

ULCERATIVE TYPES AS DETERMINED BY INHERITANCE
AND AS RELATED TO NATURAL RESISTANCE
AGAINST TUBERCULOSIS: AN EXPERI-
MENTAL STUDY ON INBRED
GUINEA PIGS.

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PLATE 23.

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Wright and Lewis (1) found that inbred guinea pigs differed by families in their natural resistance to inoculation tuberculosis. It seemed probable to the present authors that the animal material was suitable for the determination of some at least of the physiological attributes underlying natural resistance to tuberculosis. We have previously reported studies in this general direction on the allergic irritability of these animals and of tuberculous animals in general (2-5). The present report concerns the reaction of the tissues, more particularly, but not exclusively, the skin.

The experiments are unique so far as we know both in the method of observation and the character of the animal material and there is no literature bearing directly on the work. On the other hand, the results revivify in our minds discussions of diverse questions in physiology and pathology: constitution, diathesis, predisposition and local or tissue resistance, which have been more or less continuously under observation and discussion by medical men and students of inheritance for generations. It seems proper therefore to report the experiments as directly and completely as possible and to defer reference to the observations and speculations in these various fields to later pages where the bearings of the work can be analyzed.

OBSERVATIONAL PART.

The animal material was that previously used by Wright and Lewis (1) consisting of five families of guinea pig which had been inbred by continuous brother and sister mating for a long succession of generations. The families are designated by number as 35, 2, 32, 13 and 39. They decrease in resistance to tuberculosis in the order stated.

It was thought necessary, in the course of the general experiments designed to determine resistance as measured by length of life after inoculation, to vary the method of inoculation in order to make certain that the results were independent of technical details. In due course, therefore, series of animals were inoculated directly into the skin with such amounts of virulent tubercle bacilli that death from tuberculosis might be expected in about 3 months.

The constant result of the intracutaneous inoculation is the formation of a papule which increases to a nodule of considerable size. Sooner or later the center of this nodule undergoes an ulcerative process of greater or less extent. From the time the lesion is fully developed it displays processes of healing. The ulcer shrinks and may heal over. If most of the nodule has become involved in the ulcer the whole lesion may heal and leave behind a hairless linear scar. The more usual course perhaps is that the ulcer and nodule, both reduced in size, become quiescent or stagnant and persist through the life of the animal.

When this reaction was understood it was thought that there might be some significant correlation between the development of the local lesion and the length of life of the *individual* animal. And indeed there is a relation which might be measurable between length of life and the healing process above referred to but it seems of little present significance, being apparently based on the fact that the healing process is a slow one and that only those animals which live a long time give it a chance to develop fully. The tendency to heal is exhibited by nearly if not quite all the lesions about the 3rd week. It is apparently consecutive to the discharge of matter from the nodule through the ulcer.

We have studied with care the early periods in the development of the cutaneous lesion to see whether there are discernible characteristics which might, by tendency at least, render predictable the length of life of the *individual*. Such have not been found.

When the lesions are examined with reference to the *family* there are easily recognizable qualitative differences and it has been possible to express these roughly in figures so that they acquire a certain quantitative significance. The characteristics are best developed in the case of Families 35, 13 and 39, which it will be recalled are at the extremes in resistance, 35 being the most resistant, 13 being low and 39 the lowest. The work with Families 35 and 13 as concerns this matter has been exhaustive, and warrants quite final opinions. Family 39 was available in inadequate numbers early in the observation period and more recently has been unavailable. The characteristics presented by it in certain instances were definite and easy to discriminate, but gain most of their weight in formulating conclusions from the fact that they have never appeared among the very large numbers studied from other families.

When a number of animals of the two families, 35 and 13 (we have usually used twenty of each family for an experiment), are inoculated intracutaneously at the same time and with all possible care to make the inoculation uniform as to amount and location, and when these are subjected to a daily examination, differences are definite by the 10th day and continuously so thereafter.

First recognizable is the fact that the papules and nodules are somewhat larger in the case of Family 13. The ulcerative stage also appears somewhat earlier in this family. When the lesions have reached full development at about the 20th day these general differences in size persist, and do so for as long as any considerable number of the animals remain alive with unhealed lesions.

