

heard from Dr. Féré that he wrote a paper on the subject some time ago, and that it will appear shortly.

## REFERENCES.

<sup>1</sup> Ch. Féré, *La Famille Névropathique*, 2nd ed., pp. 236, 253. <sup>2</sup> 1903, vol. i, p. 781. <sup>3</sup> Féré, op. cit., p. 221. <sup>4</sup> *The Study of Children*, pp. 84 and 109, and fig. 17. <sup>5</sup> *Alburt's System of Medicine*, vol. ii, p. 110. <sup>6</sup> Op. cit., pp. 10, 206. See also *Mental Faculty*, p. 114.

## THE PATHOLOGY OF EPILEPSY.\*

[WITH SPECIAL PLATE.]

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It is not my intention to attempt an account of all the pathological features that have been observed in the brains of epileptics. I shall confine my remarks to a brief consideration of some which seem to me to have a very intimate connexion with the causation of the fits.

The view which I shall endeavour to support from my microscopical examinations and the results of experiments (by others) is that epilepsy is a disease occurring in persons with a defectively-developed nervous system associated with a morbid condition of the blood, whereby it shows a special tendency to intravascular clotting, and that the immediate cause of the fits is sudden stasis of the blood stream resulting from the blocking of cerebral vessels by these intravascular clots.

I take it that the fits are merely one of the symptoms of epilepsy, and may even be entirely wanting throughout the whole course of a case. Following the classification adopted by J. Van der Kolk<sup>1</sup> and others, I would divide the symptoms of epilepsy into two groups:

1. Those which represent the sequelae of chronic diseased conditions in the brain. These are permanent and form the epileptic character. (Attacks of intense disturbance of consciousness and complete or partial amnesia, with restitution of integrity between attacks, religiosity, aimless wanderings, etc.)
2. Those which occur only temporarily, and represent the reaction of the diseased brain to stimuli (the fits, *grand* or *petit mal*).

Probably the mechanism of all fits of a similar character, whether we term them epileptic or epileptiform, is the same. Dr. Hughlings Jackson draws a very sharp distinction between some fits which are clinically like epileptic and true epileptic fits. The former he looks upon as "middle-level" the latter as "highest-level" fits. Whether epilepsy is a disease of those parts of the nervous system which fall into his highest-level region or not, I would suggest that the convulsive fits at all events, regarded merely as one of the symptoms of the disease, are due to a disarrangement of middle-level elements in the so-called motor region.

## NERVE-CELL LESIONS.

So long ago as 1864 Dr. Hughlings Jackson<sup>2</sup> advanced the hypothesis that the pathology of epilepsy was vascular, and suggested that the fits were caused by the plugging of small cerebral vessels. My observations bear out this view, but they also seem to show that the vascular changes alone are not sufficient to account fully for all the clinical phenomena. It seems necessary to assume that a morbid condition of the nervous cells is also present, and the study of the central nervous system in epileptics shows that changes in the nerve cells are generally to be found; and, although doubtless some of these are merely the results of the disease, others are probably antecedent to it, and among these latter I would direct attention to two very common features, both of which appertain to stigmata of degeneration; these are:

- (1) A variety of nerve cell, which, as Lugaro and others have pointed out, represents an embryonic form, and which I<sup>3</sup> have shown to be common in imbeciles.
- (2) The persistence in the brain of subcortical nerve cells, a character first noted by Roncoroni.

As regards the first of these changes, it is shown most clearly in the Betz cells of the ascending frontal convolution, although the smaller pyramidal cells may also be, and frequently are, affected. This change was met with in 27 out of 35 cases examined (77 per cent.). In some of

these cases all, or a great majority, of the Betz cells were affected, in others only a few. The change resembles an early stage of *réaction à distance*, and may, indeed, owe to some extent its character to a cause which has been found sufficient to produce the axonal reaction in the cells of the spinal cord. I refer to a diminution in the normal stimuli, for more than half of the spinal cord of epileptics which I have examined (7 out of 13) show either defective development or degeneration of the posterior columns, especially the columns of Goll. Briefly stated, the changes seen are as follows:

The Nissl bodies in the central parts of the affected cells are in the form of fine granules, whilst those at the periphery and in the protoplasmic processes still retain their normal form. The cell is somewhat swollen, and its nucleus, instead of being centrally situated, is at the side or quite up in the apex. In many cases, to all intents and purposes, the nucleus appears otherwise quite natural (Fig. 1).

