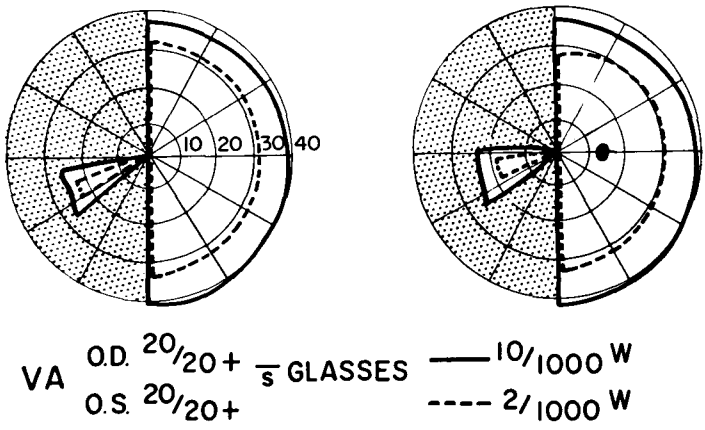

Fig. 4. Unusual triangular shaped areas of sparing in an otherwise complete homonomous hemianopsia after 8 cm. resection of right temporal lobe. The close anatomic relationship of fibers from corresponding retinal points is well illustrated by this field.

to the anterior looping; 2) that the forward looping fibers are more spread out in the temporal lobe than are the fibers subserving the lower quadrants of the visual fields; and 3) that the fibers next to the vertical meridian and subserving the uppermost portion of the visual fields loop farthest forward. As one proceeds towards the horizontal meridian, then, the forward looping becomes less. The macular fibers from a given meridian appear to loop forward less than their peripheral counterparts along the same meridian.

In other words, since the fibers from the upper visual field quadrants are spread out in the temporal lobe, as amputation of this lobe progresses upper quadrant defects of varying severity result. But these defects always begin near the vertical meridian and progress toward the horizontal. Here a sharp horizontal boundary to the field may be obtained, indicating at least a slight anatomic separation of upper and lower visual field quadrants at this point. Once the horizontal meridian is passed, the defect is usually converted into a complete homonomous hemianopsia, which indicates that the fibers serving the lower visual field quadrants are more compact.

Since all visual fields in this study were congruous, our findings contradict the view that separation of fibers from corre-

sponding retinal points occurs in the anterior portion of the radiations. Rather, our observations support the view (cf. Roenne,[12] Traquair,[2] Spalding,[4] Hughes,[5] and Falconer and Wilson[10]) that fibers from corresponding retinal points do indeed lie in juxtaposition in the anterior portion of the visual radiations. Reasoning teleologically, one infers that if fibers from corresponding retinal points were brought together in the lateral geniculate body, there would be little reason for the fibers to separate again only to be brought together once more in the visual cortex. How then do we explain the incongruity so often reported in temporal lobe tumors? There are but two possible explanations. The first and most logical hypothesis is that the optic tract may be affected in temporal lobe tumors. The tract lies just above and medial to the temporal lobe, and the inferolateral portion of the tract contains fibers serving the upper quadrants of the visual fields.[13] Thus, an upper quadrant, incongruous homonomous hemianopsia could very easily result from tract pressure. Indeed, in large tumors of the temporal lobe there is no reason why either the tract or radiations or both could not be simultaneously affected.

A second, alternative hypothesis is that neoplasms might in some way affect fibers from corresponding retinal points unequally even though they lie in juxtaposition. This possibility does not, however, seem likely.

At this point we should emphasize the importance technique and patient cooperation play in determining the congruity of a field. Poor technique or lack of alertness in a patient will invariably make a truly congruous field falsely appear to be an incongruous field. The use of a test object so small that it strains to the utmost the patient's ability to determine exactly when he sees it, favors the obtaining of a falsely incongruous field. Moreover, many patients with temporal lobe tumors are seriously ill because of the papilledema occurring more frequently in temporal lobe tumors than in any other tumors affecting the visual pathway; this condition, of course, favors an incongruous result. To be sure, although we use similar techniques and deal with similar patients in cases of occipital lobe lesion, we obtain congruous defects in these cases. This finding does not controvert the above, since the field defects of patients with occipital lobe lesions, which are usually occasioned by vascular accident, possess very steep edges. Even the rare *tumors* of the occipital area often seem to produce their defects through a vascular mechanism. These are thus entirely different from temporal lobe tumors, which give rise merely to a minimal sloping edged

defect. We urge that the field in a temporal lobe lesion be observed to be *consistently* incongruous before it is labeled as such. Under the conditions of our study—with alert and cooperative patients and with tract damage ruled out—congruous fields were obtained.

Conclusions

1. The observed congruity of field defects resulting from temporal lobe amputations indicates that fibers from corresponding retinal points lie close together in the anterior portion of the radiations.

2. Meyer's loop, with the expected normal anatomic variations, does exist.

3. Fibers serving the upper quadrants of the visual field and lying next to the vertical meridian extend most anteriorly in the temporal lobe. It is suggested that in detecting minimal defects of the anterior portions of the radiations, the region of the visual field next to the vertical meridian above be carefully tested.

4. In the anterior part of the radiation, an anatomic interval does exist between the fibers serving the upper and lower quadrants of the visual field. This interval, which is formed by the sweeping forward of the fibers from the upper visual field area, is sufficient in some cases to give a very sharp horizontal boundary to an upper quadrant field defect. This complete quadrantic, congruous, homonomous defect extending into the macula is most suggestive of a temporal lobe lesion and in rare cases could be mimicked, but only by a lesion along the lower margin of the calcarine fissure.

5. The incongruity of fields found in some temporal lobe tumors is best explained on the basis of pressure on the optic tract. Both tract and radiation may be affected, of course. Before a field is labeled incongruous, however, the patient's cooperation and the examiner's technique must be at their best. A falsely incongruous field is very easy to obtain, and this may account for some of the incongruous fields noted in temporal lobe tumors.

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Staff Meeting Report

Clinical Studies of Circulating Insulin Binding Antibodies*

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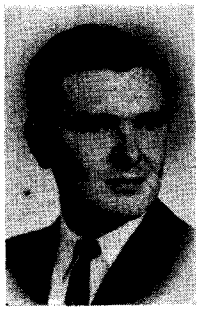
Since the introduction of insulin in the treatment of diabetes mellitus a considerable body of evidence has accumulated indicating that the insulin protein is antigenic, with antibody production following insulin therapy.[1–3] Antibody against insulin has also been induced in the experimental animal, confirming the observation of insulin antigenicity noted in the treated diabetic patient.[4–9] Antibodies have at no time been detected in the noninsulin treated patient or laboratory animal. Electrophoretic technique and protein fractionation methods have shown, with two exceptions[10,11] that the gamma globulin serum fraction is the probable site of residence of the antibodies.[12–16] A major uncertainty persists, however, as to the role of antibodies in the diabetic patient. Various studies have clearly shown that patients with gross insulin resistance have serum globulins, probably antibodies, which neutralize the effect of injected insulin.[13,17,18] That antibodies do play a role in the insulin resistance phenomenon is supported by the observation that resistance can be reversed by the use of ACTH,[15,18–20] suggesting that antibody formation or insulin-antibody union is reduced or eliminated by the corticotropin. A circulating insulin antagonist has been noted in association with diabetic acidosis.[21,22] The antagonist is absent from the serum within hours after treatment is initiated.