Examined at the period of maximum size the lesions are quite different in other respects. The lesion in the case of Family 35 is firm and very sharply circumscribed on palpation. The ulcer, usually centrally situated in the lesion, is surrounded by a wide margin of firm tissue. The ulcer itself is dry, relatively shallow, is saucer shaped when round, with sharply defined margins, the whole ulcerated surface being clearly visible.

In the case of Family 13 it is frequently difficult to define the lesion by palpation. The ulcer occupies a much larger proportion of the whole lesion. The rather narrow but thick and raised margin of the ulcer is soft and edematous. The base of the ulcer is apt to be moist,

and the ulcer seems deeper because of the raised or thicker margin. The margin is excoriated and inspection does not reveal the full extent of the ulcerated area because of undermining at the edge.

The illustrations (Fig. 1, Family 35, and Fig. 2, Family 13) show these characteristics fairly in so far as they are determinable on inspection. In the plates the lesion in the case of Family 13 *appears* to be more definitely circumscribed and no larger than that pertaining to Family 35 owing to the fact that palpable qualities could not properly be considered by the artist.

It would seem possible to apply the terminology of the surgeon to these lesions and to describe them both as active, healthy ulcerations, Family 35 presenting a restrained type, Family 13 an unrestrained and tumid one. It would probably be possible in such an experiment at the period of full development to identify the family in about 75 per cent of the cases by an inspection of the lesions. The failures in identification would be almost if not quite altogether cases where Family 13 would be wrongly assigned to Family 35 on this basis.

When in one such group experiment, six animals of Family 39 were included a condition developed which is well represented in Fig. 3. During the first 20 days there was nothing to distinguish these animals from those of Family 35. Thereafter their lesions developed and maintained till death, in increasing degree, a scaly or scabby margin to the very dry ulcer. When the scabs were removed patches of excoriation were found under them and the lesion continued to spread, not as the extension of a solid nodule with a widening central ulceration, but as minute ramifying excoriating ulcerations in the more superficial layers of the skin, covered by the scaly scabs described and pictured.

In another experiment comprising twelve animals of this family but four of them developed similar lesions and in these the peculiarities were less pronounced. Animals have not been available for further tests. The significance of the result seems beyond question however for nothing approaching this lesion in type has been seen either in any of the animals of the other families or in any stock animal intracutaneously inoculated. In surgical terms this lesion could be described as an indolent excoriating ulceration.

Family 13 has presented another distinctive departure from the

other families which is of significance in the present connection. The inoculations have been practiced in or near the midline somewhat below the umbilicus. The inguinal lymph nodes on both sides are secondarily involved without exception and are usually symmetrically enlarged. In the case of this family (13) and in no other it has happened not infrequently that the inguinal lymph nodes when quite large have become adherent to the skin and this has been followed by ulceration and the later formation of a persistent discharging sinus. Moreover in many instances in this family, but in no other, smaller secondary nodules have formed along radiating lines (presumably lymphatic) between the site of the initial lesion and the inguinal nodes. These have reached a diameter of several mm. and then broken, leaving ulcers showing a considerable persistence but with a general tendency to heal.

With these types clearly in mind we have repeatedly surveyed Families 2 and 32, as well as various crossbreds having their parentage in the five family lines in all possible combinations. We have been unable to recognize any other type of lesion and *on a purely qualitative basis* we have been unable to definitely place any other family or group with reference to these types. In other words, if we had had only Families 32 and 2 and the various crossbreds, while we could have made out the types of lesion characteristic for Families 35 and 13 they would have appeared as the extremes in a variable series of individual reactions and we should not have been able to assign type to group with reference to inheritance or resistance to tuberculosis. As will be pointed out in succeeding paragraphs rough qualitative considerations suggest a definite evaluation of Families 2 and 32 also, but with the crossbreds we have been able to make no group discrimination.

In order to arrive at a roughly quantitative description of the differences we have measured the lesion in its longest direction and in the direction of a line at right angles to the longest, both in mm., and have then multiplied these together to give a value in square measure which we have termed the area. Since all the contours are rounded and the lesion is often quite round this is not a true area but an arbitrary value. The true area would be very difficult to determine in view of the irregularities in contour. The arbitrary area agrees well with the qualitative characteristics. To those accustomed to evaluate tumor forma-

tion it may appear that thickness should also be estimated and the volume be the basis for comparison. The lesion however differs from a tumor in that at the time the ulcer is established there is a discharge of matter and thereafter volume even if determinable would, we think, be less representative.