Amongst the earliest to point out and emphasize the importance of defectively-developed nerve cells in the cortex of epileptics was Bevan Lewis<sup>4</sup>—that great pioneer in the pathological anatomy of insanity. He describes an inflated spheroidal form of nerve cell with few branches, which he looks upon as "the expression of a reversion to a more primitive type," for similar cells are normal in the pig, and he remarks that "it is in the structural peculiarity of the cell that we must learn to recognize the origin of the convulsion."

This form has been met with by many more recent observers, and does not require any further corroboration at my hands. I have singled out for more minute description another form of cell change, indicating also a primitive or defectively developed type of cell. Probably, also, Lewis has recognized this change as common in epileptics, but his method of staining does not permit him to see the finer details of the change affecting the chromatoplasm. Although it is not peculiar to epileptics, occurring as I have already mentioned in imbeciles not subject to fits, it is probably an important adjunct in the causation of the fits, for it is conceivable that stimuli which would fail to produce convulsive phenomena in persons whose nerve cells were well developed and stable, might be able to do so in those with defectively developed and probably unstable nerve cells. And, further, these affected cells may play an important part in determining the character of the fits in individual cases.

It is a recognized fact that very often a great uniformity obtains between the character of the different fits in an epileptic, one being, as it were, a replica of another, and it may be asked how a block which is liable to occur in a vessel in any part of the brain can be the stimulus which will produce such a uniform discharge. In most cases it is only some of the cells in epileptics' brains which show appearances of defective development, and I would suggest that the pattern, so to speak, of the fits of each epileptic is predetermined by the position and number of these affected cells, so that when the stimulus is present in any part of the brain which is connected by conduction paths with the areas in which these defective cells lie the resulting discharge will be of a similar character. This form of cell change seems to have no special relationship to defect of intellect, for, although most of my epileptic cases were idiots or imbeciles, a few were of quite average intellect, and in them the change was present; and, further, a large acquaintance of its occurrence in the brains of the sane and non-epileptic insane shows that it may occur in a very marked degree in cases much above the average of intelligence found in those from whom this asylum population is recruited.

With reference to the persistence of subcortical nerve cells, they exist in fairly large numbers in the lower animals throughout life, but, although found in infants, they soon, with the growth of the child, become less, and at adult age few remain. With imbeciles, whether epileptic or not, they tend to persist, so that at all ages they are met with in large numbers. All the epileptics' brains which I have examined show, some in a more marked degree than others, this characteristic.

There is still another change in the nerve cells frequently met with which, as it has not attracted much attention, and as it appears to me to have a very important bearing on the theory I am advocating, I shall

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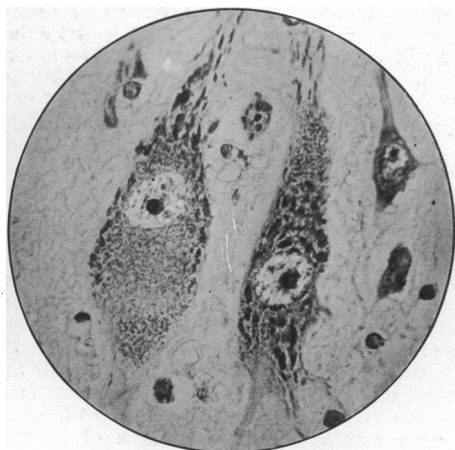


Fig. 1.—Showing the contrast between the axonal form of Betz cell (to the left of the figure) found in 76 per cent. of epileptics' brains, and one (to the right) in which the nucleus is in its proper position, and the Nissl bodies arranged in a fairly normal manner. ( $\times 400$ .)

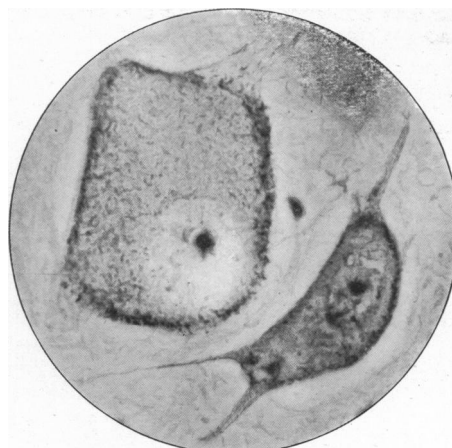


Fig. 2.—Two Betz cells from the cortex of an epileptic imbecile; the one to the left is enlarged, and its nucleus enormously swollen; the one to the right is small, and has a nucleus of greater density than normal. ( $\times 600$ .)