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Nevertheless, it has not yet been demonstrated that anti-insulin antibodies exert a significant modifying effect on insulin response in "ordinary," noninsulin resistant diabetic patients. Indeed, in a recent study Kalant and co-workers[10] conclude

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on April 22, 1960.

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that insulin response is not related to the amount of insulin bound by induced antibodies. In the present study we have observed that antibody production following various periods of insulin treatment in the noninsulin resistant patient does significantly modify the hypoglycemic response to injected insulin, both by diminishing and by delaying this response.

In an attempt to evaluate the possible contribution of an amnestic response of anti-insulin antibody production to the accentuated insulin need of ketoacidosis, we measured antibody levels during the treatment phase of diabetic acidosis in three patients. Posttreatment antibody levels were compared with those noted during the ketoacidotic state.

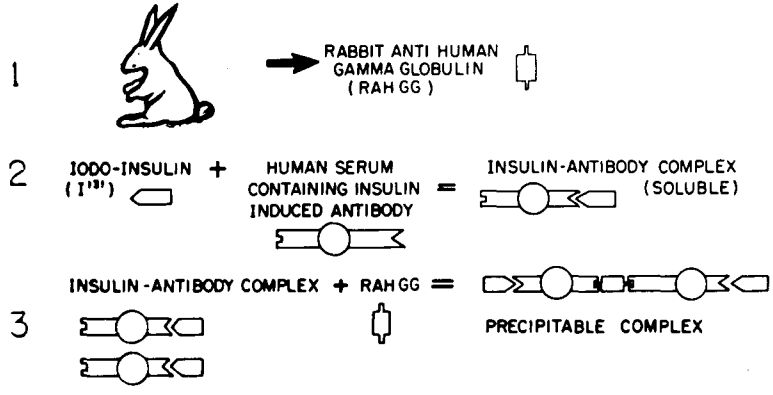
Methods

Antibody levels were demonstrated by a modification of a method devised by Skom and Talmage.[23] This method involves the precipitation of a soluble antibody-I^{131} labeled insulin complex with rabbit antihuman gamma globulin serum. Insulin antibody levels are expressed as the percentage of I^{131} labeled Beef-Pork insulin (Abbott) bound by the serum gamma globulins (i.e., antibodies) under standard conditions.

Antihuman gamma globulin was prepared by antigenically stimulating adult rabbits of 3.0 to 4.0 Kg. with sterile, pyogen free, alum precipitated, refractionated human gamma globulin. The antigen was administered intravenously in a concentration of 1 mg. gamma globulin per milliliter. Antigen was injected over a three-week period with each animal receiving a total of 12 mg. of the gamma globulin. On the eighth day following the last injection the animals were exsanguinated by femoral artery catheterization. The blood was allowed to clot and to remain overnight at 2° C., after which the serum was separated off. Following preliminary tests for antihuman gamma globulin antibodies, the sera from the antibody-producing animals was pooled. The titer of the pooled antihuman gamma globulin serum was determined by the precipitin curve method, and total nitrogen was measured by the micro Kjeldahl technique.

To 0.5 ml. of a 1:25 dilution of the human serum to be tested was added 0.5 ml. of a 0.033 microgram insulin per milliliter dilution in 1 per cent human serum albumin of I^{131} labeled insulin. The specific activity of the undiluted insulin varied from 2.56 mc/mg to 5.05 mc/mg. The serum and I^{131} insulin were incubated for two hours at 4° C. Antihuman gamma globulin serum was added in a volume that gave maximum precipitation of the incubated serum-insulin complex as determined by preliminary experiments. After standing overnight at 4° C., the mix-

ture was centrifuged at 2000 rpm, the supernatant was decanted and saved, and the precipitate was washed once with a barbital buffer of pH 8.4 (Fig. 1).



METHOD OF SKOM AND TALMAGE TO DETECT NON-PRECIPITATING INSULIN BINDING ANTIBODIES

Fig. 1. Schematic illustration of the method of Skom and Talmadge

Radioactivity of the washed precipitate and supernate was determined in a 5 ml. well scintillation counter with background less than 200 counts per minute. The percentage of precipitate radioactivity to total counts per minute was determined.

To investigate the sensitivity to insulin, the insulin-glucose tolerance test was performed according to the technique described by Himsworth and Kerr.[24] All patients were hospitalized and were kept on a constant diet on the metabolic ward; long-acting insulin was replaced by regular insulin, three to four times a day. Initially a glucose tolerance test was performed by giving 30 grams of glucose per square meter of body surface orally and measuring capillary blood samples for glucose according to the technique of Somogyi and Nelson during a one-hour period. Two days later the same amount of glucose and at the same time 5 units of glucagon-free insulin per square meter of body surface were given intravenously. Blood glucose levels were again determined over a one-hour period and the glucose curves compared. The area under each curve was measured: "G" describes the area between the glucose tolerance curve and

the base line given by the fasting level. "I" represents the area between the glucose tolerance curve and the insulin-glucose tolerance curve. The result, expressed as the ratio I/G, describes the action of insulin on hyperglycemia produced by ingestion of glucose during one hour. A ratio near 1 indicates a relatively high sensitivity to insulin, while a ratio lower than 0.5 is consistent with relative insulin insensitivity (Fig. 2).

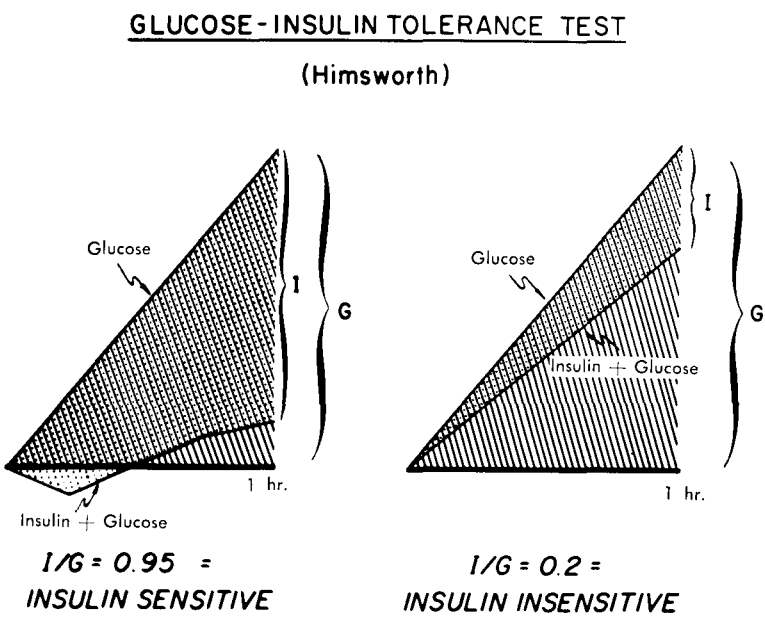


Fig. 2. Himsworth method of evaluating insulin responsiveness

Results

The percentage of insulin bound by serum globulin was compared to the responsiveness to injected insulin under the conditions noted in 35 insulin treated diabetic subjects. Pertinent clinical data are summarized in Table 1. The I/G ratios varied from 0.10 to 1.95. Insulin binding antibody levels, expressed as the percentage of total radioactive insulin bound to the precipitated gamma globulin-antigamma globulin complex, ranged from 4.6 per cent to 42 per cent. A statistically significant correlation exists between these modalities, with r (the correlation coefficient) equaling -0.50 and $p = .01$. With notable excep-