The arbitrary area of the ulcer is also determined in a similar way, and at each observation period the percentage of animals showing ulceration, and later in the experiment, complete scar formation is also noted.

The data of one such experiment in which four families were used are collected in Table I.

If the figures as given in the table for Families 13 and 35 are contrasted it is seen that for each observation period the nodules and ulcers are larger in the case of 13 than that of 35. It is also apparent that the ulcer in 13 is larger in proportion to the total area of the nodule. The percentage of animals showing ulcers is always greater for this family except during the midperiod when 100 per cent show ulcers in both. From the 68th day onward when complete healing is in evidence the number of animals showing residual scars is always much less in 13 than in 35. For these two families this is the third in a series of experiments similar in every controllable respect and with the same outcome. Family 13 then seems always to give the more severe local lesion in response to equal injections of tubercle bacilli into the skin.

With respect to Families 2 and 32 the table reveals difficulty in assigning them a definite place. Up to the 40th day they are very much alike and if the size of the ulcer alone could be considered they would in this period be clearly intermediate between 13 and 35. For the three observation periods, 19, 26 and 34 days the total lesion is even smaller than in the case of 35. The percentage of ulcers is larger than for 35. From the 40th day onward these families diverge, No. 2 rather definitely taking its place with No. 13 and No. 32 with No. 35.

The whole result as to these families would seem to place them as intermediate in respect to the character of their local lesions between Families 35 and 13, with Family 32 showing a more definite resemblance to Family 35 and Family 2 a greater likeness to Family 13.

It will be noted for all families that in the later periods of observa-

TABLE I.

Days	Lesion	Reactions by families			
		No. 35	No. 13	No. 2	No. 32
12	N	38	46	42	45
	U	3	6	4	5
	Per cent U	32	56	45	61
19	N	62	68	56	55
	U	8	13	10	10
	Per cent U	87	100	95	100
26	N	48	55	45	45
	U	6	12	9	8
	Per cent U	100	100	100	100
34	N	47	54	51	42
	U	4	11	10	9
	Per cent U	100	100	100	100
40	N	46	60	57	51
	U	3	13	11	10
	Per cent U	88	100	100	100
47	N	38	66	62	44
	U	3	14	11	8
	Per cent U	81	100	100	94
54	N	38	69	66	43
	U	3	14	11	6
	Per cent U	54	100	98	91

In the first vertical column (days) the elapsed time after inoculation is given in days. In the second vertical column there are indicated for each observation period, 1st, the average size of the nodule in sq. mm. (N); 2nd, the average size of the ulcer in sq. mm. (U); 3rd, the percentage of those animals remaining alive at any observation period which show ulceration (per cent U); and 4th, for the observation periods 68 days and succeeding, the percentage of those animals remaining alive showing only residual scars (per cent S O). Comparison of the family groups for each character observed and for each observation period is obtained by reading left to right the remaining columns headed with the family numbers 35, 13, 2, 32.

TABLE I.—*Concluded.*

Days	Lesion	Reactions by families			
		No. 35	No. 13	No. 2	No. 32
61	N	18	54	57	18
	U	3	12	13	5
	Per cent U	54	95	100	78
68	N	17	43	54	12
	U	5	9	10	4
	Per cent U	21	73	90	50
	Per cent S O	25	2	2	18
75	N	19	30	52	10
	U	4	7	11	2
	Per cent U	19	53	88	28
	Per cent S O	53	7	5	19
87	N	17	40	61	18
	U	2	6	12	4
	Per cent U	28	61	88	57
	Per cent S O	33	2	5	12
96	N	21	30	58	10
	U	4	6	12	3
	Per cent U	23	44	84	26
	Per cent S O	42	2	7	32

tion there are certain irregularities in progress from week to week in the percentages showing ulcers and scars. This is due partly to deaths, the figures being calculated on the basis of the total living at any date, and partly to the fact that progress toward healing is not steady. Ulcers heal over and break down again and again before scar formation is complete. These changes affect the average size of the ulcers but little because in this late period of successive relapses they are always very small.