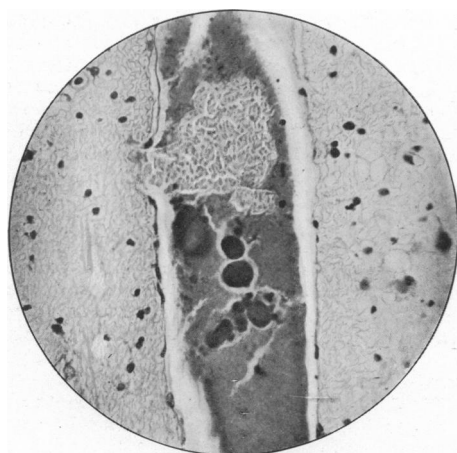


Fig. 3.—Small vein in the cortex of an epileptic idiot, who died *in status epilepticus*. The vessel is blocked by finely granular clot, in which are lying a collection of spheres of different sizes. The pale patch is composed of red corpuscles. ( $\times 200$ .)

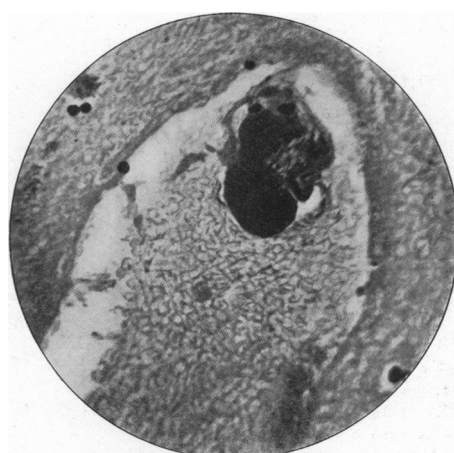


Fig. 4.—A small vessel in the cortex of the cornu ammonis which is blocked by a lobulated hyaline clot, and has ruptured. The clot can be seen partly extruded from the vessel. The perivascular space is much dilated, and filled up with red corpuscles which have escaped from the ruptured vessel. From a case of epilepsy in a weak-minded woman, who died of pneumonia and haemorrhage into the cord. ( $\times 400$ .)

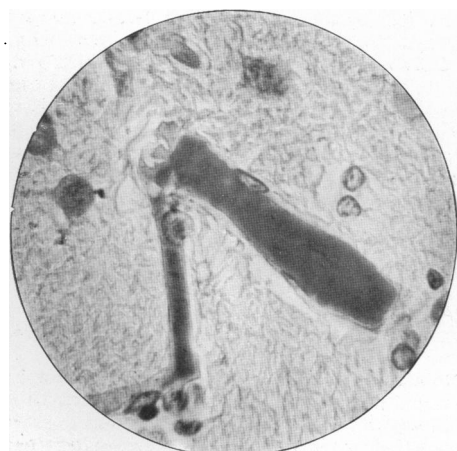


Fig. 5.—Capillaries blocked by hyaline clot. The bulging of the longer capillary shows evidence of being actively distended by the clot. From the cortex of an epileptic imbecile who died in a fit. ( $\times 600$ .)



Fig. 6.—Large hyaline spheres in a vein of the cortex of the cornu ammonis. The section from which the photograph had been taken was treated by Macallum's phenyl-hydrazin test, and the clots stained a bright green, showing the presence of phosphorus, and indicating their nucleoproteid nature. From the same case as Fig. 4. ( $\times 300$ .)

devote some attention to. I refer to cells containing an enormously swollen clear bladder-like nucleus (Fig. 2), which is sometimes so large as to cause a manifest bulging of the cell contour. In some instances the nucleus may even be ruptured or partially extruded from the cell body, or its membrane may be absent.

Such cells, chiefly in groups, are often met with (12 out of 35 cases—34 per cent.). Generally they are interspersed with groups of the darkly-stained, shrunken cells. I take it that the swollen nucleus stage is the acute form, and that in many cases the cells so affected ultimately degenerate, and then assume the darkly-stained shrunken form. The reason why this acute form seems to me of such interest is because quite similar-looking cells were met with in the cortex of a dog after ligation of its cerebral arteries. This is well seen in a photomicrograph in Mott's<sup>6</sup> Croonian Lectures (1900), and my suggestion is that in epileptics' brains they owe their presence to a like cause, namely, stasis of the cerebral circulation.