TABLE 1

Insulin Binding and I/G Ratios in Insulin Treated Diabetic Patients

Patient	Age at Onset of Diabetes	Duration of Insulin Treatment (Years)	Insulin Dose Usual	Insulin Dose Maximum	% Insulin Bound	I/G Ratio
F	16	16	47 units	47 units	42	0.51
—F	16	9	65	100	6.8	2.08
—M	35	24	40	75	11.8	0.32
—F	21	16	16	22	5.5	0.24*
—M	45	6	50	90	9.8	0.90
—M	9	12	46	50	9.8	0.47
—M	15	28	55	75	23.6	0.31
—F	50	9	10	24	5.1	0.90
—M	53	8	25	45	8.4	0.77
—M	20	23	35	80	14.8	0.59
—M	2	24	65	65	6.7	1.11
—F	66	7	10	35	30.6	0.19
—F	18	18	46	90	12.4	0.56
—M	8	26	40	60	10.7	0.41
—F	45	6	20	55	23.8	0.10
—M	14	19	40	50	10.8	0.45
—M	6	27	44	65	12.9	0.20
—M	38	27	40	40	16.2	0.23
—M	12	23	30	50	4.6	0.92
—F	63	10	20	30	4.8	0.63*
—F	41	33	25	30	22.0	0.41
—F	22	13	40	40	6.2	0.52*
—M	13	12	40	90	8.8	0.88
—F	57	10	40	80	11.4	0.33*
—F	40	21	15	60	17.5	0.61
—M	11	31	48	48	6.4	0.70
—M	6	14	45	45	27.2	0.56
—F	22	25	60	80	14.7	0.32
—F	40	14	35	45	12.4	0.78
—F	15	26	50	50	23.9	0.10
—F	63	11	30	36	6.9	0.63
—F	64	10	40	40	24.1	0.29
—F	31	14	60	80	2.5	1.00
—M	19	23	40	40	14.8	0.43
—F	47	26	120	130	26.0	0.30

*Referred to in text pages 497, 499.

tions (the starred values in Table 1), high percentages of insulin binding antibodies are associated with diminished responsiveness to injected insulin, and conversely, low insulin antibody levels are associated with intermediate to high I/G values. Four noninsulin treated patients were also studied for the presence of insulin binding antibodies and insulin responsiveness. Insulin binding was absent in all patients in this group. Interestingly, one patient (T.F.) responded only slightly to injected insulin although antibodies were undetected in his serum. The others responded normally to insulin (Table 2).

In an additional series, 15 healthy, nondiabetic, noninsulin treated subjects were studied for the presence of insulin antibodies. No antibodies were found in any of the untreated subjects.

Also of note is the lack of correlation among antibody levels, I/G ratios, and duration of insulin treatment or daily insulin needs (Table 1) confirmation of a conclusion from a previous investigation.[20]

TABLE 2

INSULIN BINDING AND I/G RATIOS IN NONINSULIN TREATED DIABETIC PATIENTS

Patient	% Insulin Bound	I/G Ratio
-F	0	1.05
-M	0	0.90
-M	0	0.10
-M	0	1.00

Insulin binding antibody levels were measured throughout the period of vigorous treatment of diabetic acidosis in three patients. No significant differences were noted between the level during treatment and the level during a stable period of the diabetes. Unfortunately, the unpredictability of clinical acidosis prohibited measurement of pre-acidosis insulin binding titers.

DISCUSSION

That different diabetic patients respond variably to a given dose of insulin is a frequently observed clinical phenomenon. This difference in physiologic response has been attributed to

many factors, including: excessive body weight, alteration of diet, blood glucose levels, infection, anxiety, adrenal steroid levels, pituitary secretions, thyroid hormone, epinephrine, chronic stress, etc. It is likely that a combination of these several factors result in one of two primary types of diabetes as noted by Himsworth and Kerr[24]—i.e., insulin sensitive or insulin insensitive. Our observations suggest that an additional acquired factor —the antibody response to treatment—combines with the inherent diabetes type to determine net responsiveness in the treated diabetic patient. It is postulated that the immediate effect of injected insulin in depressing blood glucose is diminished by the binding and inactivation of insulin by circulating antibodies. The amounts of insulin bound will of course vary, depending on the antibody concentration of the serum. High antibody levels will leave only a fraction of an injected dose unbound and thus free to exert a hypoglycemic effect.

In vitro studies by Berson and Yalow[25] indicate that two different types of antibody insulin complexes are actually formed, each distinctly differing from the other in its dissociation rate. One complex dissociates rapidly, with about 20 to 30 per cent of the total insulin bound by complex released per minute. The second complex dissociates much more slowly, with about 20 to 40 per cent of the total bound insulin released per hour. The net rate of insulin release probably lies between the extremes noted. Thus, during the one hour insulin glucose tolerance test, considerably less than the 5 units per meter squared of insulin injected is actually unbound and free to exert its physiologic effect in patients exhibiting significant antibody levels.

If the insulin as it is released from the antibody complex is unaltered, it is probably available for degradation by the insulinase mechanism[25] or free to exert its metabolic effect on the cell. The slow release of insulin from the antibody complex then provides the tissue with a continuous diminishing insulin supply for a considerable period, acting much like a depot insulin preparation. This slow release with subsequent utilization may account for the poor correlation between total daily insulin needs and the degree of insulin binding noted by the author and others.[20]

The existence of serum insulin binding globulins in patients with chronic insulin resistance (insulin daily needs above 200 units) has been clearly demonstrated as noted. It is suggested that the diminished insulin responsiveness observed during the one-hour Himsworth test in noninsulin resistant subjects is simply a quantitatively less marked manifestation of these same induced

globulins. As expected, no significant changes in insulin binding were noted during ketoacidosis.

The circulating insulin antagonist noted during clinical acidosis by Field and Stetten[21,22] is characterized as residing in the alpha globulin fraction of human serum. It is gone from the serum within six to nine hours after the onset of acidosis. In contrast, the antagonist associated with insulin resistance and present in the treated diabetic patient, as measured by the method of Skom and Talmage, is observed to travel with the gamma globulin electrophoretic fraction; this globulin remains in the serum for much longer periods. We have concluded that this globulin insulin antagonist is quite distinct from the circulating antagonist of diabetic acidosis.