It was thought possible that the different characteristics of the lesions as above described might be a reflection of an immunity developing at a different rate with advancing disease. As this if true might be associated with differences in the character of the tuberculin reaction, tuberculin skin tests were made on a selected series of these ani-

mals. A few tests were done on Family 39. Families 2 and 32 were not tested. Tests of Families 35 and 13 were adequate for conclusions.

Family 39 failed to react to tuberculin in the tests made. It seems possible that this is related to the fact that these animals are so low in resistance that the period when they could become sensitive after the establishment of the disease overlaps that period late in the disease when animals as a rule fail to react. Or it may possibly have some deeper significance.

The tests on Families 35 and 13 were interesting in that the size of the local reactive lesion in the skin differed by families in about the same degree as did the size of the initial lesion due to the living bacillus, Family 13 always presenting the larger lesion. The tests do not cover all the possible relationships as the absolute sensitivity of the animals was not measured, only the character of reaction to equivalent full doses.

The result was such as to raise a question as to whether the differences in size and quality of the skin lesions were related in any specific way to the disease-producing qualities of the tubercle bacillus. As a test in control of this point the animals were injected into the skin with various amounts of turpentine and of dilutions of tincture of cantharides, agents well known to produce acute aseptic inflammatory processes. As a reaction against these materials local nodules followed by ulcerative processes were induced, and for these also the lesions were larger and more tumid in Family 13 than in Family 35.

These processes have in common the fact that as inflammations they are characterized by a pronounced focal accumulation of leucocytes particularly the polymorphonuclear types. They were controlled by comparing mild burns of the shaved skin produced by water of various temperatures applied in flat bottom vials. The results were inconstant. No differences were made out between Families 13 and 35. The lesion here is a flat shriveling crusting disc in which the ulcerative and healing processes go on under the dead epithelium and crust without the accumulation of gross nodules.

It may therefore be concluded that the differences above described between the lesions in Families 13 and 35 are not specifically related to the injury done by the tubercle bacillus, but only incidentally to this as a part of a more general reactivity. The families differ in their

reaction to inflammatory irritants, particularly perhaps to those which cause pus formation locally, whether these act very acutely (turpentine and cantharides) or more chronically (the tubercle bacillus).

The inbred families differ from each other in another respect, of interest in the present connection, which has not so far been stated either by Wright, Wright and Lewis or the present authors. When in the course of these studies we had occasion to test the effects of the intravenous inoculation with the tubercle bacillus this was done by dissecting free the jugular vein. Families 35 and 13 were used for the comparison, twenty animals belonging to each being thus operated on in this minor way at one sitting.

In order that the experiment as a whole might have a uniform beginning we had previously practiced the technique on other animals and had standardized a simple operative procedure. It was necessary to extend the animal on a suitable board, administer an anesthetic, shave the neck, make a small incision, free and lift the vein by blunt dissection, make the injection, remove the forceps and close the wound with a single stitch. The animals weighed about 300 gm., that is they were young and the tissues were relatively soft. In case the vein or any branch of it was torn it was necessary to abandon the attempt and operate on the other side. It was found that the procedure including the change of animals on the board took 5 or 6 minutes, going on at the rate of 10 or 12 an hour. The forty animals were injected after 11 a.m. of one day. They were operated on in alternate family groups of three or four animals, and in order to finish during the working day, allowing for interruption and rest periods, it was necessary to make a conscious effort to maintain a rate of work approaching the best possible. The conditions for the following observations were therefore such that incidents which under other circumstances might have been unimpressive because of their casual and occasional character became striking by reason of the enforced attention, and were checked both by alternative repetition and the time factor involved.

It was clearly observable at once that this simple operation was easier to complete in the case of Family 35 than Family 13. In 35 the tissues were stronger, there was less loose free fat in the areolar tissue both generally in the subcutis and about the veins. The vein was thus easier to find and to expose. The vein wall was definitely stouter, less easily punctured by chance and the small branches less subject to tear. The instances in which it was necessary to go to the opposite side to complete the injection were fewer.