#### VASCULAR LESIONS.

Before describing the appearances seen in the vessels I will briefly refer to some experiments which bear on the relationship between stasis of the cerebral circulation and convulsions.

Kussmaul and Tenner<sup>7</sup> in 1857 showed that if the left subclavian and innominate arteries of a rabbit be suddenly tied, general convulsions begin in from three to forty-five seconds after. They also compressed both carotids in six men, and found that in two of these symptoms of the nature of an epileptic attack resulted. I would ask you to note that they state that both these cases were of weak intellect.

Dr. Leonard Hill<sup>8</sup> has produced spasm in himself by compressing one of his carotids, and he states that sudden occlusion of one carotid can in some persons produce "a march of epileptic spasm preceded by an aura."

The introduction of oily substances—for example, absinthe, furfural, oil of cloves—into the vascular system of animals is capable of setting up convulsions. But here again—at all events with furfural—only a certain number of the animals experimented on develop convulsions. Probably these substances act mechanically, and produce their effect by causing local stasis in the brain.

These experiments show clearly that convulsions can be set up by blocking the cerebral vessels, and the interesting point is that, in the great majority of epileptics, one is able to demonstrate in sections of the cortex a blocking (partial or complete) of the vessels by various forms of thrombi.

The most important to my mind—as it is certainly the most constant—of the vascular changes found in the brains of epileptics, have not to do with alterations in the structure of the vessels themselves, although these latter are of common occurrence. For example, hyaline thickening of the walls, varicose swellings and tortuosities, endarteritis obliterans, and deposits of calcareous matter in the form of small round glass-like bodies. The changes, however, to which I wish now to refer are changes in the blood itself, whereby it forms intravascular clots which in many cases completely occlude the lumen of the vessel in which they lie.

In every case of epilepsy so far examined (41 in number) I have also met with small cortical or meningeal haemorrhages, and there is very little doubt in my mind that these are the result of rupture in the vessels which have become blocked by the clots just mentioned, and indeed, in some cases their origin from this cause can be demonstrated (Fig. 4). Intravascular clotting, especially in the form of fibrin threads, is not peculiar to epileptics, but speaking from my own experience, whilst this phenomenon was met with in 90 per cent. of the epileptics' brains, it only occurred in 35 per cent. of control brains examined for this purpose. Further, the maximum amount of clotting found in the vessels of the latter series rarely if ever surpassed the minimum amount found in epileptics.

Roughly speaking four forms of intravascular clots can be distinguished:

- (1) Spheres: homogeneous in structure, and varying in size from smaller than a red corpuscle up to many times its diameter. Occurring singly, or massed together into a mulberry-like shape (Figs. 3, 4, 6).
- (2) Hyaline masses: attached to the side of the vessel's lumen, or else completely blocking it up (Fig. 5).
- (3) Finely granular masses (Fig. 3).
- (4) Fibrin threads.

Forms 1 and 2 are probably of like nature, and there is evidence to show that the individual spheres are formed by an amalgamation of the blood plates, which occur in large numbers in the vessels of epileptics. The spheres have the physical characters of blood plates: they stain similarly, and also when tested with Macallum's phenyl hydrazin reagent they react similarly, and assume a green colour of the same depth as the blood plates. This green colour shows the presence of phosphorus, and points to the nucleo-proteid character of the clot. Finally, one meets with all stages, from the individual blood plate to the largest spheres.

Whilst on the subject of blood plates I may mention that the blood from living epileptics showed in nearly all the cases I have examined (13 out of 14) that these little bodies existed in very large numbers, far above that usually found under physiological conditions, and that their well-known tendency to cohere was seemingly intensified, and very often delicate fibrin threads radiated spoke-like from a blood plate or stretched in various directions from one to another. This increase of blood plates is by no means a peculiarity of epileptics' blood alone; it occurs with very diverse bodily conditions and affections, and is often encountered in the blood of acute states of insanity. Still I venture to think that this does not altogether discount the importance of this sign, for at all events it shows that the conditions favourable for an increased tendency to clotting are present in the blood of epileptics.