Summary

The relationship between insulin binding antibodies and the response to injected insulin was studied in 35 insulin treated diabetic patients and four noninsulin treated patients. A significant degree of correlation was noted between the percentage of insulin bound to circulating antibodies and responsiveness to injected insulin. Patients with high levels of binding antibodies responded slightly to injected insulin under standard conditions. Those in whom antibody levels were low or absent, with notable exceptions, responded more strongly to the hypoglycemic effect of the insulin.

Antibodies were at no time detected in a series of 15 healthy, noninsulin treated nondiabetic, subjects and 4 noninsulin treated diabetic subjects.

It is concluded that an acquired factor—the antibody response to treatment—contributes to net insulin responsiveness.

Serum insulin-binding globulin levels were measured during the course of clinical diabetic acidosis in three patients. No difference was noted in the antibody levels during and after treatment. It is subsequently concluded that the circulating globulin insulin antagonist of treated diabetes is distinct from the insulin antagonist of ketoacidosis.

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Staff Meeting Report

Chronic Osteomyelitis of the Extremities; A Review of Treatment*

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The innovation of antibiotics gave physicians hope of eliminating one of the deforming and disabling diseases, osteomyelitis. The realization of this hope has not been attained. The incidence of acute osteomyelitis has been decreased by the free use of antibiotics, but the treatment of chronic osteomyelitis remains a problem. It was for this reason that the Division of Orthopedic Surgery elected to review the cases of chronic osteomyelitis treated surgically over the past twelve years at the University Hospitals.

R. D. Granquist

Historical Review

Osteomyelitis is an age-old problem, and the recognition and treatment of the chronic form following trauma was first described in the era of Hippocrates. Not until the beginning of the nineteenth century, however, with the introduction of histological techniques and of bacteriological concepts, did we arrive at a true understanding of the pathologic process.[1]

In 1827, Nathan Smith[2] of Philadelphia, using gross anatomical considerations, defined necrosis of bone as "the death of some part of the bony structure." He recognized that pus accumulated beneath the periosteum and in the shafts of the long bones between the endosteum and the cortex. Death of the bone appeared to him to result from "the consequent destruction of those vessels which from the two periostea furnish it with blood and nutrition. These last being insufficient for its nutrition, the bone consequently perishes."

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About the middle of the century, Louis Pasteur[3] demonstrated that the Staphylococcus organism could produce bone destruction. This discovery paved the way for experimental work in osteomyelitis and led to an understanding of the etiology and the pathogenesis of this disease.

Rodet[1] (1884) recognized the difference between acute hematogenous osteomyelitis and the osteomyelitis that followed compound fractures. He reported to the Academy of Sciences in Paris his experimental production of hematogenous disease in animals by the intravenous injection of staphylococci. A few years later Lexer[1] (1897) published his classic treatise on acute osteomyelitis, in which he stressed the relationship of trauma as a site of lowered resistance in the localization of the disease. He demonstrated that the nutrient artery was the main route for bacteria entering the bone. Koch[3] (1911) showed that within two hours after the intravenous injection, organisms localized in the metaphyseal veins and began forming osteomyelitic foci.

The experimental studies of Johnson[4] (1927) and Larsen[5] (1938) contributed significantly to the understanding of circulation to the bone and of the osteomyelitic process in general. Johnson selectively occluded vessels in the femur and found:

(1) The nutrient arteries furnish the greatest blood supply to the medulla and inner cortex.

(2) The periosteal vessels supply the outer cortex; following occlusion of the nutrient artery they do not establish collateral circulation to the inner cortex and the medulla for a period of four weeks.

(3) The metaphyseal vessels constitute an auxiliary supply to the inner cortex and medulla but are less important than the nutrient vessels.

Larsen[5] produced bone necrosis by injecting saline solution into the medulla and increasing the intramedullary pressure.

The care of open fractures in World War I revolutionized the treatment of osteomyelitis, and out of this experience grew the Carrell-Dakin, the Orr, and the maggot methods of treating osteomyelitis.[1,3] These methods have been used with varying degrees of success. The Orr method still serves as an adjunct to antibiotic and other forms of therapy.

Pathogenesis

Osteomyelitis results from a bacterial invasion of the bone. The bacteria gain access indirectly via the blood stream, as a septic embolus from a remote focus of infection, or they may

gain access to the bone directly, either through the open wound of an open fracture or through a surgical incision. The nature of the lesion produced and the cause of the disease process vary according to the mode of entry.

In hematogenous osteomyelitis the bacteria enter the bone through the nutrient artery and localize in the venous sinusoids of the metaphysis. There is an initial acute, exudative inflammation of the marrow tissues. The lethal effects of the toxins, thrombosis and obliteration of the vessels, and increased intramedullary pressure leads to ischemia and local bone necrosis. In this ideal medium for further bacterial growth an abscess forms. Edema fluid and purulent exudate are forced through the Haversian canals to the subperiosteal space, where the periosteum is raised from the bone isolating the outer cortex from its blood supply. The pus following the path of least resistance may reenter the cortex at a distance or may perforate the periosteum and enter the soft tissues. In the soft tissues the exudate dissects fascial planes and may gain access to neighboring joints. If the process is allowed to continue, decompression is finally established by a pointing to the skin surface and eventual external drainage.

The lesion produced by direct involvement of the bone is usually more localized. The pus escapes through the wound and decompression is obtained without extensive dissection. The periosteum is not raised, and the blood supply to the outer cortex is preserved.

Following establishment of drainage, attempts are made to localize and wall off the involved area by fibrous tissue reaction. The necrotic debris and sequestra within this area are either expelled through the openings to the surface or may in rare instances be reabsorbed. The bony defects are repaired by endosteal and periosteal new bone formations. When the periosteum has been raised, this new bone formation surrounds the previously compromised cortex and an involucrum is formed.

Etiology

Practically all pyogenic organisms have been reported as the etiological agents in osteomyelitis. The *Staphylococcus* organism, is the offender in approximately 70-80 per cent of the cases.[6,7,8] This usually originates in a skin lesion and forms bacterial emboli which enter the circulation and localize in the bone marrow. The pathogenicity of the *Staphylococcus* is believed to be due largely to the toxins which it produces. The *Streptococcus* accounts for 20-30 per cent of the cases and commonly involves the mucus membranes of the nose and

throat as a primary site, invading the bone by the hematogenous route. Other organisms which less frequently cause osteomyelitis are the *Pneumococcus, Salmonella, Brucella,* and *Escherichia coli.*

Clinical Course

Osteomyelitis may be divided into three stages: the acute, the subacute, and the chronic. In the acute stage, consitutional symptoms and acute localized inflammatory reaction predominate. When drainage or decompression has been established and widespread inflammatory changes subside, the subacute stage begins; it is characterized by bone destruction, bone reabsorption, beginning sequestration, and new bone formation. A low grade fever indicates continued activity of the infective process. The chronic stage begins with the development of the mature involucrum, a fully developed walled-off lesion, reossification of the involved area, well-defined sequestra, and foci of condensation and rarefaction evident on roentgenological examination. The surrounding soft tissue is thickened, scarred, and avascular due to sinus formation, chronic inflammation, and lymphatic obstruction. In this paper we will limit our discussion to the treatment of the chronic stage.