These differences were interpreted as evidence of some constitutional divergence in the families. The animals were more closely

scrutinized from this point of view and it was evident that making due allowance for age Family 35 is built on more compact lines and is more excitable and active. This family also has a higher muscular tonus, evident on handling. The differences in nervous irritability were, it was found, well known to the attendants. Subsequent experience has shown that these differences may be obscured by conditions. They are most apparent when the diet is somewhat restricted pointing to a general difference in "feeding quality" to use the terms of the livestock man. The differences are of the character that might generally be described as those between the "lean and hungry" type and that with the obese tendency.

These qualities as between the two families considered (35, 13) may possibly be related to the observations by Wright, that among the five families 13 was marked by the best capacity to gain weight from birth to weaning (33 days) and had the largest adult size (weight). Family 35 was second to 13 in both these respects.

But that the differences we are now considering are qualities not wholly reflected in rate of gain or adult weight as indicated by the further fact that we have so far been able to draw no definite distinction between Families 13, 2, 32 and 39, while in Wright's measurements, 2, 32 and 39 were definitely inferior to 35. It thus appears certain that the present distinctions as above described rate Family 35 as one having a definite constitutional peculiarity. Each time that we have tried to place Families 2 and 32 with respect to these qualities we have freshened an impression that 32 was more like 35 and that 2 was more like 13. This might be of interest in connection with the similar but indefinite likenesses in the character of the local ulcerative processes were it certain that the judgment in the two cases was formed independently. It is, however, true that the facts with regard to the character of the lesions were well established first and were the stimulus to the effort to formulate the impressions as to general constitution. We must therefore rest the case for general constitutional attributes on the comparative merits of the two families, 35 and 13, which even though giving an incomplete account of the animal material is essentially satisfactory in that the differences there are well defined and they are clearly at the extremes so far as these groups of animals are concerned.

SUMMARY.

In summary the observational part of this paper may be restated as follows:

1. On intracutaneous inoculation with the tubercle bacillus inbred guinea pigs develop local lesions having familial characteristics.

Family 35 which has a high natural resistance against tuberculosis as measured by length of life after inoculation develops a compact nodule with a relatively restrained type of ulceration. Family 13 which has a low natural resistance against the disease develops a softer, less well demarcated, more edematous nodule with a much less restrained, more destructive type of ulceration. Differences of the same general order develop when local lesions are created on the skin with turpentine or cantharides in these two families. In other words, the distinctions relate to the general quality of inflammatory reactions in these animals rather than to a specific reactivity against the tubercle bacillus or its product.

Families 2 and 32 which are intermediate between 13 and 35 in natural resistance develop local lesions which are on the whole intermediate also, but more like those of Family 13. In so far as it is possible to assign closer relationships it would seem that Family 32 reacts somewhat more like Family 35 and Family 2 more like Family 13.

Family 39, the lowest in natural resistance of the families available for this study presents a peculiar type of local lesion which begins with a compact nodule not to be distinguished from that of the most resistant family but often ends with an extensive indolent, excoriating, crusted ulceration. This type of lesion is not always presented by this family but has never been encountered in a very extended experience with the other families.

In the case of Family 13, but in no other, the character of the local lesion finds frequent expression in the reactions of the adjacent lymphatics and lymphatic nodes. Fresh nodules and small ulcers frequently appear along the line of the lymphatics. The lymph nodes frequently become adherent to the skin, ulcerate through and present residual persistent sinuses.

2. Families 35 and 13 present differences in the quality of their

tissues suggestive of variation in constitutional character, as observed in connection with a minor surgical operation. They also appear to differ somewhat in general conformation, muscular tone and in nervous irritability or temperament.

Interpretation.

A. Present Observations as Related to the Observed Differences in Resistance against Experimental Tuberculosis.

Our conception of disease rests on the fundamental proposition that absence of injury to either structure or function is health, and similarly when disease processes are compared, that the lesser the injury or the greater the tendency of any injury to repair the greater the approach is to health, the more favorable or inclinable to health is the condition. And in connection with local insults to tissues of all sorts age old surgical experience has crystallized into certain judgments the background for which cannot be materially reinforced by direct experiment. They are essentially axiomatic. Thus a surgeon recognizes as a healthy ulcer one which is under all the circumstances making an unmistakable active progress toward the healed condition.