With regard to the finely granular clot, I do not think that in all cases it is of the same origin. Sometimes there are features which point to its derivation from a dissolution of the red corpuscle, in others to a disintegration of the blood plates, and in others, again, to a partial resolution of hyaline clot. It stains a much paler green with Macallum's test than the other two forms, and very much the same tint as that which the red corpuscles assume with the test. The observations of P. Masoin<sup>9</sup> show that not only is there a diminution in the number of red corpuscles generally in epilepsy, but that an abundant destruction of them especially characterizes the access of an attack. But at times one meets with appearances which point rather to this granular clot as undergoing resolution, for it then shows a looser structure than usual, and may be in the form of little patches lying among the red corpuscles. These patches stain dark green in the centre, where they are nearly homogeneous, and pale green at the periphery, where they are very loosely granular.

The fibrin threads are, perhaps, the least characteristic form of clot; they are generally met with in inflammatory disorders of the body, but when they are present in epileptics (usually, also, in association with inflammatory conditions) they occur in great profusion, and in some cases they are even deposited outside the vessels, so that they lie in the perivascular space, and thickly scattered in the matrix of the brain itself.

It may be objected that the appearances I have described are either results of the fits or else phenomena occurring during a moribund condition, when, as we know, the blood is liable to clot in the still living vessels; but neither of these objections seems to me tenable. In the first place clots may occur in great quantity in those who have had no fits for a long time before death. Especially instructive in this respect were two of my cases, in which abundant evidence of intravascular clotting was forthcoming. They were both of them idiots, who had been subject to severe and frequent fits from infancy, but in both of whom the fits gradually became less and less frequent, until eventually they ceased altogether, so that for one or two years before death neither of them had had a fit. I take it that in both these cases the nerve cells had degenerated, and were unable to respond to the stimulus resulting from stasis.

The presence of phosphorus in the clot allows us, as I have elsewhere<sup>4</sup> pointed out, to declare that the phenomena are not *post mortem*; and the fact that sometimes one meets with actual rupture of a vessel due to blocking by the clot is strongly opposed to the idea that the clot is formed during the moribund condition of the patient.

There is a condition commonly met with in epileptics' brains to which I shall now devote a little attention. I refer to sclerosis and atrophy of the cornu ammonis. This, which has been recognized for the past fifty years or so,

has at different times and by different writers been passed over as of very little importance, or credited as the cause of the epileptic fits.

In 108 cases of idiopathic epilepsy I have found this condition on one or both sides in 52 (48 per cent.). Worcester<sup>10</sup> found it in 20 out of 43 (46.5 per cent.); Bratz<sup>11</sup> in 25 out of 70 (35 per cent.); Weber<sup>12</sup> in 11 out of 33 (31 per cent.). It is very rare in other than epileptics. It occurs sometimes in general paralysis, but usually as part of a general sclerosis affecting more or less the entire cerebrum.

I find it to be much more common (when only one side is affected) on the left, thus: in these 52 instances of mine, the left was sclerosed in 19, the right in 11, and both sides in 22. The proneness of the left side to suffer more than the right is greater than these figures indicate, because, where both sides are affected, very often the left is more sclerosed than the right.

These sclerosed and atrophied horns show very little change under the microscope. There is practically no appearance of an active glial overgrowth, and in fact it is usual to find more and larger glia cells in the unaffected than in the affected horns of epileptics. The nerve cells are diminished in number, and those remaining are shrunken and stain deeply. Small cortical haemorrhages are here, as in other parts of the brain, a very common feature.

I believe that the sclerosis and atrophy is due to a deprivation of the normal blood supply to the parts, as a result of entire or partial blocking of its nutrient vessels, whereby the tissues are as it were starved, and gradually shrink and at the same time become tougher.

The reason why this particular part of the brain should so frequently be the seat of this change is extremely difficult to account for satisfactorily, except on the supposition that it has a vascular origin. After the intravenous injection of clove oil into the jugular vein of a rabbit, the small haemorrhages found in the brain appeared to have a great partiality for this region—a fact which lends some colour to the idea that there is a close connexion between the lesion and the disposition of the blood vessels; and further, the fact that it so frequently affects the left side is in harmony with this idea, for the direct origin of the left carotid from the aorta would favour the deposition of thrombi carried by the blood stream in the vessels of this side.

In one instance I found a partial blocking by a fibrinous clot of one of the arteries going to this part, and the occurrence of partial or complete obstruction of the smaller vessels in the substance of the horns is very common.