Treatment

Therapy of chronic osteomyelitis is primarily surgical. Antibiotics are used adjunctively to control the residual infection. In order to treat the lesion effectively, it is necessary to eradicate the infection by removing the focus of infection and to open avenues for an effective blood supply to the involved area.

The surgical procedure includes a thorough excision of all avascular and scarred soft tissues. The infected focus must be completely uncovered, and foreign bodies, sequestra, and necrotic tissues must be removed. The rigid walled bony cavity which results may be treated by primary closure or by allowing the defect to granulate and epithelialize.

Closure by Secondary Intention

Buchman[9] (1951) states that the prerequisites for satisfactory healing of chronic osteomyelitis by secondary intention are:

1) a thorough surgical eradication of the lesion;

2) an efficient and harmless method of sterilizing the wound;

3) a means of removal of wound discharges and sloughs that occur as a result of infection and the surgical procedure;

4) an agent that will produce an even and rapid growth of

healthy granulations from the depths upward to fill the cavity completely before the circulation is impaired through scar tissue formation.

During World War I, the Carrel-Dakin method was used as a means of producing healing by secondary intention. This method included the necessary surgical procedure, with removal of wound discharges and sloughs through meticulous daily dressing changes. But the antiseptic used did not sterilize the wound, and no provision was made for rapid granulation. The dressing changes were painful, and contamination with nuisance organisms occurred frequently.

The Orr method, introduced in 1927, consists of a thorough saucerization of the bony lesion, a packing of the wound with Vaseline® gauze, plaster immobilization, and infrequent dressing changes at three- to four-week intervals. This method met most of the requirements for successful healing by secondary intention. The Vaseline gauze provided an effective drain and induced the formation of granulation tissues from the depths of the wound. Secondary contamination was avoided by infrequent dressing changes, and sterilization of the wound was thought to occur through formation of bacteriophages. This technique however, did not provide an agent to produce rapid growth of granulation tissue. Its advantages were the short period of hospitalization, the avoidance of frequent, painful dressing changes, and a lessening of wound contamination. The results of treatment by the Orr method were superior to those attained by the Carrel-Dakin technique. Orr[10] (1927) obtained cures in 35 of 47 cases. Kulowski[11] (1921) reported healing in 99 of 130 cases, with an average healing time of seven months, and hospitalization of one month. The chief disadvantages of this method are the foul odor from drainage into cast and the accumulation of pus which soaks the cast; moreover, prolonged immobilization gives rise to muscle atrophy and joint stiffness.

Baer (1931)[12] used sterile maggots in saucerized wounds and obtained healing in 98 cases in six to nine weeks. Buchman[9] (1951) after 14 years of experience with maggots, felt the results obtained were superior to those of the Dakin or Orr methods. The maggot treatment provided rapid healing of the wound by: a) physical irritation of the wound, hastening granulation tissue growth; b) production of a profuse exudate providing physical washing of the wound; c) enzymatic digestion of necrotic tissue; d) chemical inhibition of bacterial growth by changing the pH of the medium from acid to alkaline; and e) bacteriocidal action in the alimentary tract of the maggot. This

method, while popular for a time, proved to be expensive and was technically difficult to carry out.

The disadvantages entailed by all three methods included the long healing period, the prolonged or frequent hospitalizations, and the frequency of recurrence.

Closure By Primary Intention

A method that has been developed more recently is closure by primary intention. This procedure involves eradication of the lesion, a method of primary or delayed primary wound closure, and use of an agent to control the infection until the muscle flap or hematoma used to fill in dead space becomes sufficiently organized to resist infection.[4]

Dickson *et al.* (1941)[13] published perhaps the first account of primary closure of chronic osteomyelitis under antibiotic control using sulfa drugs locally and systemically. Their method consisted of thorough excision of all scar tissue and saucerization of the involved area of bone, followed by insufflation of sulfa powder into the wound; primary suture utilizing the muscle flap to fill in dead space was employed for closure, and cast immobilization for three weeks gave protection during healing. They obtained primary healing in 82 per cent of 22 cases using this method. In 1953 they reported on 140 procedures on 104 patients treated by the same method with penicillin used as an adjunct. They obtained primary healing in 83.5 per cent, secondary healing in 12 per cent, and no improvement in 4.3 per cent of the cases. The average healing period was 18.7 days, and hospitalization averaged 21 days. There were 12 recurrences in a follow-up period of six months to four years. All of the patients who represented initial failures were subjected to reoperation, and in all of them healing was noted *per primum.*

Prigges[14] (1946) obtained healing in 43 of 44 cases. Carrell and Woodword[15] (1950), and Rowling[16] (1959) reported healing in 82 per cent of 49 and 58 cases respectively. In their series they administered penicillin before and after surgical intervention, performed primary or delayed primary wound closure, and used muscle flaps to fill in the dead space when indicated. The average healing time was three weeks.

Buchman and Blair[17] (1951) reported healing *per primum* in 79 per cent of 93 lesions utilizing primary closure, without drainage and local and systemic penicillin. They allowed the hematoma to fill in the dead space and relied upon the antibiotic to prevent infection of the hematoma until it became organized. The five year follow-up showed a 3 per cent recurrence rate.

It would appear from these series that a primary or delayed primary closure under antibiotic control provides a satisfactory method of wound closure in the treatment of chronic osteomyelitis. The advantages are rapid healing of the wound with early mobilization of the involved limb, and a short period of hospitalization.

The use of a split skin graft in lesions which cannot be closed primarily because of inadequate soft tissue coverage has been successful in a high percentage of cases. This procedure has been carried out either as a definitive treatment or as a skin dressing until a plastic closure can be accomplished. Armstrong and Jarnon[18] (1936), Kelly *et al.*[19] (1945), Stein and Kapell[20] (1948), recommend that after saucerization, the wound should be packed open with fine mesh gauze. Four to seven days later the split graft is applied. During the time the graft is healing a full thickness flap or pedicle graft may be prepared. When this flap is ready for transfer, the split graft is removed and the full thickness covering applied. This method is especially suitable for the proximal tibia, where there may be insufficient soft tissue present for primary coverage of the defect.

In cases in which the strength of the bone is impaired following saucerization, bone grafting may be necessary. Knight and Wood[21] (1945), and Reynolds and Zaepfel[22] (1948) have advocated initial split thickness skin coverage to be followed in three months by excision of the skin graft, insertion of cancellous iliac graft, and primary coverage with full thickness skin. They obtained 90 to 95 per cent good results; the grafts healed without infection or sequestration, and the bony defects were eliminated.

Bickel *et al*[23] (1953) reported success in 28 of 36 cases, and Hazlett[24] (1954) observed success in 87 of 101 cases in which bone grafting was done primarily at the time of saucerization, or as a secondary procedure a few days later. Experimental work has shown that cancellous bone is vascularized quickly, thus enabling the transplant to resist any residual infection present. Hazlett stated the belief that the best results were obtained when bone grafting was done at the time of saucerization. He added that packing of the wound, especially if continued for more than a few days, deprives the tissue of blood supply and encourages secondary infection.