It seems therefore entirely justifiable to consider that in the present experiments the observations on the local lesions exhibit a considerable, perhaps an unexpectedly considerable correlation with the previously determined general resistance of the families of animals against tuberculosis. Thus Family 39 showing by all odds the least general resistance develops a local lesion which in its later phases shows neither the tendency to heal nor any appreciable measure of the activity which experience teaches must be associated with the development of such a tendency. All of the lesions in all of the other families have shown activities which if fully developed would eventually be expected to result in a healed lesion.

Family 13, next in order of increasing resistance, and in fact all of the other families exhibit a good measure of the kind of activity usually considered essential to the establishment of a healing process. But in Family 13 this is associated most definitely with an interfering, more or less progressively destructive process which cannot at present be segregated for further description but which finds its expression in

the larger, more tumid type of lesion, and particularly in the way in which the ulcer follows out to the margin of the inflammatory area.

Family 35 exhibits an active process in which this destructive tendency is under most restraint. This family also shows the largest percentage of actually healed lesions at most times.

Families 2 and 32 exhibit active lesions on the whole less clearly defined but probably intermediate in place between 35 and 13. Based on the percentage of healed lesions eventually resulting, it appears proper to say that 32 is more like 35 and 2 more like 13.

The sum total of these relationships may be expressed in the following arrangement of family numbers in order respectively of decreasing general resistance and of decreasing reactive quality. The less definite likenesses are suggested by the brackets.

General resistance: 35, 2, 32, 13, 39.

Inflammatory reactivity: 35, 32, 2, 13, 39.

With reference to our problem of locating reactive characteristics which are both based on the inheritance and capable of accounting for differences in resistance the agreement is considerable. It seems justifiable to conclude that the variations in inflammatory character partly account for the observed differences in general resistance. The fact that Families 2 and 32 do not follow the scheme makes it clear, on the other hand, that resistance is not wholly determined by inflammatory character.

B. General Considerations with Reference to Immunity against Tuberculosis.

The immunity reactions and relationships in tuberculosis are much less well understood than is the case in many other diseases. It has been the general opinion that the humoral and cellular constituents of the blood are of relatively less significance. Much weight is laid on the tuberculin reaction and the hypersensitive state of which it is the available index. There is current a suggestion that possibly immunity in this case rests largely on some peculiar relation of the tissues to the infection and the idea is summed up in the term "tissue resistance." For the most part attempts at a better definition of this

idea experimentally have resolved themselves into a study and interpretation of one or another form of the tuberculin reaction.

Analysis of the problem of tissue resistance shows that the epithelial tissues may be left out of consideration in this instance as they are but secondarily involved in the disease. The unformed constituents of the body fluids and the polymorphonuclear series of leucocytes are not to be neglected but are outside the present argument. There remain the fixed connective tissues, the blood vessels, particularly the capillaries, and the reticulo-endothelial cell system inclusive of the phagocytic macrophages and the blood cells of the mononuclear series.

The fixed connective tissues might be thought of as the point of primary injury and they certainly appear frequently in the reparative and healing process. Lewis and Newcomer (6) attempted to show some relationship between the individual capacity of the normal rabbit to form connective tissue in response to trauma and the relative susceptibility to inoculation tuberculosis of the same animal at a slightly later period. There was no such relationship shown in the experiments. The subject is difficult of approach and the negative result of one type of experiment does not exhaust it.

The other elements involved, through the hypertrophic reactions of the blood vessels give character to the process as a granuloma and by means of the temporary organization of the other cells create the typical tubercle as a second characteristic anatomical feature of the disease. It is probably not going too far to assume that factors which determine the qualities of this imperfect and more or less transient organization of the mesothelial tissues are also likely to be factors in the resistance to the progress of tuberculosis after its establishment and less tangibly perhaps in any immunity which may be naturally possessed or acquired. In this limited sense our observations appear to be in accord with the idea that tissue resistance may be a non-specific factor of import to the natural immunity to tuberculosis. Only further study can show how far, if at all, these processes can be intrinsically modified by the acquisition of a specific immunity.

C. Genetic Considerations.

From the genetic standpoint it seems necessary to assume that we are dealing here with qualities that rest on a blending type of inherit-

ance. The reaction characters themselves merge one into the other so that it is only on the average or in extreme and therefore type cases that the distinctions can be clearly seen. Moreover, in so far as we have dealt with crossbred animals, the distinctions have been blurred and appear wholly as individual variations.