The abundant, foam-like albuminous exudate found in the perivascular spaces may also further interfere with the proper nourishment of the tissues.

As a matter of fact, the cornua ammonis are by no means the only parts of the brain affected in this way in epileptics. It is not uncommon to find small areas, especially in the occipital cortex, shrunken and tough and the cerebellum is a very favourite site of these local atrophies, the sharply-defined limits of the affected parts favouring the view that they are of vascular origin. In 9 cases out of 19 examined atrophied foliae were found (47 per cent.), and when one considers what a very small part of this organ is examined microscopically in each case, and that in many instances the affected area is so small as easily to escape detection by the naked eye, it must be admitted that in all probability these figures greatly understate the frequency of the lesion in the cerebellum.

B. Onuf<sup>13</sup> has drawn attention to an atrophic condition of the thalamus in epileptics (he does not mention whether the consistency was increased). In 9 cases examined it was present seven times—three times on the left side, once on the right, and twice on both sides. This atrophy can be adequately accounted for in the same way as that of the cornu ammonis, and it is interesting to find that as with the cornu ammonis so with the thalamus, the left side seems to be more frequently affected than the right. Onuf also refers to shrinking of the foliae of the cerebellum, which he found in 3 cases. Since reading this paper I have only had the opportunity of examining the brain of four epileptics. In three of these there was very slight shrinking of one thalamus, once on the right side and twice on the left. In none was there any perceptible

increase in consistency on the smaller side, but this was scarcely to be expected as the shrinking was extremely small.

#### SUMMARY.

To summarize briefly the most important changes found, they are on the part of the nerve cells:

(a) A form indicative of imperfect development.

(b) Retention of subcortical nerve cells. Also an indication of imperfect development.

(c) Either an acute form of cell change, similar to that produced by ligature of the cerebral arteries in a dog, or

(d) Groups of darkly-stained, shrunken cells, representing a more chronic change, and very likely, at all events in some cases, the sequel of that just described.

On the part of the vascular system:

(e) Large numbers of blood plates in the blood.

(f) Different forms of intravascular clotting, probably in large measure derived from amalgamation of the blood plates, but to some extent also probably due to destruction of red blood corpuscles.

(g) Small cortical haemorrhages, which in some cases can be traced to rupture of a vessel blocked up by the aforementioned clot.

Taken together, that is the correlation of the defectively-developed and probably unstable nerve cells, with the local stasis of the blood stream resulting from intravascular clotting; I submit that these conditions constitute the pathological basis of the epileptic fit.

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## MEMORANDA: MEDICAL, SURGICAL, OBSTETRICAL.

### ERYTHEMA AFTER VERONAL.

SEVERAL cases have been reported lately of the toxic effects of veronal. In the EPTOME of the BRITISH MEDICAL JOURNAL of November 4th, 1905, Kress quotes "numerous authors who had met with unpleasant or dangerous action of this drug" when used in anything like quantity. As the drug was placed upon the market as an absolutely safe one without toxic effects, there is a probability that a reaction may set in against its use. I can testify to its great value in small—5 gr. to 8 gr.—doses in cases of slight pain, and in one instance sleep was induced by a dose of 8 gr. in severe toothache, but I have also to record a case in which a dose of 8 gr. proved toxic in its effects.

The patient is a lady, aged about 42, who has suffered for years from symptoms of dilated stomach, which is in all probability due to a scirrhus carcinoma. She has been difficult to treat medicinally for many years on account of the liability to erythema which asserts itself on the ingestion of various drugs. Morphine in very small doses, and ether, whether taken by the mouth or inhaled, has produced it. She thinks that eucalyptus produced it on one occasion. As sleeplessness and restlessness had been a distressing symptom for some time, I was induced to try veronal under the belief that it was non-toxic. The patient feared to try any new drug, and carefully inquired as to whether it would produce erythema. I reassured her on this point, and that evening she took an 8-gr. powder. An hour and a quarter later she was asleep; three-quarters of an hour later she woke with a violent attack of an erythematous rash, with oedema of the face so marked that she could scarcely see out of her eyes. There were feverishness and restlessness, and the skin "burnt like fire." This lasted to a decreasing extent for four or five days, when the skin began to peel extensively, and this continued for twelve days. There was no other untoward symptom such as Kress records, but that there is an idiosyncrasy in some persons to this drug, as to others, is well proved by such cases.

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