While amputation is rarely necessary in chronic osteomyelitis, it becomes the treatment of choice in certain circumstances; Steindler[7] listed the following indications for amputation: 1) extensive bone and soft tissue destruction with anticipated functionally useless limb even after healing; 2) persistent and

uncontrollable infection especially with involvement of the neighboring joint; 3) malignant degeneration of the sinus tract.

Review of Cases

A review was made of all patients with chronic osteomyelitis in the extremities who were admitted to the University of Minnesota Hospitals from 1947 to 1959. Those patients who were treated surgically and were given at least a one-year follow-up were selected for this study. Forty-five patients met these criteria. Of these, 24 had hematogenous osteomyelitis and 21 had post-traumatic osteomyelitis.

The area involved was the tibia in 19 patients, femur in 17, humerus in 5, radius in 3, and os calcis in one.

Cultures were obtained from 37 lesions. *Staphylococcus aureus* was the predominant organism in 29 of these lesions.

Following treatment, healing occurred in 36 cases in a period ranging from nine days to 11 months, and in 30 of these healing occurred less than 120 days. There were nine failures, and in five of these cases amputation was performed.

In every case the surgical procedure included excision of the sinus tract and the avascular soft tissue, combined with sequestrectomy, saucerization, and removal of any observed foreign material, such as metal plates and screws. The wounds were divided into three groups based on the method used for closure; i.e.: primary closure, secondary closure, and closure by secondary intention using the Orr method of treatment.

The first group consists of 15 wounds treated by primary closure. A drain was used in four cases. In ten patients there was hematogenous osteomyelitis, and in five post-traumatic osteomyelitis. Hospitalization averaged 30 days. Twelve wounds healed in an average of 23 days. Three wounds continued to drain for 4 to 11 months and then stopped spontaneously. Drainage recurred in two wounds. One healed *per primum* after sequestrectomy. There was one failure.

The second group consists of 15 wounds treated by secondary closure. Plastic closure was necessary in four tibial wounds. Coverage was obtained in two cases by using split skin grafts and in two cases by double pedicle flaps. In this group, five patients had hematogenous osteomyelitis and ten had post-traumatic osteomyelitis. Hospitalization averaged 47 days. Healing occurred in 13 wounds in an average of 64 days. The wounds failed to heal in two cases, necessitating in each case a below knee amputation. The indication for amputation in one patient was a non-united fracture of the tibia with infection which caused persistent foul drainage. The second patient had

persistent drainage from the right ankle, which was riddled with small shell fragments that could not be removed.

The last group consists of 14 wounds treated by the Orr Method—seven caused by hematogenous osteomyelitis and seven by post-traumatic osteomyelitis. The average hospitalization time of these patients was 60 days. Healing occurred in nine wounds in an average of five months. Two wounds continued to drain slightly but required no further treatment. Amputation was performed upon three patients with post-traumatic osteomyelitis because of persistent drainage. Each of these three patients requested amputation to insure permanent eradication of the infection after having previously undergone repeated surgical procedures.

Summary

In general, the principles of treatment of chronic bone infection are the same as those for any chronic surgical infection. These principles are:

1) the correction of deficiencies of blood volume, proteins, and electrolytes;

2) the use of appropriate antibiotics at therapeutic levels;

3) the excision of all necrotic and infected tissue;

4) the removal of foreign material, such as metal plates, screws, and sequestrated bone. Intramedullary fixation may be necessary to provide stability of a fracture and is usually tolerated in the presence of osteomyelitis;

5) the establishment of an effective blood supply to the area by excision of avascular soft tissue and bone;

6) the obliteration of dead space by organized hematoma or by transposition of muscle or soft tissue;

7) early wound coverage with healthy tissue by primary or secondary closure;

8) physiologic rest of the limb until the wound is healed by immobilization in a plaster cast or compression dressing.

Specifically the treatment of bone infection differs from that of soft tissue infection because of the structural peculiarities of osseous tissue. The presence of large bony defects due to trauma or necrosis may impair the strength of the bone and require stablilization to maintain its integrity. Stability is obtained internally by filling the defect with cancellous bone and externally by using a plaster cast or a brace.

Conclusions

Our best results were obtained in the group of patients treated by primary closure; it must be borne in mind however, that

SURGICAL TREATMENT OF CHRONIC OSTEOMYELITIS
REVIEW OF 45 CASES

Procedure	Site		Etiology		Culture		Hospital Stay	Wound Healing	Complications & Comments
Primary Closure Without Drain 11 cases	Femur Tibia Humerus Radius Oscalcis	3 3 3 1 1	Hemat. Trauma	6 5	Staph B Strep & Staph Paracolon No culture	5 1 1 1	30 days (5-76)	23 days (9-36)	1 case drained 11 mo. then stopped spontaneously. 1 case recurred - Sequestrectomy Primary closure - healed.
Primary Closure With Drain 4 cases	Femur Tibia	2 2	Hemat.	4	Staph Sterile No culture	2 1 1	(1) 16 da. (2) 13 da. (3) 17 da. (4) 90 da.	(1) 14 da. (2) 90 da. (3) 120 da. (4) 11 mo.	Case 2 & 4 drained slightly then stopped spontaneously. Failure - 1 Case 3 recurred after 6 month required further surgery - still draining.
Secondary Closure 15 cases	Femur Tibia	6 9	Hemat. Trauma	5 10	Staph B Strep & E Coli B Strep & Paracolon	12 2 1	47 da. (11-107)	64 da. (16-120) 13 cases	Failures - 2 (1) gunshot wound with metal left in - BK amputation (2) Nonunion tibia - BK amputation
Orr Technique 14 cases	Femur Tibia Humerus Radius	6 4 2 2	Hemat. Trauma	7 7	Staph Staph & Paracolon Staph & Proteus Paracolon No culture	9 1 1 1 2	60 da. (15-142)	5 mo. (3-9) 9 cases	Failures - 5 2 cases continue to drain slightly 3 cases continued to drain and amputation performed
Dakin Method 1 case	Tibia	1	Hemat.	1	Staph	1	36 da.	4 yrs.	Daily Dakin irrigations through Lucite tube

this method of treatment was selected for the less severe cases. The results obtained at this hospital are comparable to those reported in the literature, but the series is too small to permit definite conclusions about the most desirable method of obtaining healing of an osteomyelitic lesion.

The patients in the series were treated during the period in which antibiotics were readily available. In spite of this, failures of healing were noted in nine cases, of which five came to amputation.

Clearly, osteomyelitis continues to present problems—not only of healing of the lesion but also of functional loss of an extremity. The treatment continues to be long and tedious. Therefore, in view of the difficulty of curing an osteomyelitis once it has become established, surgical infections must be vigorously prevented by intensive care of open fractures.

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Medical School News

DR. BERNARD ZIMMERMANN TO HEAD SURGERY AT WEST VIRGINIA

Dr. Bernard Zimmermann, Professor of Surgery at the University of Minnesota Medical School, has been appointed Head of the Department of Surgery at West Virginia University Medical School.

He will assume the post July 1, 1960, in Morgantown, W. Va., taking three of his present Minnesota colleagues with him. They are Dr. Herbert A. Warden, who will become an Associate Professor; Dr. Walter H. Moran, who was named an Instructor; and Dr. Thomas J. Tarnay, who will be a Resident in Surgery.