The view is held today by specialists in the field that blended inheritance is a consequence of the interaction of multiple genetic factors. This would agree with an *a priori* conception of the case since it is difficult to see how so complicated a process as an inflammatory reaction carried through from initial stages to healing could be under the control of a single or even of any very small number of functional or morphologic units. It is nevertheless possible to see in the results some suggestion of segregating unit characters. The peculiar qualities presented by the extreme cases in Family 39 are to the point. It would seem not unlikely that they rest on a recessive trait or traits. Otherwise they should occasionally be encountered in the crossbreds. Similarly it would appear that those cases in Family 13 in which the inflammation proceeds with least restraint and in which the lymphatic channels and nodes show lesions peculiar to the family, may well be evidence of action or failure to act in part controlled by a recessive character or characters since they have not been encountered in the crosses.

D. Constitutional Considerations.

Belonging essentially to the prebacteriologic era of pathology is the conception that susceptibility to infectious disease is more or less definitely related to fundamental inheritable qualities which find expression in physical conformation, that is, "physical type," and in peculiarities of function, that is "constitution." The terminology was on the whole very loose and interchangeably employed. Constitution also was often thought to be expressed in physical characteristics. When functional characteristics were thought of as directly related to disease the term "diathesis" was frequently used. Thus people of a certain inherited "constitution" were regarded as especially liable to tuberculosis, particularly to that of the lymphatic glands on the basis of a "scrofulous diathesis."

When ideas were crystallized during and after the classical bacteri-

ological studies of the latter quarter of the last century the conception of the scrofulous diathesis was first amplified in an attempt to harmonize it with new observations, and then almost if not quite discarded as being at best inadequately grounded. The considerations advanced in amplification of the conception are of considerable interest in the present connection.

It was first shown, of course, that the lymphatic lesions characteristically associated with the diathesis were tuberculous and that they had in general the same etiology as pulmonary tuberculosis. It was soon very evident that it was difficult if not impossible to discriminate between those physical characteristics which might be preexistent and possibly reflect predisposing causes, and those which were the consequences of long continued chronic disease transmitted by contact infection from generation to generation and often persisting in the individual from earliest childhood to old age. It also appeared that many of the other lesions particularly those of the skin which had frequently been regarded as evidences of a scrofulous diathesis were not tuberculous but were due to casual infection with staphylococci, streptococci and probably other microorganisms.

This recognition of many of the appearances as "consequences" greatly weakened the whole conception. The further evidence that if there was a constitutional predisposition it was not strictly specific for tuberculosis but involved other inflammatory processes as well put the question out of touch with the progressive thought of the time, which was primarily engaged in establishing specific relationships, either of etiology or immunity.

With the coincident and tremendous improvement in hygienic conditions and nutritional well being in Europe and especially in America, tuberculosis and the minor infections referred to have a greatly diminished prevalence. It is now to be accepted that practically all of the aforesaid ability to segregate a type of people having the scrofulous diathesis (if such there are) was dependent on the continued manifestation of the infections to which they are susceptible.

We think it of interest and significance that this first experimental approach to the question with suitable material develops a picture which fits so well with the conception of a scrofulous diathesis as it stood at about the beginning of the present century. We have ob-

served an inherited group of reactive qualities which are related to susceptibility to tuberculosis and also find expression in the character of the tissue changes in tuberculosis and in some simple inflammatory reactions. Respecting the limitations imposed by species differences this would seem to be as close as it could be hoped to come to an experimental definition of the "scrofulous diathesis."* It seems possible that a study of skin reactions to various inflammatory irritants, especially such as could have no antigenic properties, would develop facts of interest in connection with more general studies on human constitution.

SUMMARY.

Five families of strictly inbred guinea pig whose general resistance to experimental tuberculosis had previously been determined by Wright and Lewis have now been studied with reference to the characteristics of the local lesion produced by intracutaneous inoculation with the tubercle bacillus.

It is found that there are clearly recognizable familial types based on the size and quality of the nodular lesion, the ulcerative lesion consecutive to this and the general effectiveness of the healing process when in evidence.