Bernard Zimmermann

Dr. Zimmermann is a St. Paul native and graduate of the Harvard Medical School. He has gained distinction as a surgeon, teacher, and researcher in the fields of cancer and adrenal hormones. He is Cancer Coordinator for the University of Minnesota Medical School and has been on the Minnesota staff since July 1, 1951.

Dr. Warden, an Instructor in Surgery at Minnesota, gained professional recognition in 1954 as an original member of the surgery team which developed the cross-circulation open cardiotomy technique at University Hospitals. He is credited with much of the preliminary research and experimental work.

Herbert A. Warden

The West Virginia University Medical School is enlarging its two year program to a four year curriculum, and is completing a new 560-bed University Hospital to serve as a teaching and research facility. Eugene L. Staples, former Assistant Director of University of Minnesota Hospitals, became Administrator of the West Virginia hospital in January, 1960. He was preceded there by Audrey E. Windemuth, another Minnesotan, who was made Director of Nursing Services.

DR. JAMES F. MARVIN DIES

Dr. James F. Marvin, 44, Associate Professor of Radiology, died April 22, 1960. He had been on leave of absence due to ill health for the preceding three months. Death was due to cancer.

Dr. Marvin was a native of Nebraska. He was a Phi Beta Kappa graduate of the University of Nebraska, and received his M.S. and Ph.D. degrees from the University of Minnesota. He was appointed an Instructor of Biophysics in the University of Minnesota Medical School in 1939, serving continuously on the staff since then.

A member of many professional societies, Dr. Marvin made numerous contributions to the Scientific literature. He will be remembered for his contributions to the Medical School's research programs, and will be deeply missed by his colleagues.

Survivors are his wife Lydia, two daughters, three sons, three brothers, two sisters, and his mother, Mrs. Henry Marvin, Lincoln, Neb. The family resides at 3044 E. 50th street, Minneapolis.

SENIOR-ALUMNI LUNCHEON HELD

More than 200 graduating senior medical students and medical alumni attended the annual Senior-Alumni Luncheon May 5 sponsored by the Minnesota Medical Alumni Association at Coffman Union.

Dr. Sheldon Lagaard (Med. '43), MMAA president, was Master of Ceremonies at the traditional event. Main speaker was Dr. William B. Hildebrand, President of the Wisconsin State Medical Society, who spoke on "Opportunities and Challenges in Medicine."

Dr. Robert O. Quello (Med. '35) and Dr. Clarence J. Rowe, Jr., (Med. '42) were Minneapolis and St. Paul chairmen for the event, at which alumni served as individual hosts to members of the graduating class at the University of Minnesota Medical School.

Student News

ALPHA OMEGA ALPHA ELECTS OFFICERS, MEMBERS

The University of Minnesota chapter of Alpha Omega Alpha, national honor medical society, has elected Patrick J. Scanlan of Minneapolis its President for the coming year. Other new officers chosen May 4, 1960 at the Society's annual banquet were Fred L. Shapiro, Minneapolis, Vice President; John A. Cich, St. Paul, Secretary; and Charles L. Murray, Minneapolis, Treasurer. All new officers are members of the present junior class in the University of Minnesota Medical School.

SCANLAN SHAPIRO CICH MURRAY

Fifteen other new members, all graduating seniors, were initiated into AOA. They are Jon E. Boline, St. Paul; Lawrence W. DeSanto, Duluth; Harold D. Gambill, Rochester; John A. Grover, Duluth; Hovald K. Helseth, St. Paul; Clement N. Herred, Miller, S.D.; Philip C. Iverslie, Mankato; John B. LaLonde, Bemidji; Michael D. Levitt, St. Paul; John D. MacArthur, Duluth; Bruce C. Nydahl, Mankato; Willard C. Peterson, Minneapolis; Odean M. Severseike, Belmond, Ia.; Paul Silverstein, Minneapolis; and Olof S. Sohlberg, St. Paul.

AOA also announced plans to sponsor an annual AOA Scholarship through the scholarship program of the Minnesota Medical Foundation. The $500.00 award will be given each year to an outstanding senior medical student.

Seventy members and guests attended the annual banquet, and about 150 attended the lecture which followed. Guest speaker was Dr. Joseph C. Hinsey, Director of the Cornell University Medical Center, New York, who discussed "Ingredients in Medical Research—The Story of a Method."

Departmental News

ADMINISTRATION

Dr. Robert B. Howard, Dean of the College of Medical Sciences, and Dr. William Fleeson, newly appointed Assistant Dean, addressed the Red River Valley Medical Society May 2, 1960 in Crookston, Minn.

PEDIATRICS

Dr. Richard W. Von Korff, Assistant Professor and biochemist, has been awarded a five year U.S. Public Health Service Senior Research Fellowship. Forty-three other scientists at 32 research and teaching institutions were named to share in the 1961 program, averaging support of $13,000 each during the first year. The Federal program is designed to increase manpower for research in the preclinical sciences.

Dr. Robert L. Vernier, Assistant Professor, has been awarded a Guggenheim Fellowship, and will also continue his research as an Established Investigator of the American Heart Association during the 1960-61 academic year. He will conduct his research at the Serum Institute in Copenhagen, Denmark, where he will study the development of the kidney, and the blood-brain barrier in human fetuses utilizing an electron microscope.

Papers presented by the Pediatrics Department at the 30th Annual Meeting of the Society for Pediatric Research May 3-4, 1960 in Swampscott, Mass., included "Morphologic Studies of the Mechanism of Proteinuria" by Dr. Robert Vernier; "Total Pulmonary Resistance in Normal Infants and Children" by Dr. Russell Lucas; "Identification in Human Serum of an Inhibitor of Staphylococcal Satellite Proteolysis (Miller Phenomenon)" by Dr. Paul G. Quie; "Exudative Enteropathy, Hypoproteinemia, Edema, and Iron Deficiency Anemia" by Dr. William Krivit; and "Specific Deficiency of Vitamin B_{12} Absorption" by Dr. Eleanor Colle and Dr. William Krivit.

PHYSICAL MEDICINE AND REHABILITATION

Dr. Frederic J. Kottke, Professor and Head, addressed a luncheon meeting of the Fergus Falls (Minn.) Hospital Auxiliary April 20th and lectured before the Hospital's general staff the following morning.

Dr. Kottke and Dr. Glenn Gullickson, Assistant Director of the Rehabilitation Center, participated in the Board of Gover-

nors meeting of the American Congress of Physical Medicine and Rehabilitation April 24-25 in Chicago, Ill.

New appointments in the Department include James Canterbury, Laboratory Technician; Joyce Johnson, OTR, Occupational Therapist in Pediatrics; and Joan Mitchell, OTR, Occupational Therapist in the Rehabilitation Center.

SCHOOL OF NURSING

Mrs. Katharine Densford Dreves, Emeritus Director, was awarded a diamond honorary pin by the American Nurses Association at its 1960 meeting in Miami Beach, Fla. A former president of A.N.A., Mrs. Dreves was honored for "long and outstanding service to the professional association and contributions to achievement of its objectives." She retired as Director of the School of Nursing, University of Minnesota, in 1959.

DERMATOLOGY

Of candidates successfully passing the examinations of the American Board of Dermatology during the past seven years, more have been graduates of the University of Minnesota Medical School than any other Medical School. This unusual interest in Dermatology is a tribute to the quality of teaching in the Division of Dermatology. Dr. Henry E. Michelson, now retired, was Professor and Head of the Division, through 1957, when he was succeeded by Dr. Francis W. Lynch.

SCHOOL OF PUBLIC HEALTH

Dr. Edith M. Lentz, Associate Professor, spoke in Duluth, Minn. May 16, 1960, at the annual interprofessional relations dinner sponsored by the St. Louis County Medical Society for related medical institutions and nursing organizations. Dr. Lentz is the author of the book, "The Give and Take in Hospitals," and has made important contributions to research projects in business and industry.

ALUMNI DEATHS

Dr. Robert P. Gallagher (Med. '43), died March 5, 1960 in Amarillo, Texas of multiple sclerosis at age 45. He was on the staff of the Veterans Administration Hospital, where he died, and was a veteran of World War II. Dr. Gallagher served his internship at Queen's Hospital in Honolulu, Hawaii, and had been editor of his local medical society's Bulletin in Amarillo. He was a member of the American Medical Association.

Dr. Frank E. Wheelon (Med. '00), died February 23, 1960 in Lake City, Fla., where he lived in retirement. He was 82 years old. Dr. Wheelon formerly practiced in Esmond, N.D., and Minot, N.D., and was a veteran of World War I. He was a member of the American Medical Association.

Memorial Gifts

Recent contributions to the Minnesota Medical Foundation have been received in memory of:

Mr. Allen D. Berry
Nashville, Tenn.

Memorial gifts are a practical means of honoring the memory of a friend or loved one while providing needed assistance for the University of Minnesota Medical School. Dignified acknowledgments are made by the Foundation to both the donor and to the family of the deceased.

Alumni Notes

◆ **1926**

C. A. Saffert was named Health Officer for the City of New Ulm, Minn. Dr. H. A. Vogel (Med. '31) was also named to the Board of Health.

◆ **1928**

R. N. Berke is in practice in Hackensack, New Jersey, and has specialized in Ophthalmology since 1930.

C. R. Wall was elected a member of the Board of Directors of the Billy Graham Evangelical Association. Dr. Wall is in practice in Minneapolis.

◆ **1932**

Leonard F. Johnston was elected Secretary-Treasurer of the Winona County Medical Society. He succeeded Dr. Charles W. Rogers (Med. '32), also of Winona.

◆ **1934**

Theodore J. Stransky of Owatonna has been elected Chief of Staff of the Owatonna, Minn., City Hospital.

◆ **1935**

Leonard S. Arling was elected Secretary of the Industrial Medical Association at its 1960 national meeting in Rochester, N.Y. He is affiliated with the Northwest Industrial Clinic, Minneapolis.

◆ **1936**

Emma F. Mickelsen Fronk is now limiting her medical practice to that of being school physician at University (Minneapolis) High School. She is married to a Minneapolis cement company executive, and has two sons of high school age. Mrs. Fronk was recently featured by a Minneapolis Star article on wives of men prominent in the community.

◆ **1938**

Col. Philip R. Beckjord is now on duty in Korea with the U.S. Army medical Corps as Commanding Officer, 65th Medical Group. He has been in the Army since 1940.

◆ **1940**

Theodore Wellner was elected Vice President of the medical staff at Olmsted Community Hospital, Rochester, Minn.

Philip H. Soucheray, St. Paul internist, has announced the association of Dr. Everett H. Karon (Med. '54) in practice of medicine. Dr. Karon has completed a Fellowship in Internal Medicine at Mayo Clinic, Rochester.

Robert J. Anderson, Assistant Surgeon General, U.S. Public Health Service, delivered the John W. Bell Lecture May 2 before the Hennepin County (Minneapolis) Medical Society. His address was titled "Virus in the Public's Health." It was co-sponsored by the Hennepin County Tuberculosis Association. Dr. Anderson is presently Chief of the Communicable Disease Center in Atlanta, Ga. He is a pioneer in mass chest X-ray programs, and a native of Winona, Minn.

◆ **1941**

Frank G. Kiesler has been appointed Psychiatrist and Medical Director of the Tri County Mental Health Center, Grand Rapids, Minn.

◆ **1943**

Wayne Chadbourn of Minneapolis was chosen President-Elect of the newly formed Twin Cities Society of Pathologists, which was organized Feb. 4, 1960. Dr. Walter Subby of Wayzata (Med. '40) was elected Secretary-Treasurer.

Raymond A. Sanford is the new President of the medical staff at St. Joseph's Hospital, Mankato, Minn. Dr. H. J. Setzer (Med. '24) was named Secretary. Reappointed to the executive committee were Dr. M. I. Howard (Med. '25); Dr. A. A. Schmitz (Med. '38); and Dr. J. C. Von Drasek (Med. '48).

H. P. Van Cleve, general practitioner affiliated for the past 10 years with the Austin Clinic, Austin, Minn., spoke on "The Practicing Physician of Today and Tomorrow" at Medical Sciences Day observed April 23 at the Medical School. The Austin Clinic has 15 staff physicians, six of whom spend full time in the general practice of medicine.

◆ **1951**

Theodore M. Gill was elected Chief of the medical staff at Naeve Hospital, Albert Lea, Minn.

◆ **1952**

Robert P. Koenig has begun the practice of Ophthalmology in new offices at 410 Granite Exchange Building, St. Cloud, Minnesota.

◆ **1954**

D. W. Sontag, Lake City, Minn. physician, is serving as Secretary-Treasurer of the Southern Minnesota Chapter of the Minnesota Academy of General Practice.

◆ **1955**

Gordon L. Backer has been appointed a fellow in Ophthalmology at the Mayo Foundation, Rochester, Minn.

◆ **1956**

Lt. Alan C. Stormo, U.S. Navy Medical Corps, has been transferred to duty as a Resident at the U.S. Naval Hospital, St. Albans, N.Y.

Dale C. Lindquist has begun practice in Elbow Lake, Minn. in association with Dr. V. A. Doms (Med. '46) and Dr. C. F. Peikert (Med. '56) at the Elbow Lake Clinic.

◆ **1958**

Lt. Richard H. Hedenstrom, a flight surgeon with the U.S. Navy, is now on duty with an antisubmarine air group aboard an aircraft carrier.

Capt. Gerald J. Anderson is on duty in Korea with the U.S. Army Medical Corps. His address is: Capt. Gerald J. Anderson, 05501112, Hq. 1st Recon. Sqdn., 9th Cavalry, APO 24, San Francisco, Calif.

◆ **1959**

Ronald J. Nelson, who is nearing the completion of his internship at King County Hospital, Seattle, Wash., used part of his vacation to visit the University of Minnesota Medical School in April. He expects to enter a seminary following his intern period. He was President of the Class of 1959 at the Medical School.

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