Family 39 which has the lowest general resistance forms an initial papule which does not differ appreciably from that formed by Family 35 which is the most resistant. In the ulcerative stage Family 39 shows an indolent excoriating process which exhibits none of the qualities which would be expected to make for healing.

Family 35 exhibits a firm primary papule and nodule followed by an active healthy type of ulceration which is definitely restrained in comparison with that of the low resistance Family 13. Family 35 also presents the largest number of completely healed lesions in the later observation periods.

* For a modern discussion of the whole question of constitution and physical type as related to susceptibility to particular diseases or disease groups, reference may be made to the recent monograph of Draper (7) and a still more recent essay by Stockard (8). These authors do not consider the scrofulous diathesis. The most recent extended review of the subject with which we are familiar is by Schluter (9).

Family 13 shows a larger, softer, primary papule and nodule than any of the others. The ulcer when formed is less restrained; that is, it is larger in proportion to the total size of the lesion. It is also more generally destructive. This family also shows a singular tendency to the formation of secondary ulcers along the lymphatic channels leading toward the adjacent lymph nodes. The adjacent lymph nodes are likewise more severely affected and frequently ulcerate through the skin giving rise to residual discharging sinuses.

Families 2 and 32 are less definitely characterized. They are of the same order as 35 and 13 in that the ulcerations are active and healthy. Such similarities as are recognizable place Family 2 more nearly with 13 and Family 32 more nearly with 35.

In general the qualities of lesion exhibited are such as to agree with the general resistance as previously determined and it is believed that the qualities underlying the tissue reaction may be safely considered to be among the influential factors in the make-up of the natural resistance against tuberculosis.

The differences in reaction are in part manifested against agents causing simple inflammation also, and hence must be designated as non-specific with reference to the tubercle bacillus.

There are definite indications of other "constitutional" differences in the character of the tissues and the general make-up of these families.

The accumulated evidence from the study of the separate families and intercrosses between them is to the effect that the differences in question are transmitted by the blending type of inheritance and are therefore controlled by multiple unit characters. It is also suggested by the observations that certain of the significant characters are recessive in nature.

It is of considerable interest that the observations agree very well with the older conception of an inherited, predisposing, constitutional diathesis as a significant factor in the incidence of tuberculosis.

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EXPLANATION OF PLATE 23.

FIG. 1. Typical lesion on Family 35.

FIG. 2. Typical lesion on Family 13.

FIG. 3. Typical lesion on Family 39.

The animals were from a series inoculated on the same day, intracutaneously, with 1/10 mg. of a culture of bovine type of tubercle bacillus. The drawings are natural size and were made on the 20th day after inoculation.



FIG. 3.



FIG. 2.

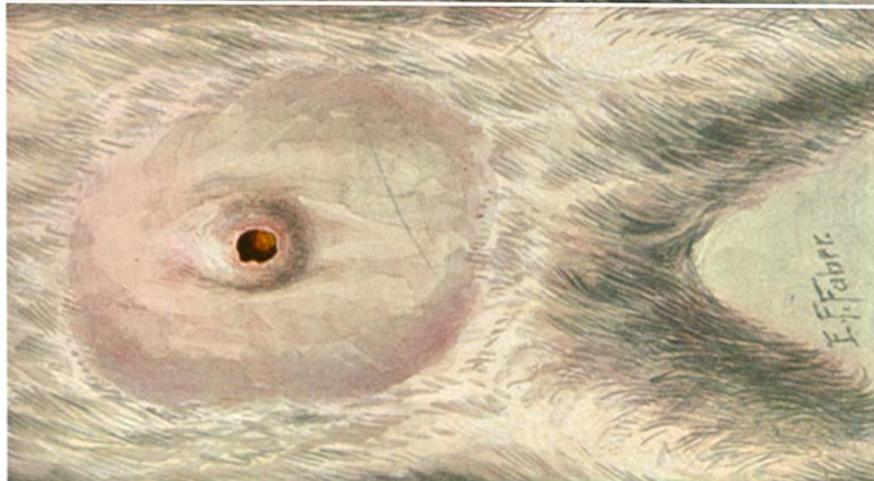


FIG. 1.

(Lewis and Loomis : Ulcerative types and inheritance.)